



Spondyloarthropathies "Explore the Hidden part of the Iceberg"

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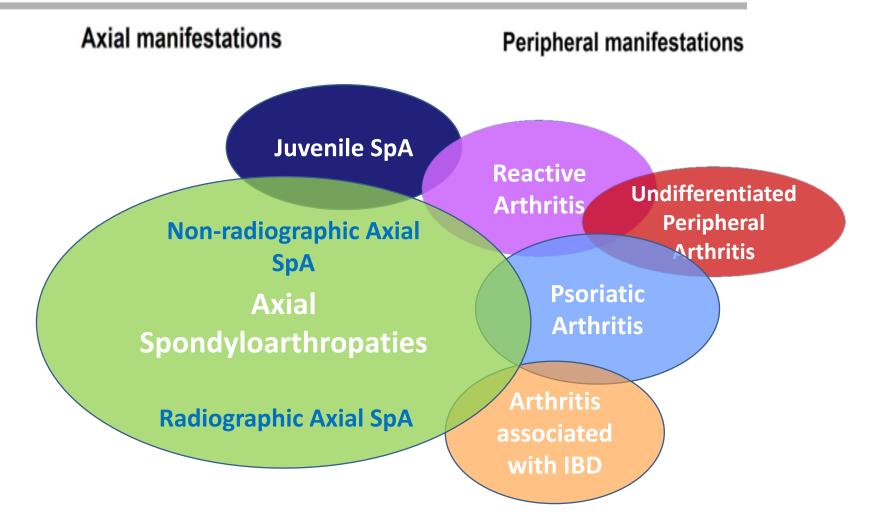
In the next 20 minutes.....

- Concept of SpA
- Relationship between PsA, PsO and IBD
- Innate and adaptive immunity in SpA
- Pathogenesis of SpA
- Conclusion



Spondyloarthritides (SpA)

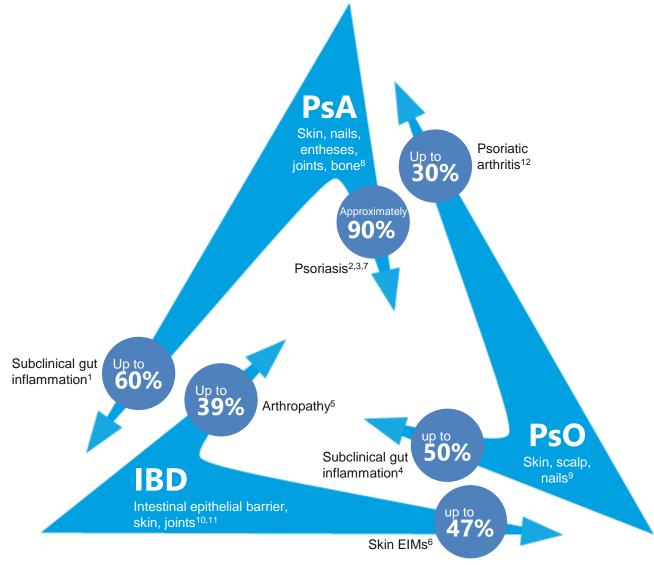
- HLA-B27 positivity
- Familial aggregation
- Sero-negative (negative RA and ACPA)
- Extra-articular
 manifestation
 (Uveitis, Oral ulcers,
 bowel ulcerations..)





Relationship Between PsA, PsO, and IBD

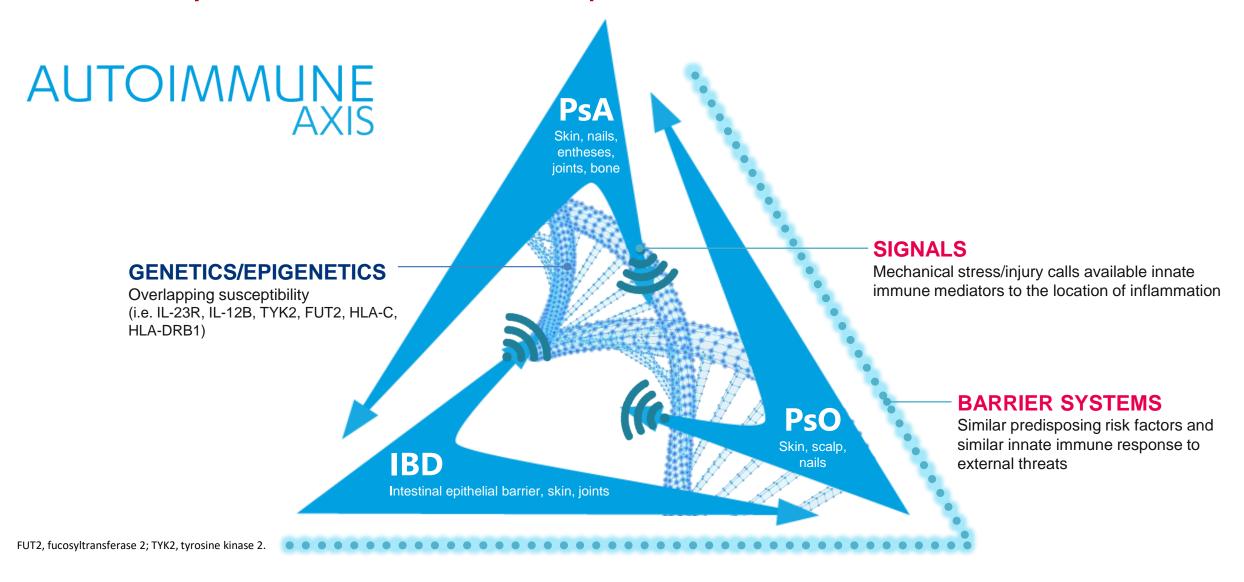




EIMS, extraintestinal manifestation.

1. Ciccia F, et al. Arthritis Rheumatol. 2016;68:1922-31. 2.Mease PJ, Armstrong AW. Drugs. 2014;75:423-41. 3. Ciocon DH, Kimball AB. Br J Dermatol. 2007;157:850-60. 4. Sanchez IM, et al. Curr Dermatol Rep. 2018;7:59-74. 5. Arvikar SL, Fisher MC. Curr Rev Musculoskel Med. 2011;4:123-31. 6. Greuter T, et al. Clin Rev Allergy Immunol. 2017;53:413-27. 7. Liu JT, et al. World J Orthop. 2014;5:537-43. 8. Suzuki E, et al. Autoimmunity Rev. 2014;13:496-502. 9. Lowes MA, et al. Annu Rev Immunol. 2014;32:227-55. 10. Levine JS, Burakoff R. Gastroenterol Hepatol (N Y). 2011;7:235-41. 11. Matricon J, et al. Self NonSelf. 2010;1:299-309. 12. Mease PJ, et al. J Am Acad Dermatol. 2013;69:729-35.

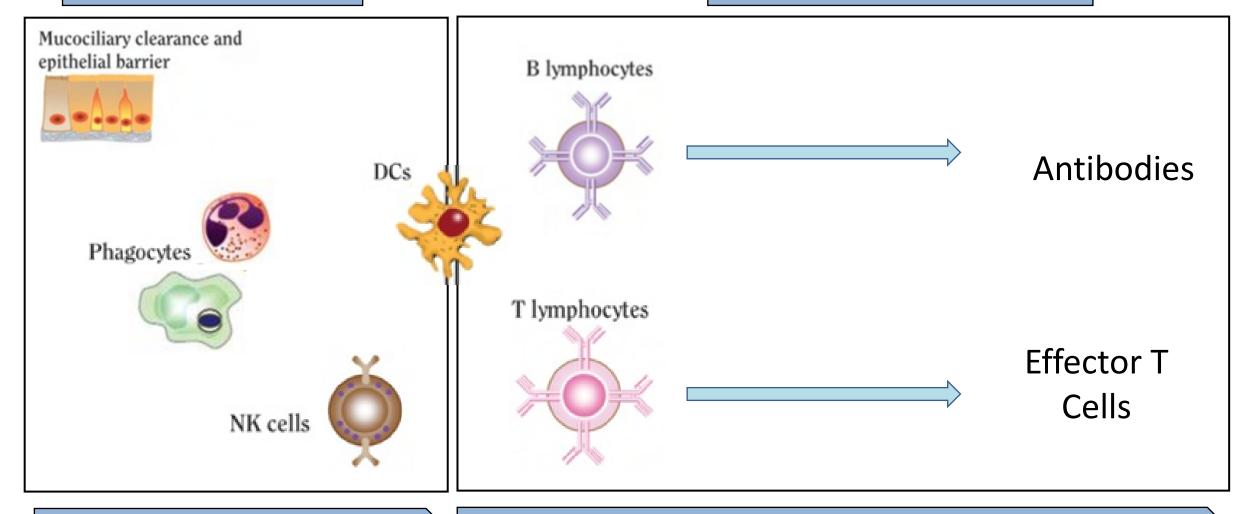
Why Is There a Relationship Between PsA, PsO, and IBD?



1. Boutet MA, et al. Int J Mol Sci. 2018;19:pii E530. 2. Gracey E, et al. Curr Opin Rheumatol. 2019;31:62-9. 3. Suzuki E, et al. Autoimmunity Rev. 2014;13:496-502. 4. Genetics Home Reference. Psoriatic arthritis. Available from: https://ghr.nlm.nih.gov/condition/psoriatic-arthritis#genes. Accessed January 2020. 5. Genetics Home Reference. Crohn disease. Available from: https://ghr.nlm.nih.gov/condition/crohn-disease#genes. Accessed January 2020. 6. Siegel RJ, et al. ACR Open Rheumatol. 2019;1:571-9. 7. Chandran V, et al. Rheumatology (Oxford). 2014;53:233-9. 8. Castro-Santos P, et al. Innate Immun. 2017;23:476-81. 10. McGonagle DG, et al. Ann Rheum Dis. 2019;78:1167-78. 11. Yip KH, et al. Semin Immunopathol. 2019;41:401-10.

Innate Immunity

Adaptive Immunity



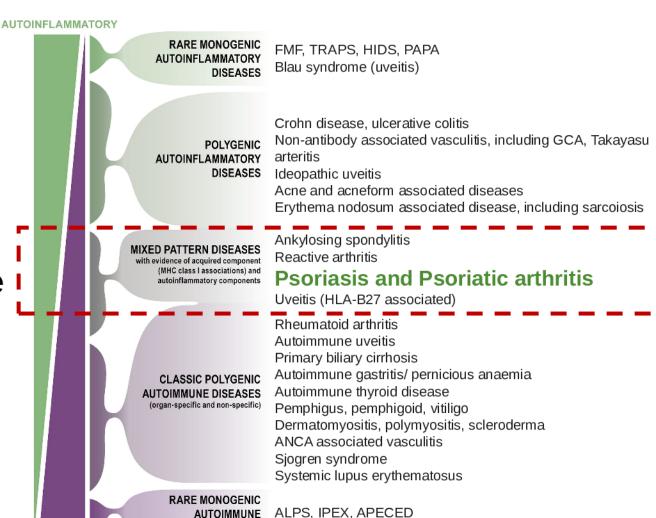
Hours

Days

Spectrum: autoinflammatory - autoimmune diseases

Psoriasis and PsA are

immune-mediated inflammatory diseases with activation of both the innate and acquired immune response, but without the formation of disease specific auto-antibodies.



DISEASES





AUTOIMMUNE

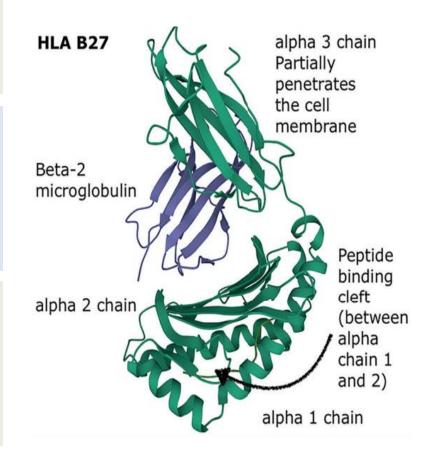


Axial Spondyloarthritis

Axial spondyloarthritis (axSpA) is a chronic, rheumatic disease characterized by inflammation of the sacroiliac joint, spine, and entheses



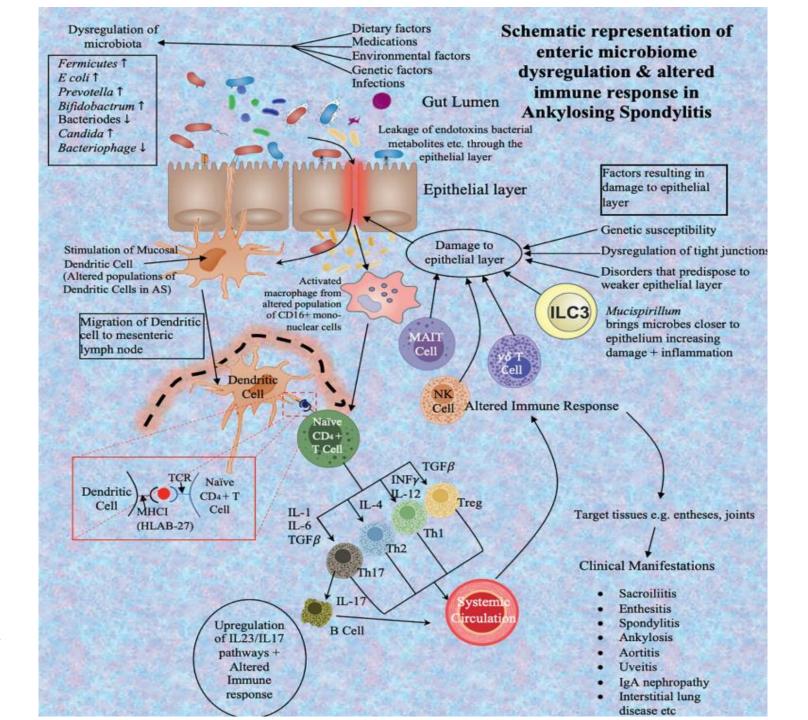
- HLA-B730 HLA-B16, HLA-B35,31,32 HLA-B38 and HLA-B3933. These genes have been identified across a variety of ethnic groups and are associated with HLA-B27-negative AS, although the mechanism is not yet clear¹
- ERAP1 (coding for endoplasmic reticulum aminopeptidase 1 (ERAP1)), ERAP2 (coding for ERAP2). Gene—gene interactions between HLAB27 and ERAP1 appear to be responsible¹
- IL23R. The genetic association of IL23R loci with AS was first reported in 2007. Interestingly, the same SNP also affects the risk of developing inflammatory bowel disease and psoriasis, another conditions closely linked to AS²
- Killer immunoglobulin-like receptor (KIRLR) is up-regulated on activated CD4+ T-cells and they are increased in the terminal ilium of patients with AS³



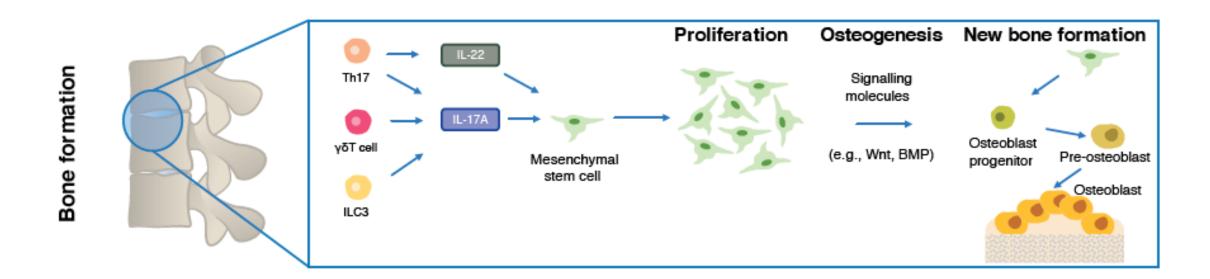
^{1.} Zhu W, et al. Bone Research. 2019;7:22.

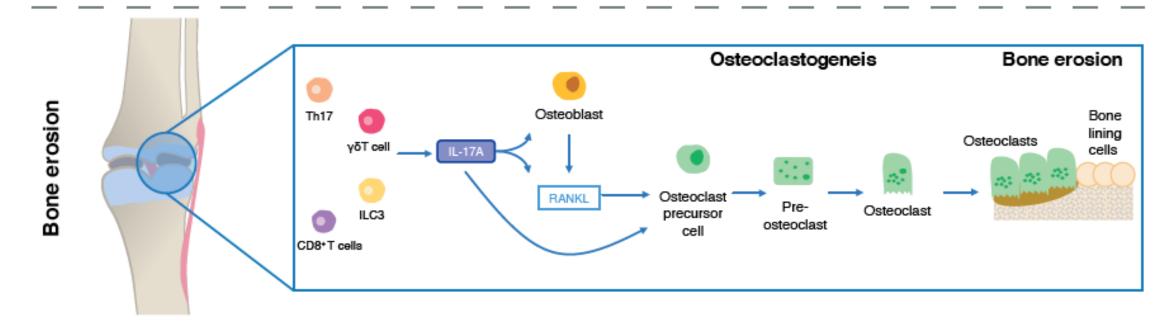
^{2.} Nancy Z, et al. Frontiers in Immunology. 2021;12:624632.

^{3.} Breban M, Hill G. Chapter 8: Immune mechanisms: Adaptive immunity. In: Inman R, Sieper J, editors. The Oxford Textbook of Axial Spondyloarthritis. Oxford University Press; 2016



Harkins P, Burke E, Swales C, Silman A. 'All disease begins in the gut' — The role of the intestinal microbiome in ankylosing spondylitis. Rheumatology advances. Practice. 2021;5(3):rkab063. DOI: 10.1093/rap/rkab063





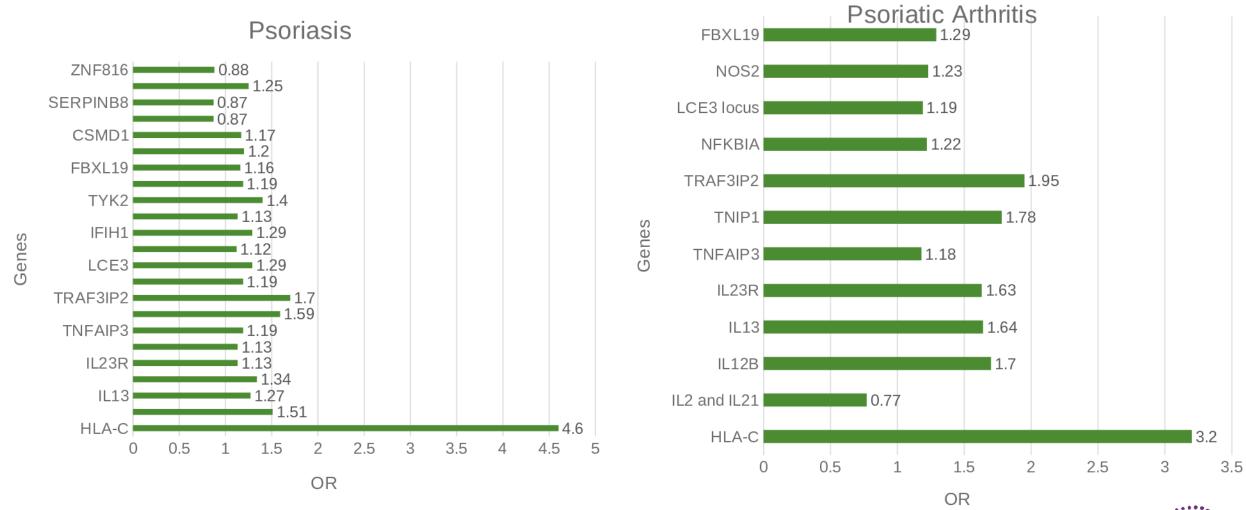


Psoriasis

Psoriasis is a chronic, immune-mediated, systemic, inflammatory disorder characterized by skin plaques and, often, nail disease and arthritis that contribute to reduced quality of life

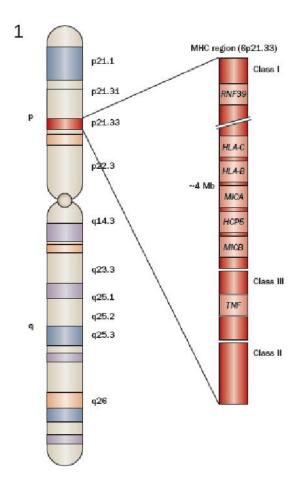


Genes identified in psoriatic disease exhibit low genotype relative risk, so most genes do not provide clinically actionable outcomes





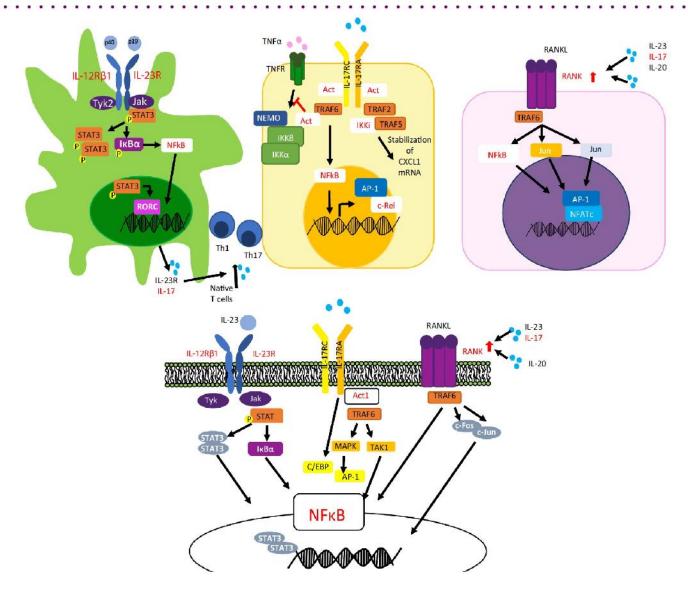
HLA associations provide the most robust genetic associations in psoriatic disease







Psoriatic susceptibility genes can also potentially be linked to pathways interrogated by therapeutic agents such as the IL23/IL17 pathway





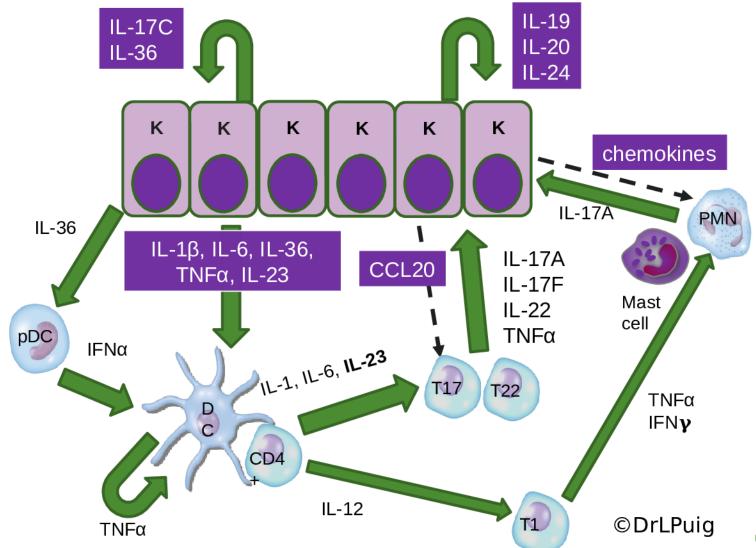


Interactions between the innate and adaptive immune systems in psoriasis skin

Innate

Adaptive









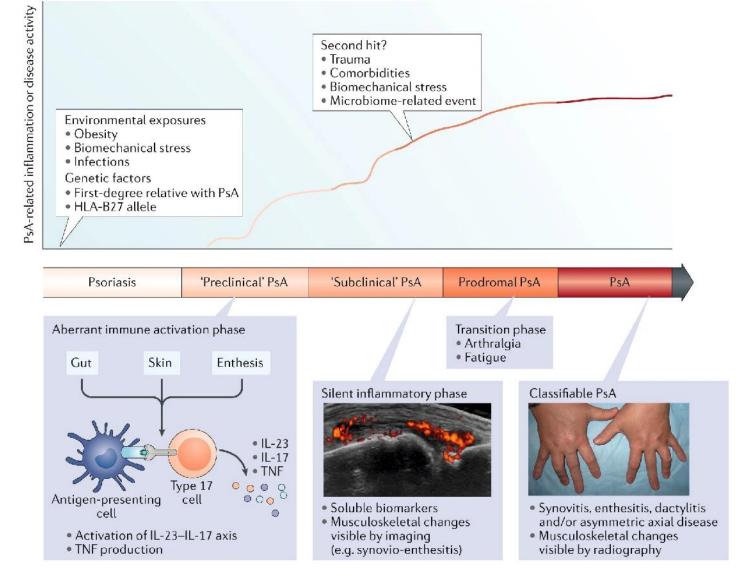
Psoriatic Arthritis

The annual incidence of PsA in patients with psoriasis is 2.7% and the reported prevalence of PsA among patients with psoriasis has varied between 6% and 41%

In nearly 70% of patients, cutaneous lesions precede the onset of joint disease; in 20%, arthropathy starts before skin manifestations; and in 10%, both occur concurrently



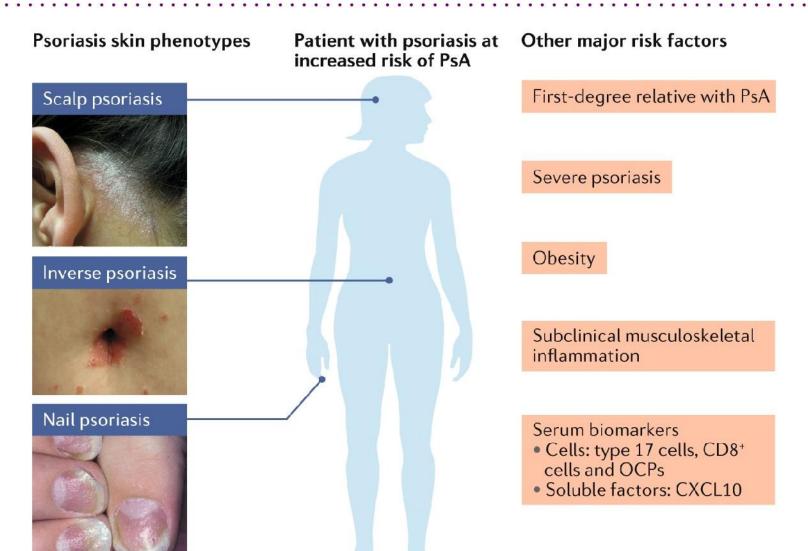
Transition from psoriasis to PsA







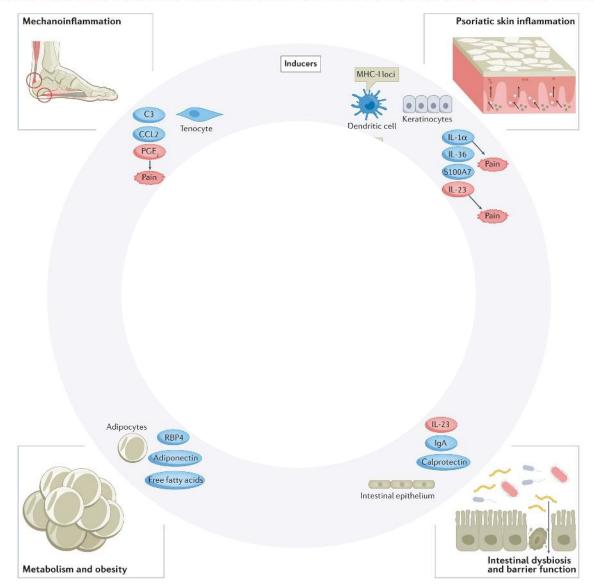
Factors conferring an increased risk of PsA development in patients with psoriasis







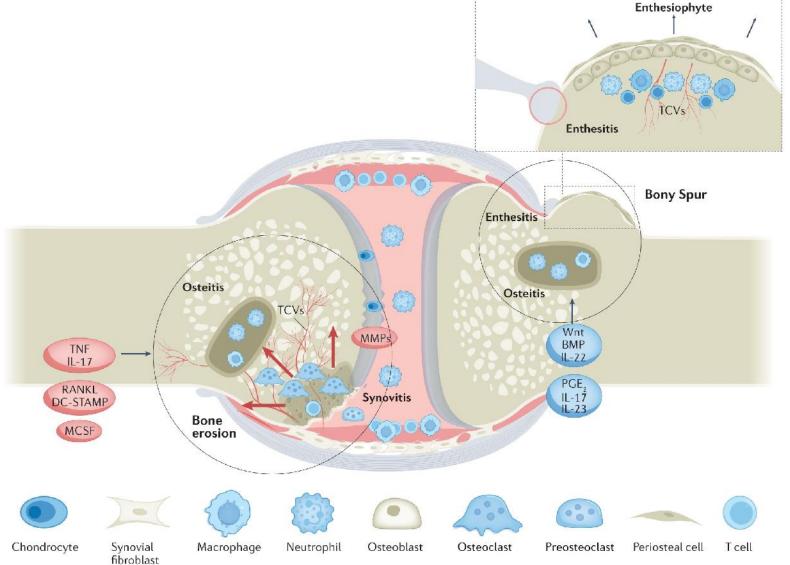
Mechanistic model of PsA







Structural changes in PsA









Enthesitis

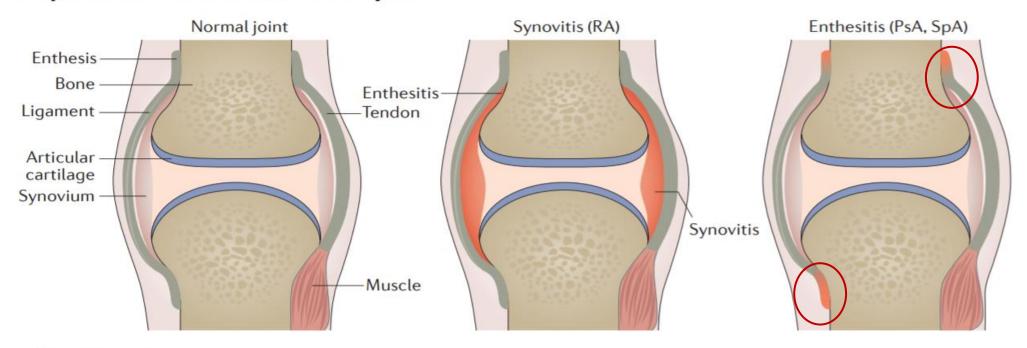
• Entheses are insertion sites of tendons and ligaments to the bone surface and are essential structure for locomotion

• Entheses contain as specific immune microenvironment which is activated by a combination of factors that include mechanical stress, genetic susceptability and microbial-triggered immune activation

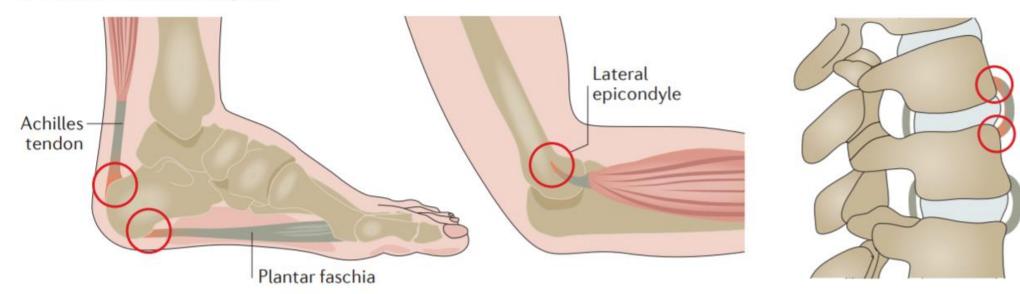
 Enthesitis is a pathognomonic feature of PsA and SpA, where it occurs frequently, often affects more than one enthesis and shows a remarkable degree of chronicity



a Synovial and entheseal structures in the joints



b Entheses distant from joints



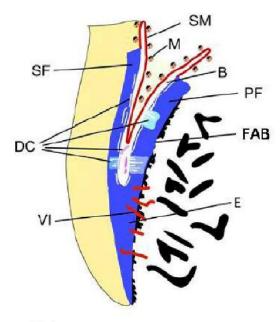
Enthesitis

Entheses

- Connect tendons and ligaments to bone.
- Confer stability and transduce mechanical forces

Enthesitis

- Often triggered by mechanical stress and can be physiological.
- Hallmark of PsA and other forms of SpA, where exaggerated inflammatory responses to mechanical stress are observed.
- Mediators of enthesitis include prostaglandin E2, IL-23, IL-17 and TNFα.
- Chronic enthesitis is associated with new bone formation.



B bursa **E** enthesis

DC degenerative changes

FAB subchondral bone plate

M macrophages

PF periosteal fibrocartilage

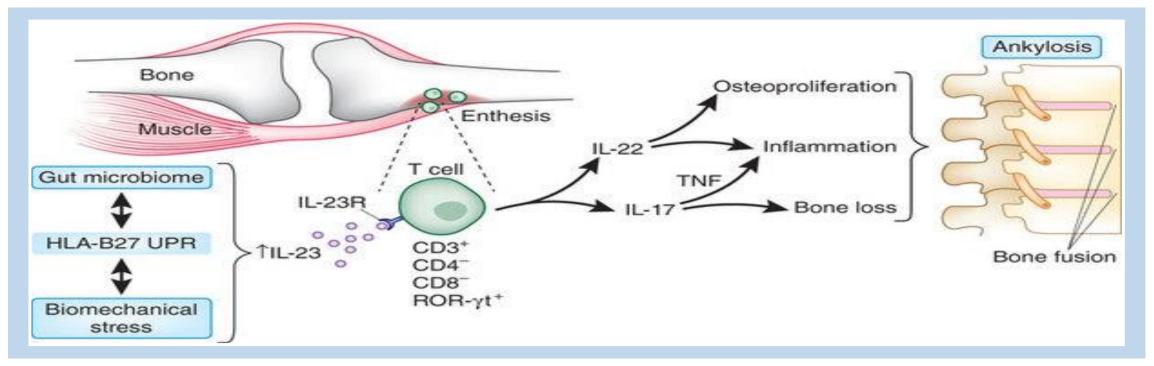
SF Sesamoid fibrocartilage

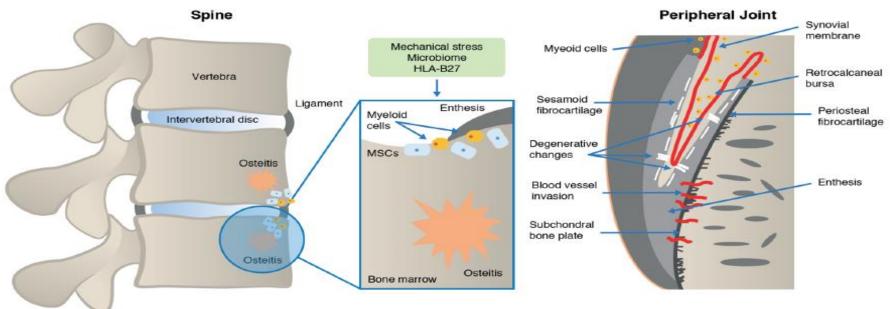
SM synovial membrane

VI blood vessel invasion



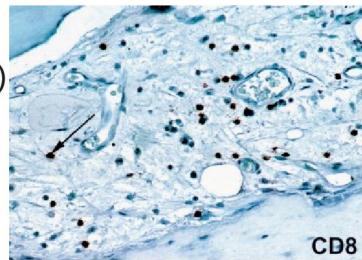






Enthesitis

- In entheses from people with SpA compared with RA and OA, there is:
 - Increased oedema
 - Increased inflammatory cell infiltrate
 (CD3+, CD4+, CD8+ and CD20+ cells)
 with predominant CD8+ T cells
 - Hyperosteoclastic erosive lesions









To Conclude

- Spondyloarthritis refers to a group of disorders that includes ankylosing spondylitis (AS), nonradiographic axial SpA (nr-axSpA), undifferentiated spondyloarthritis (USpA), reactive arthritis, and the arthritis and spondylitis that may accompany psoriasis and inflammatory bowel
- In SpA there is activation of both Innate and Adaptive immune systems with production of many cytokines but without formation of disease specific autoantibodies





To Conclude

 Pathogenesis of SpA is suggested to be induced by arthritogenic peptides, an unfolded protein response, HLA-B*27 homodimer formation, malfunctioning endoplasmic reticulum aminopeptidases, along with gut inflammation and dysbiosis

• Key cytokines, such as IL-23, IL-17 and TNF, orchestrats the various phases of the inflammatory disease process and are therapeutic targets







Thank You

Samah El-Bakry





Diagnosis & Assessment of Psoriatic Arthritis

Dr. Mohamed Nabil
Professor of Internal Medicine, Rheumatology &
Immunology
Beni-Sueif University







Agenda

Psoriatic arthritis

- Introduction
- Epidemiology
- Diagnosis
- Assessment of disease activity & structural damage
- Conclusion









Psoriatic arthritis (PsA)

• In 1964, Moll and Wright defined it as an inflammatory arthritis plus the presence of psoriasis, in the absence of a rheumatoid factor.

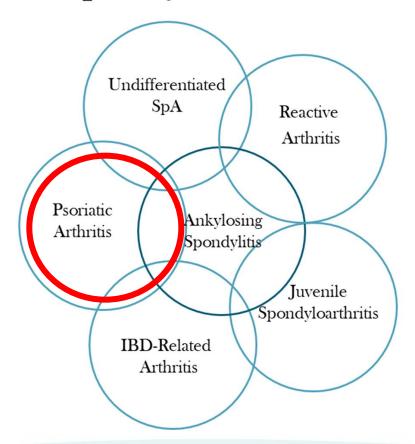
• A multifaceted disease, with a high impact on patient's psychological & physical health.

• It shares many clinical features with other spondyloarthropathies.





Spondyloarthritis





Epidemiology of PsA

- A 2019 meta-analysis described an overall pooled prevalence of PsA of 20 -30% in psoriatic patients.
- Estimates of the global prevalence of PsA range widely from 0.05 to 0.25% of the general population.

• Affects middle age (30-50 years) subjects, males and females are equally affected.

Rheum Dis Clin North Am (2015)





Epidemiology of PsA

- Symmetrical polyarthritis & juvenile forms are more common in females.
- Axial involvement has historically been thought to be more common in men than women.
- The presence of HLA-B27 gene variants is associated with more severe PsA & found more frequently in patients with axial involvement.
- Genes identified by GWAS that are considered prominent in psoriasis include HLA-Cw6, IL12B, IL23R, IL23A, TYK2, and ERAP1.

Clin Rheumatol, (2018)





Psoriatic arthritis (PsA)

- Psoriasis appears to precede the onset of psoriatic arthritis in 60-80% of patients .
- In 15-20% of cases, arthritis appears before psoriasis.
- Occasionally, arthritis and psoriasis appear simultaneously.

J Am Acad Dermatol., 2021





PsA Subtypes

- 1. Asymmetric oligoarthritis.
- 2. Symmetric polyarthritis.
- 3. Distal interphalangeal (DIP) predominant arthritis.
- 4. Arthritis mutilans.
- 5. Psoriatic spondylitis, arthritis of the sacroiliac joints & spine.







Comorbidities

- Ocular: uveitis, conjunctivitis, keratitis.
- Gastrointestinal: inflammatory bowel disease
- Non-alcoholic fatty liver disease
- Obesity & metabolic syndrome
- Cardiovascular disease
- Osteoporosis
- Depression
- Fibromyalgia.

Rheum Dis Clin North Am. 2015





Diagnosis











CASPAR Criteria

Table 1

CASPAR criteria for PsA17

To meet the CASPAR criteria for PsA, the patient should have inflammatory joint disease (peripheral, axial or enthesitis) and achieve three or more points, based on the following categories

1. Evidence of psoriasis

Current	2 points
Personal history	1 point
Familial history	1 point

2. Psoriatic nail dystrophy

Pitting onycholysis hyporkoratosis

Titting, Onythonysis, Hyperkeratosis	- Politic	
3. Negative test result for rheumatoid factor	1 point	

4. Dactylitis

Current inflammation of an entire digit	1 point	
History of dactylitis	1 point	

5. Radiological evidence of juxta-articular new bone formation

Well-defined ossification close to joint margins on plain 1 point radiographs of hands and feet

Sensitivity: 91%; specificity: 99%.



1 moint





Poor Prognostic Factors In PsA

- 1. A strong family history of psoriasis
- 2. Disease onset younger than the age of 20 years
- 3. Expression of HLA-B27, HLA-Cw6, or HLA-DR4 alleles
- 4. Dactylitis & enthesitis
- 5. Polyarticular & erosive diseases
- 6. Extensive skin involvement





Dactylitis is associated with joint erosions & enthesitis is associated with radiographic damage in psoriatic arthritis.

Arthritis Care Res 2017

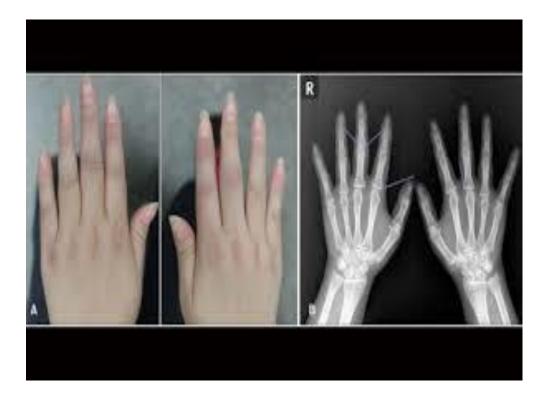


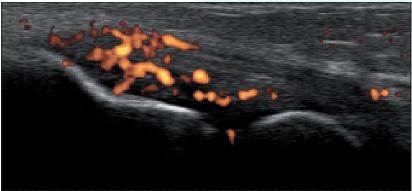


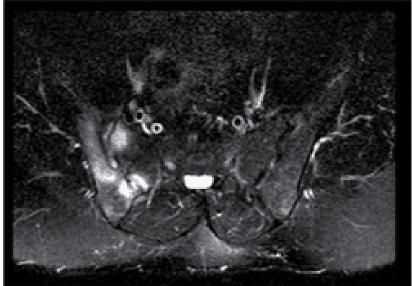




Imaging











Imaging

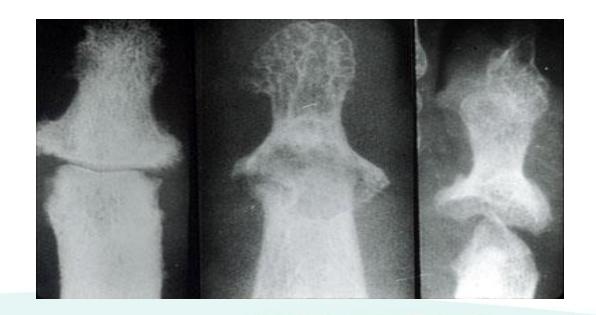
- 1. Plain X-Ray
- 2. Musculoskeletal ultrasonography
- 3. MRI
- 4. Novel modalities
- HRpQ-CT
 Can detect new bone formation in early stages.
- DECT





Imaging (x-ray hands

PsA is characterized by the combination of erosive changes with new bone proliferation, in a predominantly distal distribution.







langes.





> J Rheumatol. 2019 Apr;46(4):384-390. doi: 10.3899/jrheum.171465. Epub 2018 Oct 15.

Development of a Preliminary Ultrasonographic Enthesitis Score in Psoriatic Arthritis - GRAPPA Ultrasound Working Group

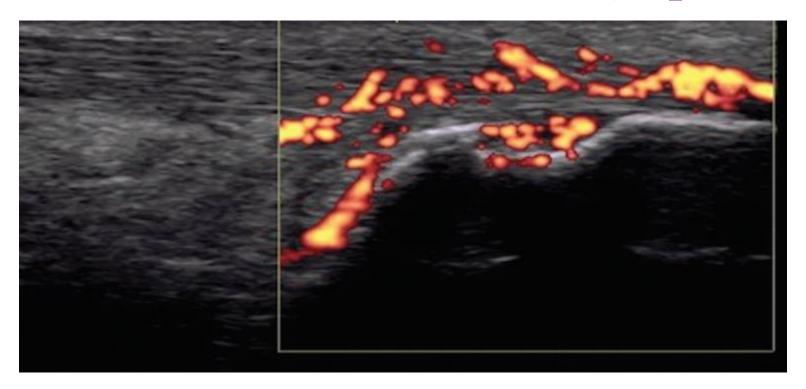
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Stephanie Tom <sup>1 2</sup>, Yujie Zhong <sup>1 2</sup>, Richard Cook <sup>1 2</sup>, Sibel Zehra Aydin <sup>1 2</sup>, Gurjit Kaeley <sup>1 2</sup>, Lihi Eder <sup>3 4</sup>
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The Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) is currently developing a *new enthesitis scoring* system for PsA that aims to distinguish PsA from other conditions.





Musculoskeletal ultrasonography



Achilles tendon enthesitis with Doppler; erosion of calcaneus.





Clinical and genetic associations of radiographic sacroiliitis and its different patterns in psoriatic arthritis

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Abstract Objective

We aimed to 1) identify clinical and genetic associations of sacroiliitis (SI) in patients with psoriatic arthritis (PsA), and 2) describe the different radiographic patterns of SI in PsA and their clinical and genetic associations.

Methods

283 PsA patients, fulfilling CASPAR criteria, underwent detailed skin and rheumatologic assessments. In addition, HLA-B*27 and B*080101 status was recorded, which have been shown as the key genetic markers of radiographic SI in PsA. Grade 2 Unilateral or bilateral radiographic changes of SI were required for inclusion and involvement was further defined as asymmetrical or symmetrical.





Axial affection in PsA

Conclusion

- **25%** of the patients had radiological sacroilitis (asymmetric 73%, in patients with history of back pain 100%).
- Sacroiliitis was significantly associated with peripheral joint erosion (p = 0.043), high psoriasis activity and severity scores (PASI) (p = 0.041) and early onset of PsA ($p \le 0.001$)

Clin Exp Rheumatol (2017).





• Bu ari lui

• Bo an fus

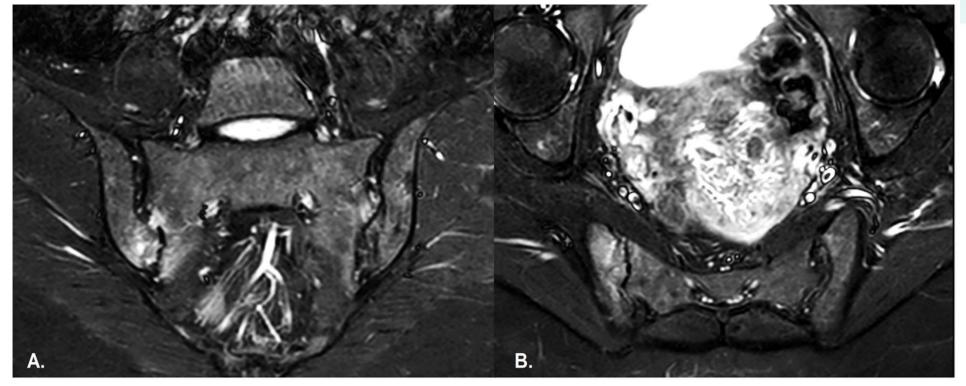
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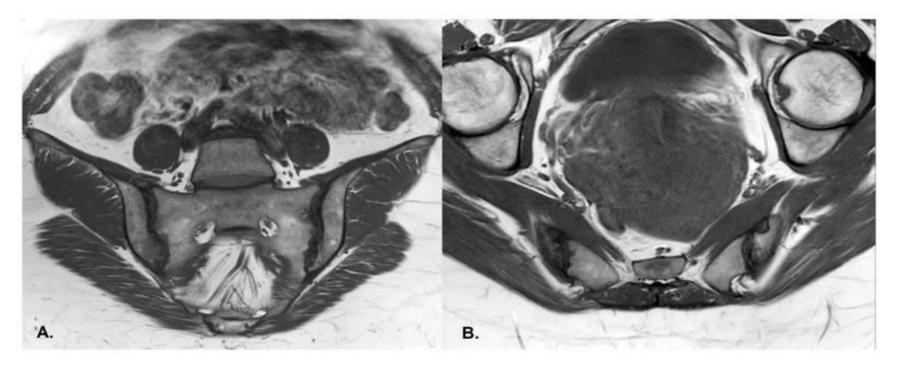
MRI SI joints



 $\bf A$)Coronal and $\bf (B)$ axial STIR sequences show extensive subchondral oedema involving the sacroiliac joints, mainly on the right side, consistent with active sacroiliitis in a patient with psoriasis.







A) Coronal and **(B)** axial T1-weighted sequences of the sacroiliac joints demonstrate subchondral sclerosis and erosions, predominantly on the right side, in the same patient.





Structural Damage Assessment

In 2016, (GRAPPA) & (OMERACT) Core Domain Set for PsA, advocated that structural damage should be measured at least once in the evaluation of a drug in randomized controlled trials (RCTs) and longitudinal observational studies (LOS).

Semin Arthritis Rheum (2018)





Structural damage Assessment

- Radiographs have been the standard approach for assessment of structural damage in clinical trials of PsA over the last 20 years .
- Assesses peripheral joint damage (e.g., bone erosions, osteolysis, subluxation, ankylosis), determine involvement of the sacroiliac joint and joints of the spine, and identify spurs at the entheses.

Clin Exp Rheumatol. 2015





Scoring methods

Several semi-quantitative scoring systems have been developed for the assessment of structural damage progression in PsA.

They are used for trials of biologic or targeted synthetic DMARDs.

- 1. Sharp scoring method for PsA
- 2. Sharp-van der Heijde scoring method for PsA
- 3. Psoriatic Arthritis Ratingen score

Ann Rheum Dis. 2014





Radiographic Disease Progression Modified Total Sharp Score (mTSS)

What does it assess?

Degree of articular damage

What does it mean?

mTSS scores range from 0–528

Higher scores = more articular damage

How is it assessed?

- Erosions and joint space narrowing graded in:
 - 20 locations per hand
 - 6 locations per foot
- Erosions scored from 0–5 (hands) or 0–10 (feet); maximum score = 360
- Joint space narrowing scored from 0–4;
 maximum score = 168
- mTSS = sum of erosion and joint space narrowing scores

How is it reported?

Generally reported as the change in score from baseline





Assessment Tools for PsA

• In order to measure disease activity, progression & change with therapy in PsA, it is important to use accurate, reliable & feasible outcome measures that can ideally be employed in clinical practice, cohorts& clinical trials.

 The Tight Control Of Psoriatic Arthritis (TICOPA) trial confirmed the benefit of regular disease activity assessment using objective outcome measures.





Disease Monitoring



Disease Activity



Structural Damage





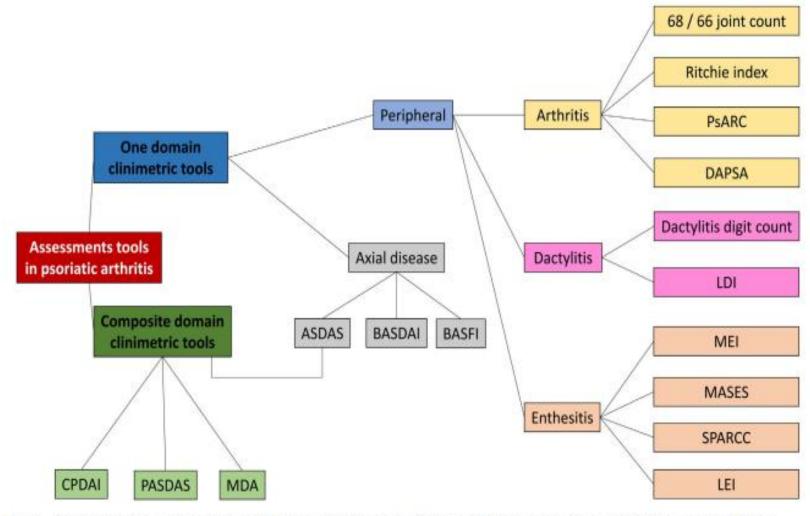


Fig. 1 – Clinimetric tools in psoriatic arthritis. PsARC: Psoriatic Arthritis Response Criteria. DAPSA: Disease Activity in Psoriatic Arthritis. LDI: Leeds Dactylitis Index. MEI: Mander/Newcasttle Enthesitis Index. MASES: Maastricht Ankylosing Spondylitis Enthesitis Index. SPARCC: Spondyloarthritis Research Consortium of Canada. LEI: Leeds Enthesitis Index. ASDAS: Ankylosing Spondylitis Disease Activity Score. BASDAI: Bath Ankylosing Spondylitis Disease Activity Index. BASFI: Bath Ankylosing Spondylitis Functional Index. CPDAI: Composite Psoriatic Arthritis. PASDAS: Psoriatic Arthritis Disease Activity Score. MDA: Minimal Disease Activity.



Disease activity scores

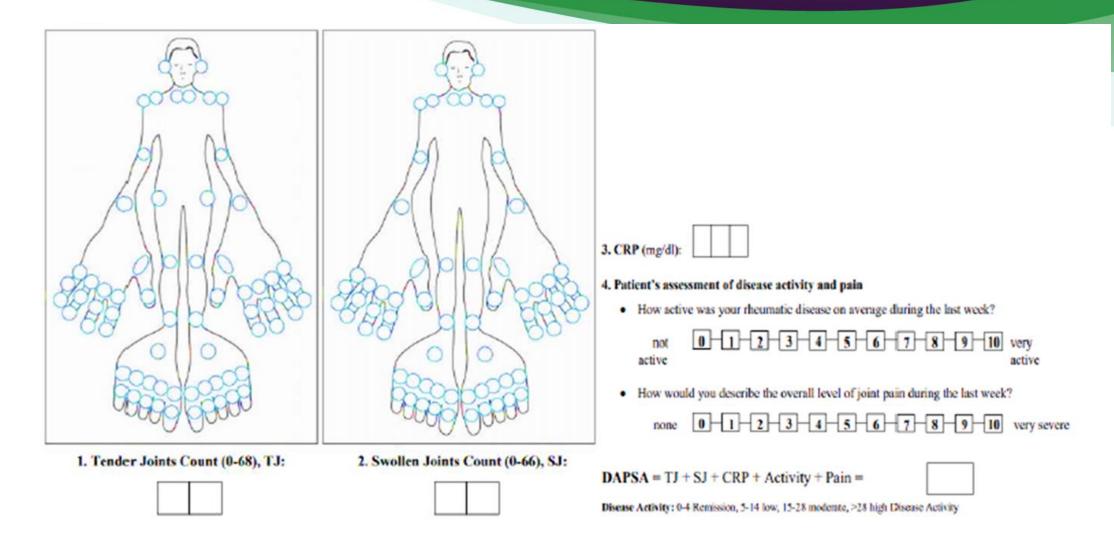
Composite domain clinimetric tools

- 1. DAPSA (Disease Activity Index for Psoriatic Arthritis)
- 2. CPDAI (Composite Psoriatic Disease Activity Index)
- 3. PASDAS (PsA Disease Activity Score)

One domain clinimetric tools

- 1. Tender & swollen joint counts of 68 and 66 joints, respectively, in peripheral arthritis
- 2. Clinimetrics for dactylitis
- 3. Enthesitis assessment instruments



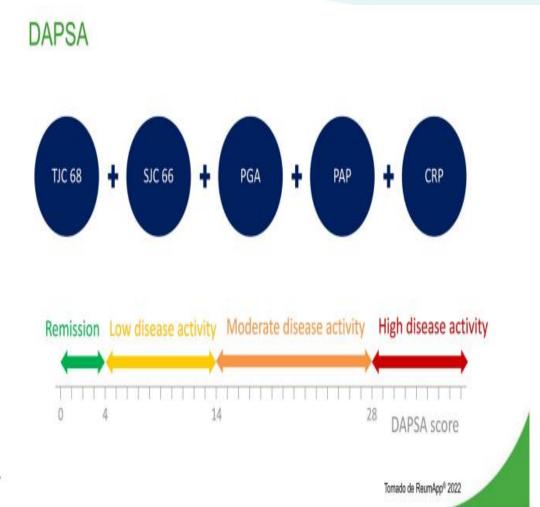


DAPSA = TJ + SJ + CRP + Activity + Pain = Disease Activity: 0-4 Remission, 5-14 low, 15-28 moderate, >28 high Disease Activity





Figure 1 Screenshot from the GRAPPA app MDA calculator. GRAPPA, Group for Research and Assessment of Psoriasis and Psoriatic Arthritis; HAQ, health assessment questionnaire; VAS, visual analogue scale.







MDA

A patient is classified as in MDA when 5 of the following 7 criteria are met:

Tender joint count ≤1

Swollen joint count ≤1

PASI ≤ 1 or BSA ≤ 3

Patient pain VAS ≤15

Patient global activity VAS ≤20

HAQ ≤ 0.5

Tender enthesial points ≤ 1





CPDAI

- Calculated as the sum of the following 5 PsA domains:
 - Peripheral arthritis (TJC, SJC, HAQ-DI)
 - Skin disease (PASI, Dermatology Life Quality Index)
 - Enthesitis (LEI, HAQ-DI)
 - Dactylitis (dactylitis digit count, HAQ-DI)
 - Axial disease (Bath Ankylosing Spondylitis Disease Activity Index [BASDAI], Ankylosing Spondylitis Quality of Life)

Score of each domain ranges from 0–3, according to the disease activity and impact.





Composite Psoriatic Disease Activity Index (CPDAI)

	Not involved: 0	Mild: 1	Moderate: 2	Severe: 3
Peripheral arthritis	ilivolved: 0	≤4 joints (swollen or tender)Normal function (HAQ < 0.5) ^a	≤4 joints with impaired function; or > 4 joints with normal function	>4 joints and impaired function
Skin disease		PASI ≤10 and DLQI ≤10	PASI ≤10 with DLQI >10; orPASI >10 with DLQI ≤10	PASI > 10 and DLQI > 10
Enthesitis		≤3 sites; normal function (HAQ < 0.5) ^a	≤3 sites with impaired function; or >3 sites with normal function	>3 sites and impaired function
Dactylitis		≤3 digits; normal function (HAQ < 0.5) ^a	≤3 digits with impaired function; or >3 digits with normal function	>3 digits and impaired function
Spinal disease		BASDAI < 4; normal function (ASQI < 6)	BASDAI > 4 with normal function; or BASDAI < 4 with impaired function	BASDAI > 4 and impaired function table-entry





PASDAS

Recently, the (GRAPPA) and (OMERACT) initiatives recommended that the PsA Disease Activity Score (PASDAS) should be used in clinical trials but not in routine clinical practice

Rheumatol, (2014)





68 Tender joint count	
66 Swollen joint count	
CRP	
Patient's global VAS	
Physician's global VAS	
Leeds Enthesitis Index	
Dactylitis	
SF-36 (12) health questionnaire	
Total	0-10





Clinimetrics for dactylitis

• Dactylitis is a uniform soft-tissue inflammation of the entire digit, from the MCP to the DIP joints.

 Dactylitis involves feet more than hands, and may affect several digits simultaneously, with the 2nd & 5th toes most frequently involved.

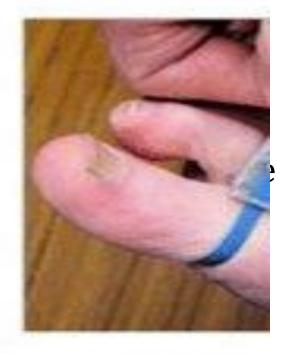
Semin Arthritis Rheum, (2018)



Leeds Dactylitis Index







Circumference involved digit (A)	Circumference contralateral Digit (or Tables) (B)	Tenderness score (C)	Final se [((A/B)



Enthesitis assessment instruments

1. Leeds Enthesitis Index LEI;

2. MASES:

Maastricht Ankylosing Spondylitis Enthesitis Score;

3. SPARCC:

Spondyloarthritis Research Consortium of Canada)





Leeds Enthesitis Index (LEI)

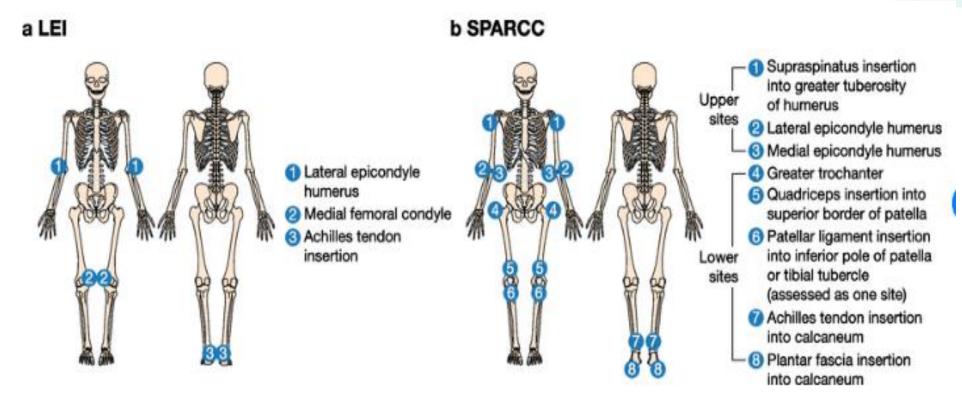
It was developed by the Bradford National Health Service.

<u>6 easy-access entheseal sites</u>:

- 1. Achilles tendon, (left and right)
- 2. Humerus lateral epicondyle, (left and right)
- 3. Femur medial condyle, (left and right)
 - ➤ The exam of each of the **6 sites** registers tenderness as present **(1)** or absent **(0)**, for a general score ranging from 0 to 6.







Enthesitis sites evaluated by LEI or SPARCC. LEI, Leeds Enthesitis Index; SPARCC, Spondyloarthritis Research Consortium of Canada Enthesitis Index. Adapted from Mease PJ, et al. J Rheumatol. 2017;44:599–608. Reproduced with permission





Structural Damage & functional Assessment

1) Health Assessment Questionnaire Disability Index (HAQ-DI)

2) Radiographic Scoring methods

3) Assessment of quality of life in PsA





Health Assessment Questionnaire Disability Index

What does it assess?

Impact of disease on ability to conduct activities of daily living

How is it assessed?

- 20 questions grouped in 8 categories, each scored from 0–3:
 - Dressing
 - Rising
 - Eating
 - Walking

- Hygiene
- Reach
- Grip
- Usual activities

What does it mean?

Higher scores = more disability / reduced physical function *Clin Exp Rheumatol*. 2005





HAQ-DI

• The HAQ-DI has been widely employed in interventional clinical trials of PsA treatment.

• It has been adapted for the spondyloarthropathies (HAQ-S) by adding five items related to disability due to spinal involvement.

J Rheumatol, (1990)





Assessment of quality of life in PsA

PsA-specific HRQoL measurements with elements related to functional impairment, include

- 1. PsAQoL
- 2. PsA Impact of Disease (PsAID)
- 3. VITACORA-19 questionnaires

Ann Rheum Dis, 73 (2014)





PsAQoL

It is a self administered, 20-item questionnaire.

The items address domains including social participation, fatigue, mood & daily activities.





PsA Impact of Disease (PsAID)

Domains of health	Category of impact
Pain	Physical impact (predominantly related
Work and/or leisure activities	to joints)
Functional capacity	
Discomfort	
Skin problems	Impact related to skin
Embarrassment and/or shame	
Fatigue	Psychological and social impact
Sleep disturbance	
Coping	
Anxiety, fear and uncertainty	
Social participation	
Depression	





Take home message

- Psoriatic arthritis is a heterogeneous disease with a wide spectrum of clinical manifestations.
- Recently, there has been much progress in the development of assessments tools, that provide an objective measure of disease activity and treatment response involving clear benefits if applied in routine clinical practice.
- Structural damage in patients with PsA is associated with decreased quality of life and physical function.
- Radiographic progression is an important outcome measure in clinical trials that is needed to identify effective therapies for patients with PsA.





