

# I JORNADA FORMATIVA DE REUMATOLOGÍA

para Atención Primaria de la Provincia de Alicante

## ACTUALIDAD EN ARTROSIS

José Raúl Noguera Pons

- **Definición de artrosis**
- **Epidemiología**
- **Guías de tratamiento**
- **Endotipos/Biomarcadores/Fenotipos**
- **La artrosis como proceso continuo**
- **Novedades en el tratamiento**
- **Artrosis y Ejercicio**
- **Resumen**

## DEFINICIÓN DE ARTROSIS (OA)

Trastorno que afecta a las articulaciones móviles caracterizado por **estrés celular** y **degradación de la matriz extracelular**

Se inicia por **micro- y macro-lesiones** que activan **respuestas de reparación no adaptativas**, incluyendo las vías proinflamatorias de la inmunidad innata

La **manifestación inicial es un desarreglo molecular** (alteración del metabolismo del tejido articular)

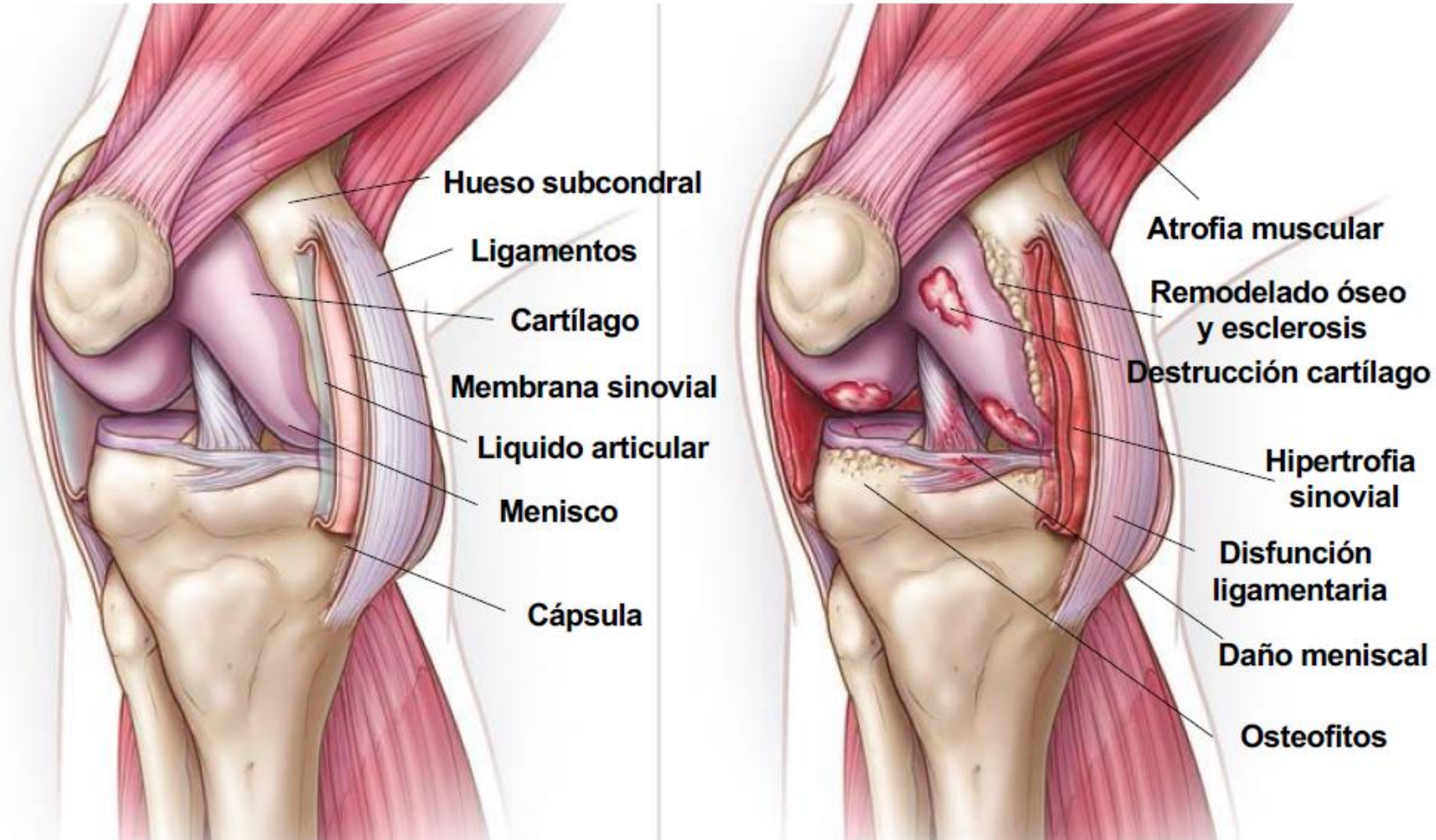
Después aparecen **desarreglos de tipo anatómico y/o fisiológico**:

degradación del cartílago → remodelado óseo → formación de osteofitos → inflamación articular → pérdida de la función articular normal

**Resultado final es la enfermedad sintomática**

**DEFINICIÓN DE ARTROSIS**

**OA: enfermedad global articulación (órgano)**



**Rodilla normal**

**Rodilla artrósica**

### Epidemiología

- La prevalencia en España es de 29,35% (IC 95%: 27,77-33,97) e incrementa con la edad.
- Es más frecuente en mujeres, sobre todo a partir de los 60 años.

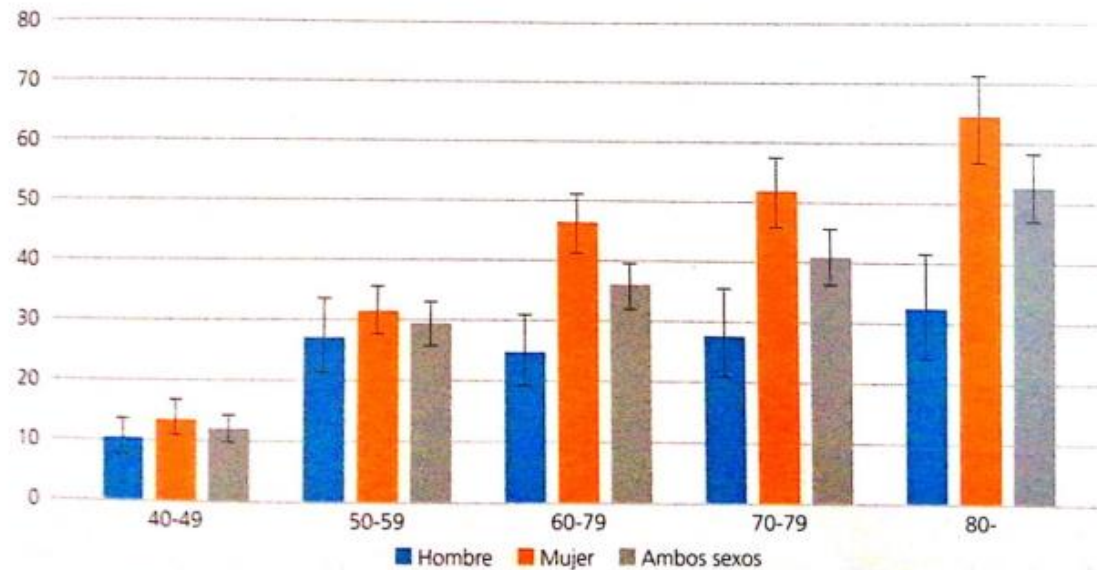


Figura 1. Prevalencia (estimador puntual e IC al 95%) de artrosis por sexo y edad.

## Epidemiología

W.J. Scheuing, A.M. Reginato, M. Deeb et al.

Best Practice & Research Clinical Rheumatology 37 (2023) 101836

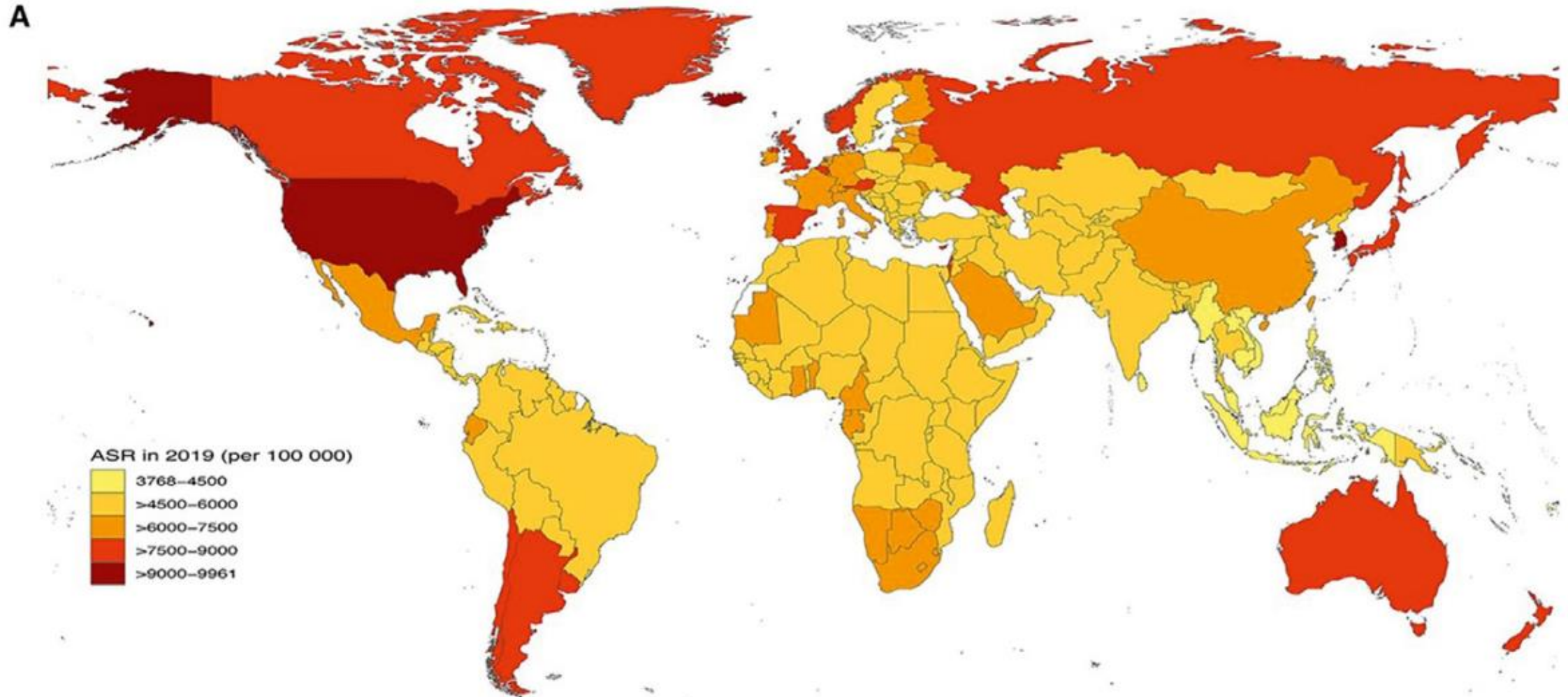
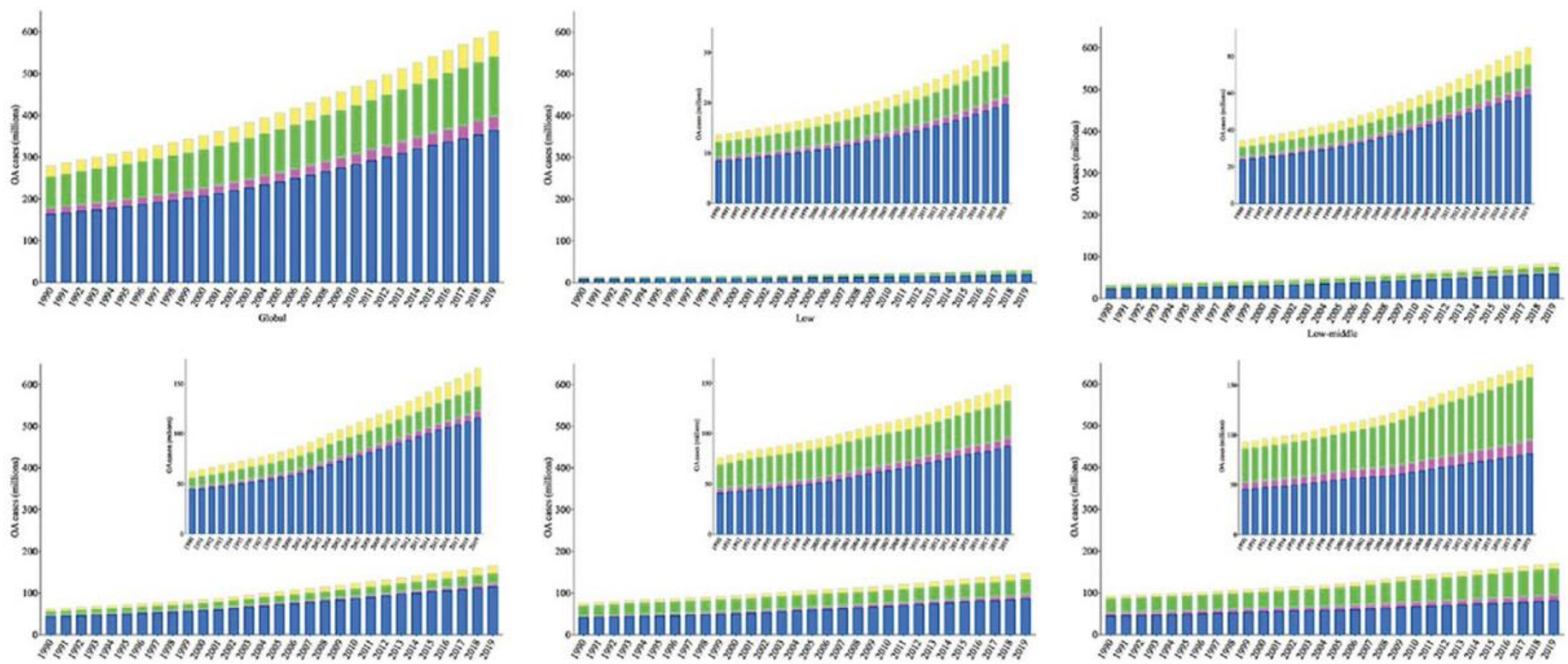


Fig. 1. Prevalence of OA across 204 countries and territories from 1990 to 2019. (A) Age-standardized prevalence rate (ASR) of OA in 2019.

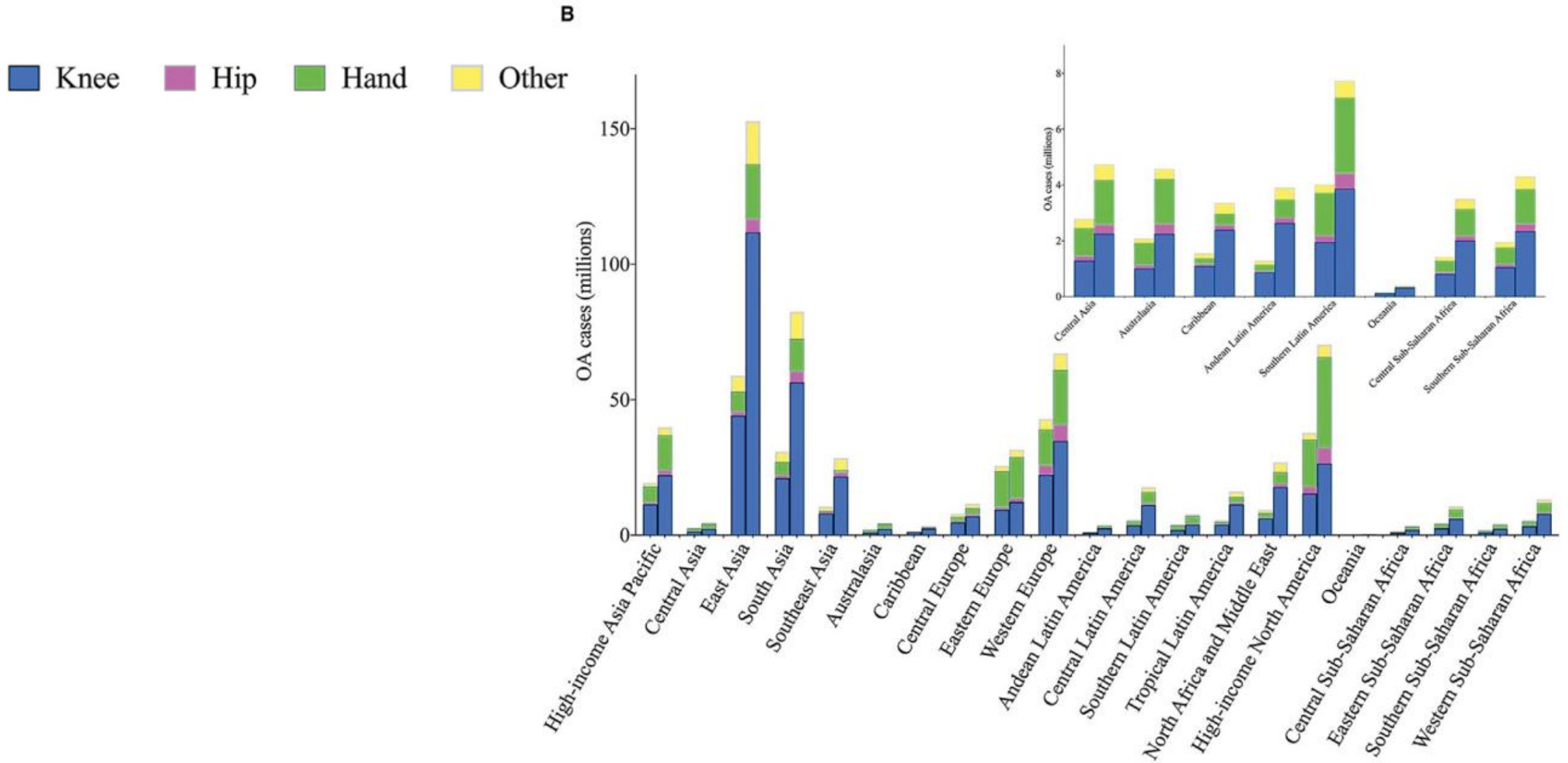
**Fig. 2. Changes in site-specific OA prevalence over time between 1990 and 2019, by Socio-demographic Index (SDI) category and geographic location. (A)** OA prevalence by anatomic location (knee, hand, hip, and other sites) between 1990 and 2019, both globally and by SDI category (low, low-middle, middle, high-middle, and high) **(B)** Site-specific and total prevalence of OA by geographic area. For each geographic area, the left column shows data for 1990 and the right column shows data for 2019. (From: Long H, Liu Q, Yin H et al. Prevalence Trends of Site-Specific Osteoarthritis From 1990 to 2019: Findings From the Global Burden of Disease Study 2019. *Arthritis Rheumatol.* 2022 Jul;74(7):1172–1183.).



**A**



**Fig. 2. Changes in site-specific OA prevalence over time between 1990 and 2019, by Socio-demographic Index (SDI) category and geographic location. (A)** OA prevalence by anatomic location (knee, hand, hip, and other sites) between 1990 and 2019, both globally and by SDI category (low, low-middle, middle, high-middle, and high) **(B)** Site-specific and total prevalence of OA by geographic area. For each geographic area, the left column shows data for 1990 and the right column shows data for 2019. (From: Long H, Liu Q, Yin H et al. Prevalence Trends of Site-Specific Osteoarthritis From 1990 to 2019: Findings From the Global Burden of Disease Study 2019. *Arthritis Rheumatol.* 2022 Jul;74(7):1172–1183.)





# Osteoarthritis and Cartilage



Review

## Recommendations for the management of hip and knee osteoarthritis: A systematic review of clinical practice guidelines<sup>☆</sup>



Alison J. Gibbs # \$ † \* <sup>1</sup>, Bimbi Gray ‡ §, Jason A. Wallis \$ †† ‡‡, Nicholas F. Taylor \$ §§,  
Joanne L. Kemp # \$, David J. Hunter ‡ § <sup>2</sup>, Christian J. Barton # \$

**Table 3**

Hip-specific recommendations from higher quality guidelines.

		RACGP* <sup>2</sup>	ACR* <sup>29</sup>	OARSI* <sup>4</sup>	NICE** <sup>3</sup>	EULAR** <sup>30</sup>	APTA* <sup>31</sup>
Exercise	Land/unspecified	●	●	●	●	●	●
	Aquatic	●	●	●			
Education	Provided	●	●	●	●	●	●
	Formal program	●	●	●	●	●	
Weight loss		●	●	●	●	●	●
Adjuncts	CBT	●	●	●		●	
	Walking aids	●	●	●	●	●	●
	Insoles	●	●		●	●	
	Manual therapy	●	●	●	●		●
	Acupuncture	●	●	●	●		
	TENS	●	●	●	●		
	US	●	●	●	●		●
	IFT	●		●	●		
	Laser	●		●	●		
	Heat therapy	●	●	●			
	Cold therapy	●	●	●			

RACGP = Royal Australian College of General Practitioners; \*= Guideline with joint specific recommendations; ACR = American College of Rheumatology; OARSI = OsteoArthritis Research Society International; NICE = National Institute of Healthcare Clinical Excellence; \*\*= guideline with general osteoarthritis recommendations; EULAR = European League Against Rheumatism; APTA = American Physical Therapy Association; Land = Land-based exercise; CBT = Cognitive Behavioural Therapy; TENS = Transcutaneous Electrical Nerve Stimulation; US = Ultrasound Therapy; NSAIDs = Non-Steroidal Anti-Inflammatory Drug; ● = strong for; ● = option can be considered within strong for recommendation; ● = conditional for; ● = neutral; ● = conditional against; ● = strong against; ● = recommendation Good Clinical Practice statement as part of healthy lifestyle.

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Pharmacology	Paracetamol	●	●	●	●		
	NSAIDs	●	●	●	●		
	Selective NSAIDS	●		●			
	Topical NSAIDs	●		●	●		
	Weak opioids		●			●	
	Other opioids	●	●	●	●		
	Transdermal opioids	●		●			
	Duloxetine	●	●	●			
	Topical capsaicin	●		●			
	Injections	Corticosteroid	●	●	●	●	
Hyaluronic acid		●	●	●	●		
Platelet Rich Plasma		●	●	●			
Stem cell		●	●	●			
Prolotherapy		●	●	●			
Nutraceuticals		Chondroitin	●	●	●		
	Curcumin	●		●			
	Fish Oil/Omega 3	●	●	●			
	Fatty Acids		●	●			
	Glucosamine	●	●	●	●		
	Vitamin D	●	●	●			
Surgical	Arthroscopy				●		

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**Table 4**

Summary knee-specific higher-quality guideline recommendations.

		RACGP* <sup>2</sup>	ACR* <sup>29</sup>	OARSI* <sup>4</sup>	NICE** <sup>3</sup>	EULAR** <sup>30</sup>	BMJ* <sup>32</sup>
Exercise	Land/unspecified	●	●	●	●	●	
	Aquatic exercise	●	●	●			
Education	Provided	●	●	●	●	●	
	Formal program	●	●	●	●	●	
Weight loss		●	●	●	●	●	
Adjuncts	CBT	●	●	●		●	
	Walking aids	●	●	●	●	●	
	Insole unspecified	●			●	●	
	Medial wedge	●	●	●			
	Lateral wedge	●	●	●			
	Brace unspecified		●	●	●	●	
	Brace varus unloader	●		●			
	Brace valgus unloader	●		●			
	Brace patellofemoral	●	●	●			
	Manual therapy	●	●	●	●		
	Acupuncture	●	●	●	●		
	TENS	●	●	●	●		
	US	●	●	●	●		
	IFT	●		●	●		
	Laser	●		●	●		
	Heat therapy	●	●	●			
	Cold therapy	●	●	●			

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	Other opioids	●	●	●	●		
	Transdermal opioids	●		●			
	Duloxetine	●	●	●			
	Topical capsaicin	●	●	●			
	Injections	Corticosteroid	●	●	●	●	
Hyaluronic acid		●	●	●	●		
Platelet Rich Plasma		●	●	●			
Stem cell		●	●	●			
Prolotherapy		●	●	●			
Nutraceuticals	Chondroitin	●	●	●			
	Curcumin	●		●			
	Fish Oil/Omega 3	●	●	●			
	Glucosamine	●	●	●	●		
	Vitamin D	●	●	●			
Surgical	Arthroscopy	●			●	●	

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## Guías de tratamiento: conclusión



**Recomendaciones consistentes**  
como cuidados de **primera línea**  
(atención primaria) para:

*Ejercicio*

*Educación*

*Pérdida de peso*



Considerar **AINE** en función de **comorbilidades**



**Variabilidad para inyecciones intraarticulares.**



**Recomendación en contra de :**

*Artroscopia*

*Células madre*

*Opioides potentes.*

## Concepto de fenotipo/endotipo

- Fenotipo: diferentes manifestaciones **clínica**
  - Genotipo + factores ambientales
  - Rasgos observables
- Endotipo: diferentes vías o mecanismos de acción que nos llevan a la expresión clínica
  - Comparten características **moleculares**

**Artrosis: endotipos**

**ARTROSIS**  
MADRID, 4-5 / 9 / 2022

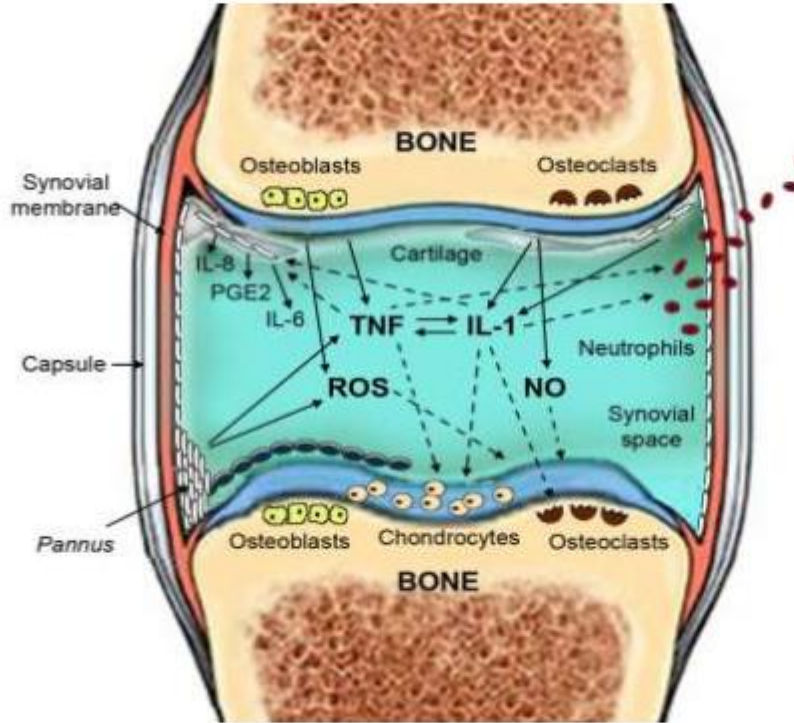
Sociedad Española de Reumatología

#artrosis22

**Apoptosis**  
**Autophagy**  
**Senescence**

**Tissues:**  
**Synovium**  
**Bone Marrow**  
**Subchondral Bone**  
**Cartilage**

**Cells:**  
**Synoviocyte**  
**MSC**  
**Osteoclat/Osteoblast**  
**Chondrocyte**



FJ Blanco; Farreras 2015

**1. Enzymes**

- ↑ MMPs,
- ↑ Aggrecanases

**2. Lipid Mediators**

- ↑ PGE<sub>2</sub>,
- ↑ cLTB<sub>4</sub>

**3. Free Radicals**

**Nitric Oxide ( iNOS)**

*MMPs*  
*Cell Death*  
↓ NO synthesis ⇒ ↓ Cartilage deg.

**4. Cytokines**

**Proinflammatory (IL-1β, TNF-α)**  
*Participate in OA process*  
*MMPs, Type I Collagen*  
*COX-2*  
*NO*



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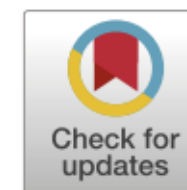
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journal homepage: [www.elsevierhealth.com/berh](http://www.elsevierhealth.com/berh)



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## Biomarkers for osteoarthritis: Current status and future prospects



*A. Mobasher, C.S. Thudium, A.-C. Bay-Jensen et al.*

*Best Practice & Research Clinical Rheumatology 37 (2023) 101852*

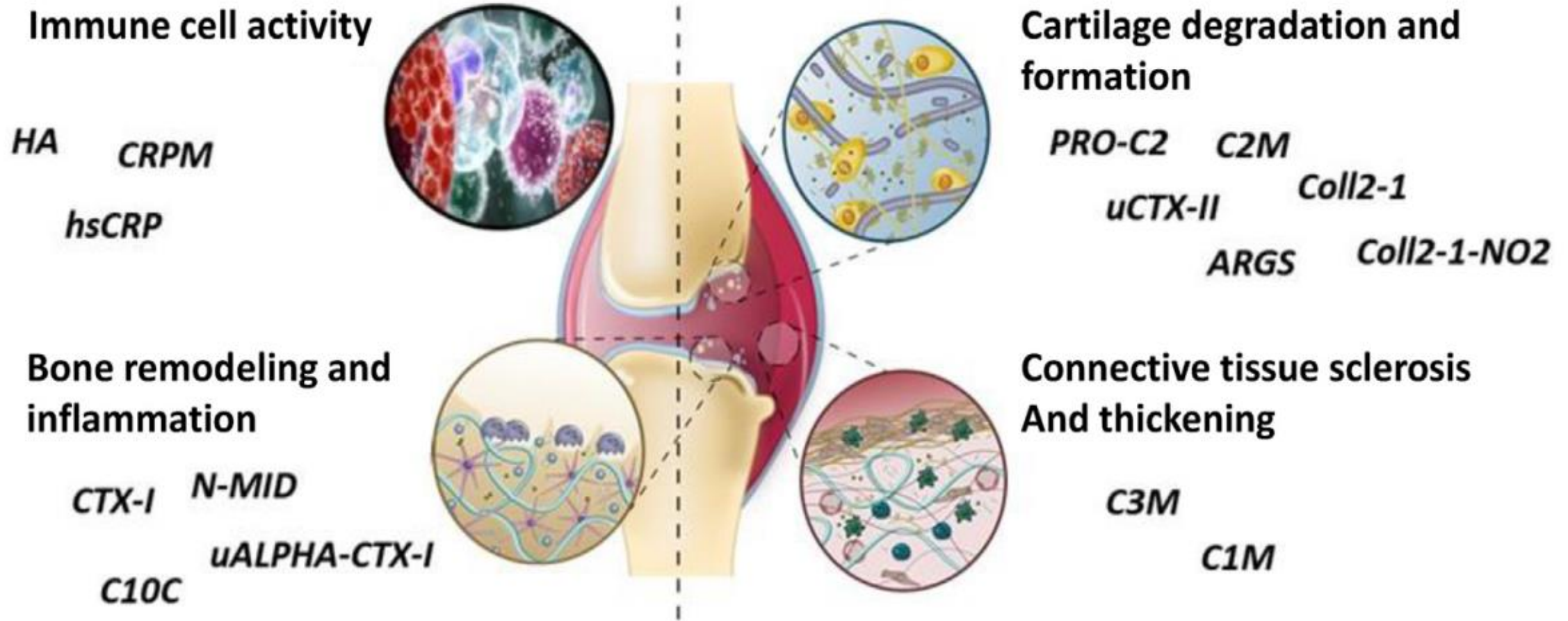
### **Box 3**

Original and updated definition of biomarker.

**Original definition of biomarker:** A characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.

**BEST updated definition of biomarker:** A defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention, including therapeutic interventions. Molecular, histologic, radiographic, or physiologic characteristics are types of biomarkers. A biomarker is not an assessment of how a patient feels, functions, or survives. However, it may be used as a surrogate outcome measure to strategically guide investigators and sponsors of clinical trials.

**Biomarcadores**



**Fig. 3.** Soluble biomarkers measured at baseline in serum or urine samples from participants in the APPROACH cohort. The biomarkers measured reflect four different processes: immune cell activity, cartilage degradation and formation, bone remodeling and inflammation, and connective tissue sclerosis and synovial thickening.



## Artrosis: fenotipos

### FENOTIPOS FISIOPATOLÓGICOS

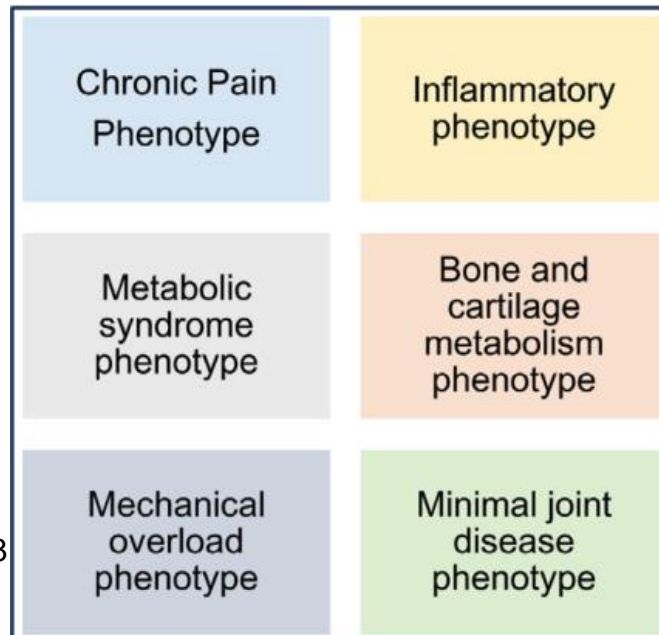
### FENOTIPOS PRONÓSTICOS

### FENOTIPOS DE RESPUESTA

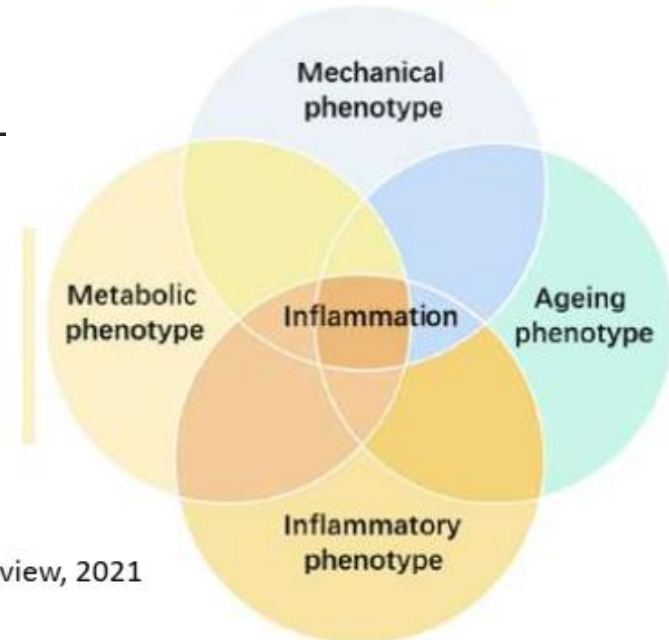
Mechanistic subgroups	Prognosis	Response to therapy
Inflammatory OA	Disease stage	Disease stage
Cell senescence	Pain intensity	Type of pain (e.g. neuropathic vs non-neuropathic)
Mechanical overload	Mechanical factors (obesity, malalignment)	Synovitis/effusion
Metabolic	Contra-lateral knee OA	Subchondral bone lesions
Genetic	Family history	Gender
Oestrogen deficiency	Knee injury	Presence of co-morbid conditions
	Single vs multi-joint OA	Single vs multi-joint OA



Deveza LA, et al. Rheumatology (Oxford) 2018; 57:iv34-iv42



Zeng L et al Aging Res Review, 2021



Mobasheri A et al. F1000Res. 2019;8 :F1000 Faculty Rev-2091





# Fenotipos + Endotipos = Pacientes (perfiles)

Adaptado de Blanco FJ, 2º Curso de Artrosis de la SER, 2022



**Fenotipos**

**Edad**

**Biomecánico**

**Metabólico**

**Inflamatorio**

**RPOA**

**Endotipos**

Senescencia  
Autofagia  
Apoptosis  
Baja reparación

Sobrecarga mec.  
Malalineamiento  
Baja reparación

Dislipemia  
Diabetes  
Hiperuricemia

Sinovitis  
Hofman  
Estrés oxidativo/ROS  
Citokinas

LMO  
Extr meniscal  
OP sucondral

**Tratamiento**

Senolíticos  
Senomórficos  
Med regenerativa

Cirugía  
Med regenerativa

Corregir  
Metabolismo

Anti-inflamatorio

Metabolismo óseo?





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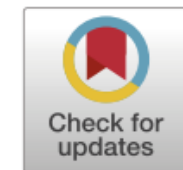
journal homepage: [www.elsevierhealth.com/berh](http://www.elsevierhealth.com/berh)



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# What is new in pharmacological treatment for osteoarthritis?

Halise Hande Gezer <sup>a</sup>, Andrew Ostor <sup>b, \*</sup>



## 1. Treatments targeting inflammatory processes

### Conventional Synthetic Disease-Modifying Drugs

Hydroxychloroquine [11]	200–400 mg/day oral	Hand	153
Hydroxychloroquine [14]	400 mg/day oral	Hand	196
Methotrexate [15]	10 mg/week oral	Hand	64
Methotrexate [16]	10–25 mg/week oral	Knee	160

### Biological Disease-Modifying Drugs

Adalimumab [17]	10 mg intra-articular	Knee	56
Adalimumab [18]	40 mg subcutaneously every other week	Hand	
Etanercept [19]	50 mg subcutaneously per week	Hand	90
Etanercept [20]	50 mg subcutaneously per week	Hand	90

Tocilizumab [21]	4 weeks apart (8 mg/kg intravenous)	Hand	104
<i>IL-1 receptor antagonists</i>			
Anakinra [25]	50 or 150 mg intraarticular	Knee	170
Canakinumab [27]	50 mg, 150 mg, or 300 mg subcutaneously once every 3 months	Knee	10,061
Lutikizumab [22]	25, 100, or 200 mg subcutaneously every 2 weeks for 50 weeks	Knee	347
Lutikizumab [28]	200 mg subcutaneously every two weeks for 24 weeks	Hand	132
AMG 108 [29]	100 mg or 300 mg) subcutaneously once every four weeks for 12 weeks	Knee	228

### Inhibidor de NLP3.(inflammasoma)

DFV890: 25 mg/vo/2v dia

## 2. Treatments targeting cartilage

### *Wnt pathway inhibitors*

<u>Lorecivivint [32]</u>	0.03 mg, 0,07 mg, or 0,23 mg intraarticular	Knee	455
<u>Lorecivivint [33]</u>	0.03, 0.07, 0.15, or 0,23 mg intraarticular	Knee	700

### *Cathepsin-K inhibitors*

Balicatib [37]	50 mg/day oral	Knee	223
MIV-711 [39]	100 or 200 mg/day oral	Knee	244

### *MMP/ADAMTS inhibitors*

PG-116800 [56]	25 or 50 or 100, or 200 mg twice daily oral	Knee	401
AGG-523	1800 mg once a day	Knee	32
M6495 [59]	1 mg, 5 mg, 20 mg, 75 mg, 150 mg, 300 mg subcutaneously	Healthy male subjects	107

### *Recombinant Human Fibroblast Growth Factors*

<u>Sprifermin [41]</u>	10 µg, 30 µg, and 100 µg intraarticular	Knee	192
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<u>Sprifermin [42]</u>	30 µg, and 100 µg intraarticular	Knee	549
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<u>Sprifermin [43]</u>	100 µg or 30 µg intraarticular	Knee	378
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Tissue Gene-c [50]	Intraarticular	Knee	102
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Tissue Gene-c [51]	Intraarticular	Knee	57
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Tissue Gene-c [52]	Intraarticular	Knee	163
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### *Activating AMPK pathway*

<u>Metformin [64]</u>	Oral	Knee	818
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<u>Metformin [91]</u>	Oral	Knee	968
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### 3. Treatments targeting subchondral bone

Clodronate [68]	200 mg intramuscular daily for 15 days and then once weekly	Knee	74
Clodronate [69]	200 mg intramuscular daily for ten days, followed by the daily dose of 200 mg for 6 days	Hand	40
Zoledronic acid [71,92]	5 ml intravenous	Knee	223
Denosumab [73]	60 mg subcutaneously every 3 months	Hand	100
Calcitonin [74]	0,8 mg oral twice daily	Knee	1176 and 1030
Strontium [75]	1 g/day, 2 g/day oral	Knee	1371

### 4. Treatments targeting pain processes

Tanezumab [81]	2,5 mg or 5 mg subcutaneously	Hip or knee	849
Tanezumab [83]	2,5 mg or 5 mg subcutaneously	Hip or knee	3021
Fasinumab [86]	1 mg, 3 mg, 6 mg, or 9 mg subcutaneously every 4 weeks	Hip or knee	421
<u>Mavatrep [90]</u>	A single dose of 50 mg	Knee	33

**Resiniferatoxina                      Intrarticular                      Rodilla**

## Lista de potenciales senoterapéuticos para la artrosis

Compounds	β-Gal activity	Cell number	Autophagic flux	Target
Bupivacaine hydrochloride	1142	865	1.60	Sodium ion channels
Minoxidil	1185	950	1.59	Potassium channels
<b>Fenofibrate</b>	<b>1234</b>	<b>997</b>	<b>1.57</b>	<b>Peroxisome Proliferator Receptor α</b>
Pentolinium bitartrate	1162	964	1.59	Unknown
Tomatine	1142	970	1.57	Na,K ATPase
Benzylamine hydrochloride	1196	1016	1.57	Cyclooxygenase
Ciproheptadine hydrochloride	1031	914	1.6	Histamine H1 and Serotonin receptors
Lomefloxacin hydrochloride	1155	1046	1.58	DNA replication
Flutamide	1091	995	1.57	Androgen receptor
Digitoxigenin	1382	1262	1.59	Na,K ATPase
Guanethidine sulfate	1101	1030	1.58	Adrenergic system
Antipyrine	997	1046	1.61	Prostaglandin G/H synthase 1 and 2
Astemizole	712	770	1.63	Histamine H1 receptor
Pherphenazine	878	985	1.62	Dopamine D2 receptor

## El FN es un senolítico que

- Elimina selectivamente células senescentes mediante apoptosis
- Protege frente a la degradación del cartílago articular
- Mejora las condiciones clínicas de los pacientes con artrosis de rodilla
- Protege frente al daño articular en un modelo preclínico de artrosis post-traumática

Estudio Clínico Fase 2, randomizado, controlado por placebo, doble-ciego para evaluar la eficacia y la seguridad de fenofibrato, un fármaco con actividad senolítica, en pacientes con artrosis de rodilla

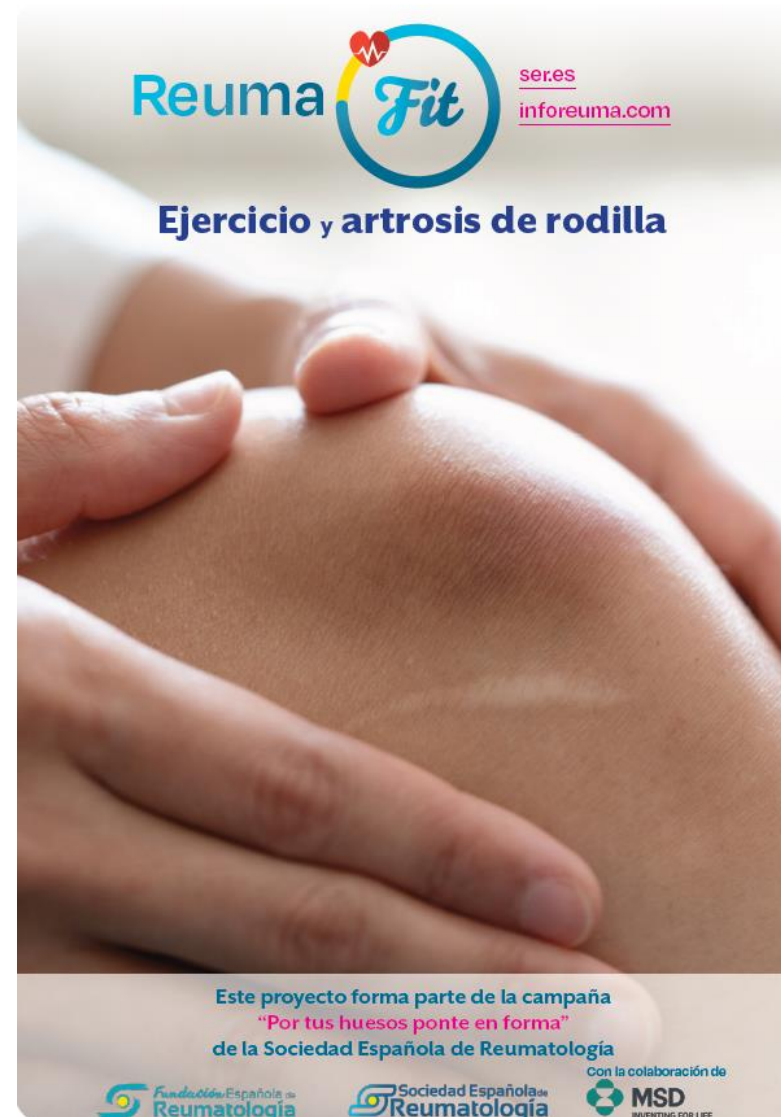


Estudio en Fase 1, aleatorizado, doble ciego, para evaluar la seguridad, la farmacocinética y la farmacodinámica de la liberación prolongada del senolítico FN administrado mediante inyección IA en pacientes con OA de rodilla

<https://inforeuma.com/actividad-fisica-y-artrosis-de-rodilla/>



<https://inforeuma.com/reumafit/>



## Actividad física y artrosis de rodilla

### Recomendaciones generales sobre el ejercicio para artrosis de rodilla



### Ejercicio isométrico de cuádriceps



### Ejercicio de elevación activa de la pierna estirada



### Ejercicio de extensión completa de rodilla sentado



### Ejercicio de extensión de 45° de rodilla sentado



### Ejercicio de sentarse y levantarse de una silla



### Ejercicio de sentadilla parcial con apoyo en la pared



### Ejercicio de sentadilla parcial sin apoyo



### Ejercicio de flexión de rodilla de pie



### Ejercicio de flexión de rodilla tumbado



### Ejercicio del puente en supino



### Extensión de cadera de pie



### Ejercicio de elevación de la pierna extendida en decúbito lateral



### Ejercicio de ponerse de puntillas de pie con ambos pies



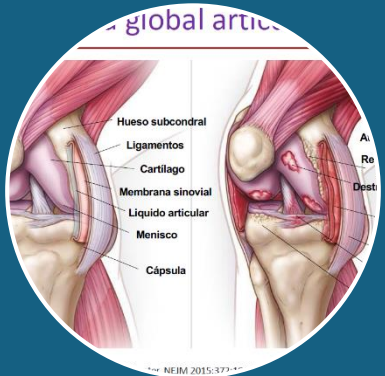
### Ejercicio de ponerse de puntillas de pie con un solo pie



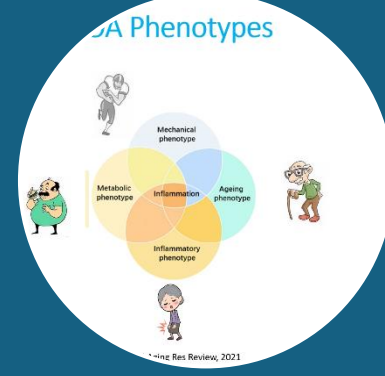
Actividad física y artrosis de rodilla (PDF)

- 15 vídeos
- 7 v: Fortalecimiento cuádriceps con varios niveles de dificultad
- 2 v: Fortalecer los flexores de la rodilla
- 3 v: Centrados en la musculatura de la cadera (2 de fortalecimiento de extensores y 1 de abductores)

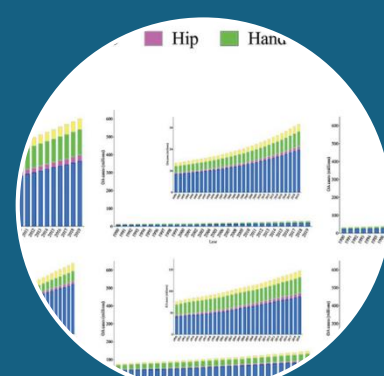
• 2 v: Fortalecer los gemelos (tríceps sural).



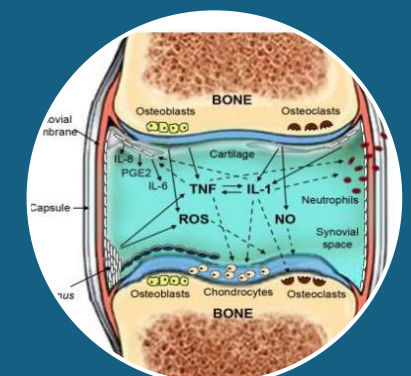
La **OA** es un **síndrome complejo** de órgano (se puede afectar cualquier tejido de la articulación) más que una enfermedad única, con una **expresión clínica muy heterogénea**



La **clasificación** de la OA en **fenotipos** intenta **avanzar** en el **conocimiento** y **mejorar** su manejo **terapéutico**.



la OA es una enfermedad **muy prevalente y discapacitante**, actualmente con **opciones terapéuticas limitadas**



Avances recientes en la fisiopatología de la OA han revelado **varias dianas terapéuticas posibles**:

- Inflamación
- Hueso subcondral
- Cartilago
- Vías nociceptivas







LOS **DISTINTOS SUBTIPOS Y RESPUESTAS** EN LOCALIZACIONES DIFERENTES COMPLICAN LA **ELECCIÓN TERAPÉUTICA**.



DADO QUE LA DESTRUCCIÓN DEL CARTÍLAGO SE CONSIDERA UNO DE LOS MECANISMOS PATOGENÉTICOS BÁSICOS LAS NUEVAS **TERAPIAS DIRIGIDAS AL CARTÍLAGO** SON LAS MÁS **PROMETEDORAS**.



**EJERCICIO, EJERCICIO, EJERCICIO.**



**RETOS: DIAGNÓSTICO Y TRATAMIENTO PRECOZ** PARA EVITAR DAÑO ARTICULAR PROGRESIVO SINTOMÁTICO E INCAPACITANTE



¡Muchas gracias por su atención!