Facultad de Medicina y Odontología

Universitat de València

Programa de Doctorado en Medicina 3139

Departamento de Medicina

“Artrosis precoz de rodilla. Revisión crítica de los criterios diagnósticos”

TESIS DOCTORAL POR COMPENDIO DE PUBLICACIONES

Presentada por: Dña. Luz M. Herrero Manley
Graduada en Medicina

Enero 2024

Directores: Enrique Viosca Herrero, Mª Fe Mínguez Rey
Tutora: M ª Fe Mínguez Rey

AGRADECIMIENTOS:

Para la elaboración y redacción de esta tesis doctoral debo agradecer a muchas personas que de alguna manera han contribuido para que sea posible.

Gracias a Enrique Viosca por su labor como director de la tesis, por su infinita disponibilidad, paciencia y entusiasmo hasta el final.

También quiero agradecer a Mª Fe Mínguez por aceptar la dirección y tutoría de esta tesis doctoral, por sus aportaciones académicas y su disponibilidad en todo momento.

A Ana por haber sido como una hermana mayor y apoyarme a seguir adelante en los momentos de claudicación. A Luis por haber sido uno de los motores principales en el proyecto.

También debo dar las gracias a Alfonso por resolver siempre mis dudas, mostrarme siempre su apoyo y contagiarme de sus ganas de seguir aprendiendo.

Y sobre todo debo dar gracias a mi familia. A mi padre, por haberme enseñado la importancia de la paciencia y la perseverancia con su propio ejemplo. A mi madre, por su disponibilidad y su incondicionalidad. A mis hermanas, por estar siempre y por haberme guiado a tomar las decisiones correctas. Y a Mateo y Sami, la nueva generación de la familia, que les deseo que logren disfrutar de su vida profesional tanto como yo.

ÍNDICE:

GLOSARIO:

- AEMPS: Agencia Española de Medicamentos y Productos Sanitarios
- ATR: Artroplastia total de rodilla
- CEIm: Comité de Ética de la investigación con medicamentos
- EKOA: Early Knee Osteoarthritis
- EOA: Early Osteoarthritis
- EULAR: European Alliance of Associations for Rheumatology
- EVA: Escala Visual Analógica
- HA: Ácido hialurónico.
- HDL: Lipoproteínas de alta densidad
- HS: Healthy subjects (pacientes sanos en riesgo de desarrollar artrosis)
- ICOAP: Intermittent and Constant Assessment of Pain
- IMC: Índice de masa corporal
- KL: Kellgren y Lawrence
- KOA: Knee Osteoarthritis
- KOOS: Knee Injury and Osteoarthritis Outcome Score
- LDL: Lipoproteínas de baja densidad
- OA: Osteoarthritis
- PCR: Proteína C reactiva
- PIICP: Procollagen type II C-terminal propeptide
- PRP: Plasma rico en plaquetas
- RM: Resonancia magnética
- STROBE: Strengthening the Reporting of Observational Studies in Epidemiology
- VAS: Visual analogue scale
- WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index

TABLA DE CONTENIDOS:

Índice de figuras:

Índice de tablas:

ORIGEN DEL TRABAJO:

Como médico especialista en Medicina Física y Rehabilitación, me surge la necesidad de contar, con métodos diagnósticos y de seguimiento fiables, de las patologías del aparato locomotor, tal y como existen en otras especialidades. Es decir, contar con criterios diagnósticos validados y aplicables a la práctica clínica diaria.
El principal problema de la patología musculoesquelética es que la mayoría de las veces uno de los criterios diagnósticos necesarios es la presencia de dolor. Esto supone un desafío para el médico, ya que el dolor puede ser fluctuante y es algo muy subjetivo y dependiente del umbral del paciente.
Dado que mi especialidad se basa en el tratamiento conservador de las patologías, cobra especial importancia la detección de las enfermedades en su fase inicial, donde la rehabilitación puede ejercer su máximo efecto.
Es por ello, que tras surgirme la oportunidad de participar en el proyecto OActive para la investigación de la artrosis precoz de rodilla, decido realizar una revisión sistemática de los criterios diagnósticos presentes en la literatura. Posteriormente, usando los criterios más aceptados, decido aplicarlos a nuestra muestra de pacientes, observando una clara fluctuación en el diagnóstico de los participantes. Tras encontrar estos resultados, que confirman la falta de fiabilidad diagnóstica para la artrosis precoz de rodilla, intento buscar otros hallazgos que nos ayuden a establecer un diagnóstico fiable de esta patología.

RESUMEN:

Objetivo:
El objetivo de esta tesis consiste en revisar la fiabilidad y aplicabilidad en la práctica clínica de los criterios diagnósticos actualmente propuestos para la artrosis precoz de rodilla y proponer nuevas herramientas para un diagnóstico más preciso.

Material y métodos:
En primer lugar, se realizó una revisión sistemática de los criterios presentes en la literatura de acuerdo a un protocolo predefinido basado en la declaración PRISMA. Posteriormente, se realizó un estudio longitudinal piloto con 105 pacientes que se dividieron en 2 grupos, los que cumplían criterios de artrosis precoz de rodilla (EKOA) y los sujetos sanos en riesgo de desarrollar artrosis (HS). Los participantes fueron clasificados usando los criterios diagnósticos de dos autores diferentes (Luyten *et al*., 2012,2018 y Mahmoudian *et al.,* 2021), y que se consideran los más aceptados en la actualidad. Por último, se llevó a cabo un estudio transversal de 96 participantes, de los cuales 48 fueron clasificados como EKOA y 48 como HS. En este caso, se aplicaron los criterios de Luyten *et al*., 2012,2018 para clasificar a los pacientes y se valoraron parámetros bioquímicos, como el perfil lipídico y los marcadores inflamatorios en los dos grupos de participantes.

Resultados y discusión:
La revisión sistemática evidenció que existen múltiples propuestas de diferentes autores para diagnosticar la artrosis precoz de rodilla sin llegar a un acuerdo común. El estudio longitudinal mostró una fluctuación en la clasificación de algunos pacientes; pasando de pertenecer al grupo de EKOA a HS a lo largo del seguimiento y viceversa. Esta variabilidad en la clasificación pone de manifiesto la falta de fiabilidad de los criterios diagnósticos actuales. Con el estudio transversal se objetivó que los pacientes del grupo EKOA tenían niveles más elevados de colesterol total, lipoproteína de baja densidad (LDL), ácido úrico y proteína C reactiva (PCR) en comparación con los sanos. Esta relación entre los parámetros bioquímicos y la artrosis precoz de rodilla podría considerarse como una ayuda para establecer un correcto diagnóstico de esta patología.

Conclusiones:
Actualmente no existe un consenso entre los autores acerca de los criterios diagnósticos de la artrosis precoz de rodilla. Los criterios clínicos actualmente aceptados no son fiables en la práctica clínica, pudiendo llevar a un diagnóstico erróneo.
Se podrían considerar los parámetros del perfil lipídico e inflamatorio como una herramienta útil para establecer un diagnóstico fiable de artrosis precoz de rodilla.

I.INTRODUCCIÓN:

La artrosis es considerada la enfermedad crónica articular más prevalente, además es una de las principales causas de discapacidad física en la actualidad(1). Su incidencia se encuentra en alza debido al envejecimiento de la población y al aumento de la obesidad en la sociedad(1). En las últimas décadas, los casos de artrosis han aumentado un 14,8% en la población general mayor de 30 años(2). Pero lo realmente preocupante es que se estima que la incidencia de esta patología continuará aumentando, dando lugar a una sobrecarga de los sistemas de salud a nivel mundial y a un aumento del gasto sanitario(2). Teniendo en cuenta todas las articulaciones que se pueden ver afectadas, la artrosis de rodilla es de las más prevalentes(2). A pesar de la alta incidencia de esta patología su patogenia sigue siendo desconocida(3).

I.1. Concepto:

Con frecuencia, la artrosis se relaciona con un proceso de desgaste. Esto no es del todo correcto, ya que, se trata más bien de una remodelación anormal de los tejidos articulares impulsada por una serie de mediadores inflamatorios dentro de la articulación afecta. Los factores de riesgo más comunes para la artrosis de rodilla incluyen la edad avanzada, el sexo femenino, la obesidad, la predisposición genética y factores mecánicos, como la mala alineación articular, la forma anormal de la articulación, la debilidad muscular y las lesiones articulares previas, como alteraciones meniscales y lesiones de ligamentos(4,5).

La artrosis fue definida por la OMS en 1995 como un proceso degenerativo articular que se produce como consecuencia de trastornos mecánicos y biológicos que desestabilizan el equilibrio entre la síntesis y la degradación del cartílago articular, estimulando el crecimiento del hueso subcondral y con la presencia de sinovitis crónica de intensidad leve(6).
Según el American College of Rheumatology, la artrosis puede definirse como un grupo heterogéneo de condiciones que conducen a síntomas y signos articulares que se asocian con defectos en la integridad del cartílago articular, además de cambios relacionados con el hueso subcondral y con los márgenes articulares(6).

Actualmente, se ha propuesto un nuevo paradigma en la artrosis que pasa de ser una enfermedad específica del cartílago a ser considerada una enfermedad en la que la sinovitis y la patología sistémica desempeñan un papel importante(3,7).
Se ha visto que la asociación de factores cardiovasculares y metabólicos puede aumentar el riesgo de artrosis, dando lugar a una condición identificada como síndrome metabólico(8,9).

I.2. Patogenia:
Varias teorías han intentado explicar la patogénesis de la artrosis y su relación con el síndrome metabólico, llegando al consenso de que tanto los factores mecánicos como los mediadores humorales están involucrados en el curso de esta patología(10,11).

Siguiendo este nuevo escenario conceptual de la artrosis, existen estudios que plantean una relación entre esta patología y el perfil lipídico de los pacientes, encontrando datos que sugieren una relación entre la dislipidemia y la presencia de artrosis, especialmente en la rodilla(12). Se cree que el colesterol puede tener un papel importante en la condrogénesis y la osteogénesis endocondral, y que algunos procesos inflamatorios pueden ser desencadenados por el aumento de lipoproteínas de baja densidad (LDL) en la matriz extracelular del cartílago(13,14).
Por otro lado, también existen estudios que sugieren que tanto la proteína C reactiva (PCR) como el ácido úrico podrían estar implicados en la patogénesis de la artrosis, encontrando niveles más elevados de estos parámetros en pacientes con artrosis(15–17).

I.3. Retos clínicos actuales:
El problema asistencial que se plantea, a la vista de los conocimientos actuales sobre la artrosis de rodilla, es que los cambios estructurales son detectados cuando el tratamiento conservador resulta poco útil. Es decir, cuando ya hay un un daño estructural severo de la articulación, necesitando muchos de los pacientes tratamiento quirúrgico(18,19). Este tratamiento quirúrgico suele consistir en la realización de una artroplastia total de rodilla (ATR). La ATR es uno de los procedimientos ortopédicos más comunes realizados en los Estados Unidos. Se estima que para el año 2030, la demanda de ATR aumentará a 3.48 millones de casos anuales(20). Esto supone un importante gasto para el sistema sanitario; además, debemos tener en cuenta las complicaciones

asociadas a esta cirugía como pueden ser la infección de la herida quirúrgica o de la prótesis, trombosis venosa profunda e incluso dolor crónico(20).
De hecho, el dolor crónico y la insatisfacción con los resultados, según el estudio de Beswick *et al.,* 2012, ocurren en un 10% a 34% de los pacientes 12 meses después de la ATR(21). Entre los factores de riesgo de dolor crónico tras ATR sugeridos se incluye las intervenciones en pacientes con grados más leves de artrosis de rodilla(22,23).

Por tanto, si se pudiera detectar a estos pacientes en las fases precoces de la artrosis de manera fiable, se podría evitar llegar al tratamiento quirúrgico y a sus complicaciones asociadas, suponiendo una mayor calidad de vida para el paciente y un menor gasto sanitario.
Por otro lado, la artrosis de rodilla no solo causa discapacidad física y dolor, sino también afecta a la esfera psicosocial, ya que está relacionada con alteraciones mentales y sociales(24).
Por tanto, teniendo en cuenta que la artrosis se desarrolla y empeora con el tiempo, la posibilidad de disponer de un diagnóstico precoz fiable podría proporcionar una amplia posibilidad de oportunidades para intentar modificar su curso y evitar su empeoramiento hacia fases avanzadas(24).
Es por esta razón que, en general, la investigación ha comenzado a centrarse en el concepto de "artrosis precoz", con el objetivo de proporcionar al paciente un tratamiento en las primeras etapas del proceso patológico y así poder prevenir la progresión y los cambios estructurales en la articulación, que están asociados con las etapas posteriores de la artrosis(25,26).

I.4. Tratamiento:
Existen tratamientos como el ejercicio físico, tratamientos con Condroitin Sulfato o la medicina regenerativa que podrían retrasar la progresión de la artrosis precoz de rodilla(24,27,28). Si bien es cierto que estos tratamientos muestran mejores resultados cuando el daño de la articulación es mínimo, de ahí la importancia de contar en la práctica clínica habitual con criterios fiables de artrosis precoz de rodilla(28).
En cuanto al tratamiento de esta patología en sus etapas tempranas, el primer escalón terapéutico se basa en la educación del paciente y en cambios en el estilo de vida, con el objetivo de reducir la carga mecánica en la rodilla, favorecer el fortalecimiento muscular y la pérdida de peso(29).
El ejercicio físico terapéutico se considera un eslabón fundamental en las primeras fases de la artrosis precoz ya que mejora los síntomas como el dolor y la rigidez(29).
De hecho, existen estudios que investigan el efecto del ejercicio físico en la artrosis y sugieren que este puede producir un aumento en la síntesis de glicosaminoglicanos, citocinas antiinflamatorias y proteínas morfogénicas óseas, así como contribuir en la disminución de citocinas proinflamatorias y metaloproteinasas de matriz en los tejidos articulares (29). También ha demostrado mejorar la lubricación de las articulaciones y modular la producción, viscosidad y composición del líquido sinovial(29).
En cuanto al tratamiento con infiltraciones, la viscosuplementación intraarticular con ácido hialurónico (HA) representa una estrategia terapéutica válida para personas con

artrosis de rodilla leve o moderada. El ácido hialurónico es un glicosaminoglicano, un componente natural del líquido sinovial y de la matriz extracelular del cartílago articular, con propiedades lubricantes y viscoelásticas(29).
Por otro lado, cabe mencionar el tratamiento con infiltraciones de plasma rico en plaquetas (PRP). Se cree que el uso local de PRP en la articulación estimula una cascada de curación natural y acelera la reparación del cartílago(30).
Hay estudios que sugieren que el tratamiento con PRP presenta mejores resultados en pacientes en estadios iniciales de artrosis de rodilla(30).
Se debe tener en cuenta que es necesario continuar con la investigación de los posibles tratamientos para poder validar su efectividad.

Pero precisamente para poder comprobarlo, necesitamos en primer lugar, un diagnóstico claro de artrosis precoz de rodilla.

I.5. Diagnóstico:

En los últimos años se han propuesto criterios para el diagnóstico precoz de esta patología. Estos criterios suelen incluir síntomas como dolor y signos como la rigidez articular y crepitación, además de hallazgos radiológicos(24,31). Sin embargo, a pesar de los esfuerzos para intentar definir esta patología, continua siendo una asignatura pendiente, ya que los signos y síntomas pueden ser fluctuantes o mínimos en las fases iniciales del proceso, manifestándose solo en determinadas situaciones(18,32).
Para dificultar más esta labor, es frecuente encontrar signos de artrosis en resonancias magnéticas de pacientes totalmente asintomáticos. Estos hallazgos resaltan el hecho de que los cambios estructurales de la artrosis precoz de rodilla pueden ser asintomáticos, dando lugar a que el dolor y la rigidez aparezcan en una etapa más avanzada de la enfermedad(18,32).
Por tanto, lograr un diagnóstico 100% fiable de artrosis precoz de rodilla es a día de hoy un verdadero desafío.

En la misión de establecer unos criterios diagnósticos de artrosis precoz de rodilla es importante destacar los trabajos de Luyten *et al*.,2012, 2018 (31,33) que proponen los siguientes criterios diagnósticos basados en cuestionarios, exploración física y hallazgos radiológicos:

A. Cuestionarios como el Knee Injury and Osteoarthritis Outcome Score (KOOS):
   2 de las siguientes 4 subescalas del KOOS (síntomas, dolor de rodilla, función y calidad de vida relacionada con la rodilla) debían puntuar como "positivas" (≤85%).

B. En la exploración física: al menos un criterio debe estar presente:
   - crepitación de la rodilla.
   - dolor en la interlínea articular.

C. En cuanto a las radiografías, se propone como criterio un Kellgren y Lawrence (KL) grado 0-1 en radiografías en carga.

En cuanto al ritmo del dolor, Luyten *et al.,* 2012,2018 se plantean si diferenciar entre dolor mecánico o inflamatorio, pero llegan a la conclusión de que carecen de datos suficientes para determinar que la artrosis precoz de rodilla se asocia a un patrón de dolor específico(33). De hecho, la escala KOOS incluye preguntas acerca del ritmo del dolor y puntúa como positivo tanto el dolor mecánico como el inflamatorio.

Posteriormente Mahmoudian *et al*., 2021 llevan a cabo un análisis de estos criterios diagnósticos, dando mayor importancia a criterios de la exploración física como la presencia de derrame articular o nódulos de Heberden. Además, proponen como criterio, la puntuación positiva (≥80%) en la escala KOOS de 4 de las 5 subescalas (dolor, síntomas, actividades de la vida diaria y calidad de vida relacionada con la rodilla)(34). También proponen una clasificación de KL solo de grado 1. Estos autores tampoco diferencian el ritmo del dolor.

En la búsqueda de unos criterios fiables y objetivos hay artículos que propugnan utilizar pruebas funcionales como puede ser el estudio biomecánico de la marcha. Un ejemplo es el de Emery *et al.,*2019, en el que se resalta la importancia de la biomecánica para aportar información acerca de los mecanismos subyacentes de la progresión de la artrosis, de la causa inicial de esta patología y del grado de severidad(35). No obstante, señalan que se requieren más estudios de la biomecánica en la artrosis precoz de rodilla y reconocen que no está del todo aceptado su uso en la práctica clínica diaria(35).

El estudio de la biomecánica de la marcha nos da información acerca de la mecánica articular (movimiento articular, la carga o los patrones de activación muscular). Algunos indicadores de alteración de la mecánica articular asociados con un mayor grado de artrosis de rodilla son; las alteraciones de la alineación articular, el aumento del varo de rodilla o alteraciones en el momento externo de adducción(36). Otros factores asociados al desarrollo de artrosis de rodilla y que de alguna manera se pueden analizar con la biomecánica, son alteraciones en la estabilidad dinámica de la articulación, atrofia muscular, inhibición neuromuscular y mecanismos compensatorios de activación muscular(37–41). En este campo cabe destacar el trabajo de Li *et al.,* 2022, en el que defienden que el análisis de la biomecánica de la marcha puede tener utilidad en la artrosis de rodilla para valorar su grado de afectación(42).

II.HIPÓTESIS:

Los criterios actuales de artrosis precoz de rodilla propuestos por los autores no parecen totalmente fiables, ni aplicables a la práctica clínica habitual. La valoración de otros criterios objetivos, como los parámetros bioquímicos o estudios de biomecánica de la marcha pueden ayudar a realizar un diagnóstico más válido y fiable.

III. OBJETIVOS Y CORRELACIÓN ENTRE ARTÍCULOS:

La investigación desarrollada en esta tesis doctoral consta de tres objetivos que se han llevado a cabo en las tres publicaciones:

El primer objetivo consistía en aclarar los criterios diagnósticos de la artrosis precoz de rodilla. Para ello, se realizó una revisión sistemática de los criterios propuestos en la literatura acerca de esta patología. Este objetivo se ha conseguido con la publicación titulada:

Classification criteria for early knee osteoarthritis: a review article

Tras conocer los resultados de esta revisión se llevó a cabo un estudio piloto de carácter longitudinal y prospectivo para valorar la aplicabilidad en la práctica clínica de los criterios diagnósticos de artrosis precoz de rodilla a una muestra de pacientes reales, consiguiéndolo con el artículo:

Early Knee Osteoarthritis Classification and Clinical Evolution:
A Longitudinal Observational Pilot Study.

Como conclusiones de estos dos artículos se confirmó la falta de fiabilidad de los elementos diagnósticos actuales de artrosis precoz de rodilla. De aquí, surge el tercer artículo, que tiene como objetivo analizar de nuestra muestra de pacientes los parámetros bioquímicos (perfil lipídico y marcadores inflamatorios) para intentar buscar una relación con el diagnóstico de artrosis temprana de rodilla y obtener así, unos criterios válidos. Esto queda reflejado en el siguiente artículo:

Serum lipid biomarkers and inflammatory cytokines associated with
onset and clinical status of patients with early knee osteoartritis.

Por tanto, el objetivo principal de esta tesis fue revisar los criterios diagnósticos de artrosis precoz de rodilla realizando una revisión bibliográfica y, posteriormente, comprobando la aplicabilidad de estos criterios a nuestra muestra de pacientes, realizando un estudio piloto. Finalmente, se planteó además, buscar posibles factores que ayuden a un diagnóstico objetivo y más fiable de esta patología, dejando iniciadas unas futuras líneas de investigación que complementan esta tesis doctoral. Dentro de estas nuevas líneas de trabajo se está realizando un análisis de los resultados del estudio biomecánico de la marcha y pronto se realizarán nuevas publicaciones.

IV.MATERIAL Y MÉTODOS:

IV.1. Diseño del estudio:

Esta investigación fue llevada a cabo a cargo del servicio de Medicina Física y Rehabilitación del Hospital la Fe en Valencia (España), como parte del proyecto OACTIVE H2020. Se realizó un estudio observacional y prospectivo con una muestra no probabilística.

La revisión sistemática se llevó a cabo de acuerdo a un protocolo predefinido basado en la declaración PRISMA(43). Esta declaración consta de una lista de verificación de 27 ítems y un diagrama de flujo de cuatro fases, que ayuda en la presentación de revisiones sistemáticas.
Se incluyeron en la revisión solo aquellos artículos que trataban sobre los criterios diagnósticos de la artrosis temprana de rodilla, incluyendo tanto criterios clínicos como radiológicos. Se aceptaron estudios sin restricción de idioma y se seleccionaron artículos publicados solo en los últimos 10 años. Dos revisores independientes realizaron la búsqueda de artículos científicos, llegando a un acuerdo para la selección inicial de los estudios, después de lo cual se buscaron las concordancias.
La búsqueda de artículos científicos se realizó utilizando las bases de datos de MEDLINE (Pubmed), Web of Science, Scopus, EMBASE, PEDro, CINAHL y Google Scholar. En estas bases de datos, se utilizaron los siguientes términos de búsqueda y combinaciones: "artrosis precoz" Y "Clasificación", "artrosis precoz" Y "Diagnóstico", "artrosis precoz" Y "Criterios" y "artrosis precoz".
Una vez realizada la búsqueda se llevó a cabo una evaluación, por parte de dos revisores independientes, de la relevancia de los estudios con respecto a la pregunta y el objetivo de la investigación. Este primer análisis se basó en la información del título, resumen y palabras clave de cada estudio.
En una segunda fase de análisis, considerando el texto completo, se verificó si los estudios cumplían con los criterios de inclusión. Las diferencias entre los dos revisores se resolvieron mediante un consenso moderado por parte de un tercer revisor. Los datos obtenidos de estos artículos fueron extraídos mediante el protocolo estructurado que garantiza la obtención de la información más relevante de cada estudio.

Para el estudio longitudinal se llevó a cabo un estudio observacional piloto, con una muestra no probabilística de 105 participantes. Los pacientes fueron reclutados y clasificados como sujetos sanos en riesgo de desarrollar artrosis (HS) o con artrosis precoz de rodilla (EKOA) siguiendo los criterios de Luyten *et al.,*2018 y la clasificación de Mahmoudian *et al.,* 2021(33,34).
En cuanto al estudio de los marcadores bioquímicos se realizó un estudio transversal con una muestra no aleatorizada en un total de 96 pacientes.
El diseño del estudio se adhirió a las recomendaciones internacionales para el Fortalecimiento del Informe de Estudios Observacionales en Epidemiología(44). Todos los participantes fueron informados detalladamente sobre los procedimientos del

estudio, los cuales se planearon de acuerdo con los estándares éticos de la Declaración de Helsinki y fueron aprobados por el Comité de Ética de Investigación de Medicamentos del hospital (CEIm 2017/0147). A cada uno de los pacientes se les explicó claramente el propósito del estudio y las pruebas específicas a las que se someterían, y todos ellos proporcionaron después, un consentimiento informado por escrito.

IV.2. Participantes:

En cuanto al estudio longitudinal se reclutó un total de 105 participantes que se dividieron en 2 grupos, los que cumplían criterios de artrosis precoz de rodilla (EKOA) y otro de sujetos sanos en riesgo de desarrollar artrosis (HS). Estos 105 pacientes fueron clasificados usando las dos propuestas de criterios diagnósticos más aceptados en la actualidad para la investigación de la artrosis precoz de rodilla.

Por una parte, se aplicaron los criterios de Luyten *et al*., 2012,2018 (31,33) y por otro lado, los criterios de Mahmoudian *et al*., 2021 (34) a la misma muestra de pacientes, con el objetivo de compararlos y ver la evolución de estos pacientes en el tiempo. Se les hizo dos revisiones clínicas, una a los 9 y otra a los 12 meses, para comprobar si se mantenían en el mismo grupo diagnóstico o si había variaciones. El diagrama de flujo del estudio se muestra a continuación:

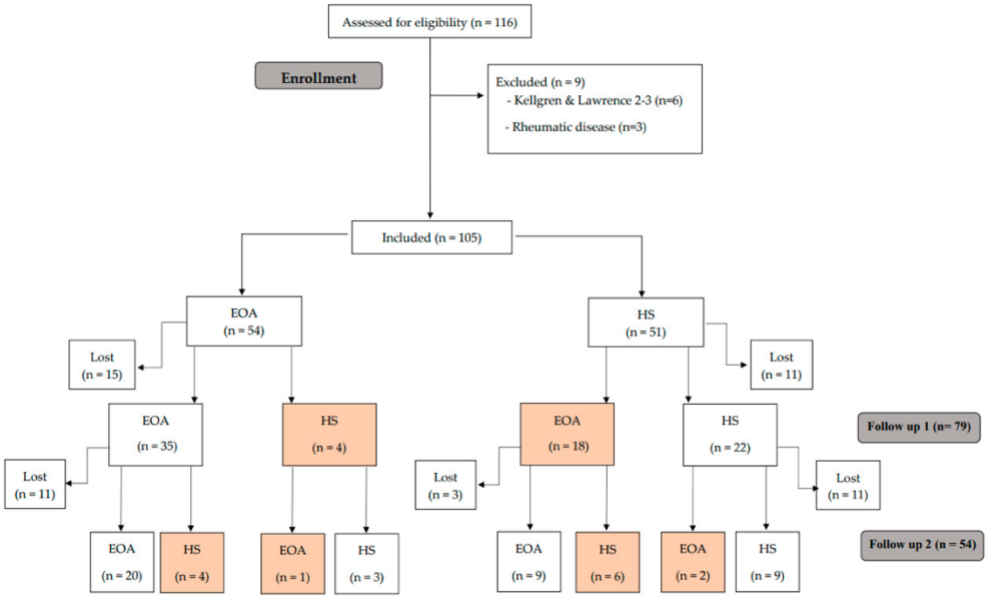


Figura1: Diagrama de flujo del estudio con los criterios de Luyten *et al.,* 2012,2018

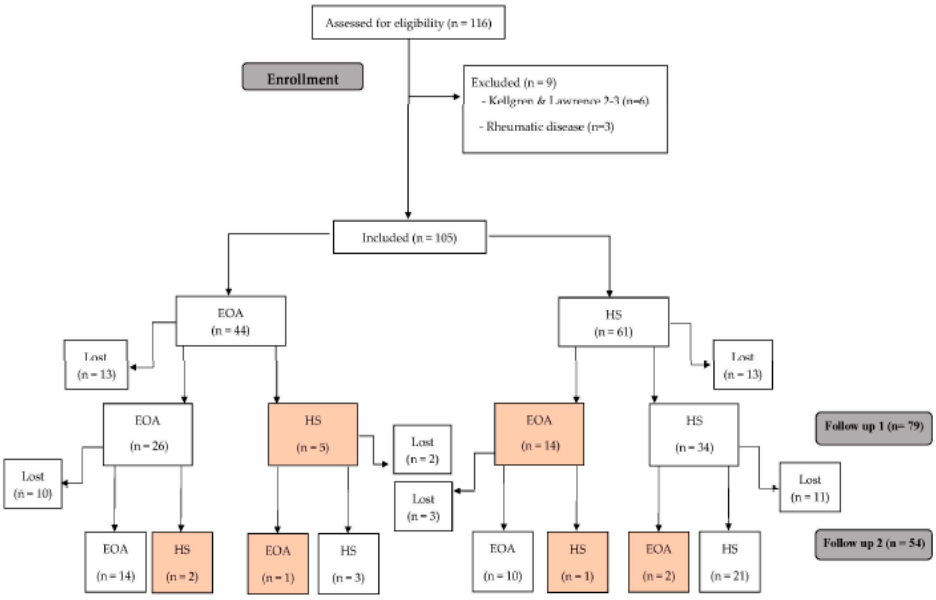


Figura 2: Diagrama de flujo del estudio con los criterios de Mahmoudian *et al.,* 2021

Por otro lado, para el estudio de los parámetros bioquímicos solo se aplicaron los criterios de Luyten *et al*., 2012,2018 para clasificar a los pacientes(31,33). En este caso se analizaron un total de 96 participantes. De los cuales 48 fueron clasificados con artrosis precoz de rodilla y 48 como personas sanas en riesgo de desarrollar artrosis.
La diferencia en el número de participantes de ambos estudios se debió al abandono de algunos participantes por la pandemia mundial por COVID19, o también, en algún caso, por motivos personales.

Los criterios de inclusión de los voluntarios sanos en riesgo de desarrollar artrosis precoz de rodilla eran:

1. Grado de Kellgren y Lawrence 0-1.
2. En cuanto al límite de edad, los pacientes debían tener 40 años o más.
3. Los participantes debían tener sobrepeso, con un índice de masa corporal (IMC) de al menos 25.

Los criterios de exclusión utilizados fueron los mismos para ambas muestras de pacientes, quedando fuera del estudio los pacientes que tuvieran enfermedades reumáticas, autoinmunes o infecciosas. Además, se excluyeron a aquellos participantes cuyo nivel cognitivo, discapacidad, o nivel de comprensión del idioma español insuficiente, fuera un impedimento para participar en el estudio.

IV.3. Variables recogidas:

- Parámetros inflamatorios y perfil lipídico: se recogieron datos del perfil lipídico en suero (colesterol total, triglicéridos, HDL y LDL) y de marcadores inflamatorios (proteína C-reactiva, ácido úrico).

- Variables de dolor y discapacidad: se utilizó la escala analógica visual (VAS) para valorar el dolor, tanto en reposo como con la deambulación, la escala Western Ontario and McMaster universities osteoarthritis index (WOMAC) y la Knee Injury and Osteoarthritis Outcome Score (KOOS).

- Variables funcionales: se realizó una medición de la velocidad de la marcha y la prueba "*five times sit-to-stand test".*

- Variables demográficas: se recogieron datos demográficos de la muestra en estudio como sexo, edad, estado, civil, hábitos tóxicos, etc.

  Todas estas variables están explicadas con mayor detalle en los artículos originales indexados al final de esta tesis.

V.RESULTADOS:

A continuación, se describen los resultados obtenidos con cada artículo:

V.1. Classification criteria for early knee osteoarthritis: a review article:

La estrategia de búsqueda del estudio se muestra en forma de un diagrama de flujo (figura 3). Se seleccionaron siete artículos que cumplían los criterios de inclusión. A continuación se reflejan las conclusiones a las que llega cada uno de los artículos, como resultado de nuestra revisión sistemática.

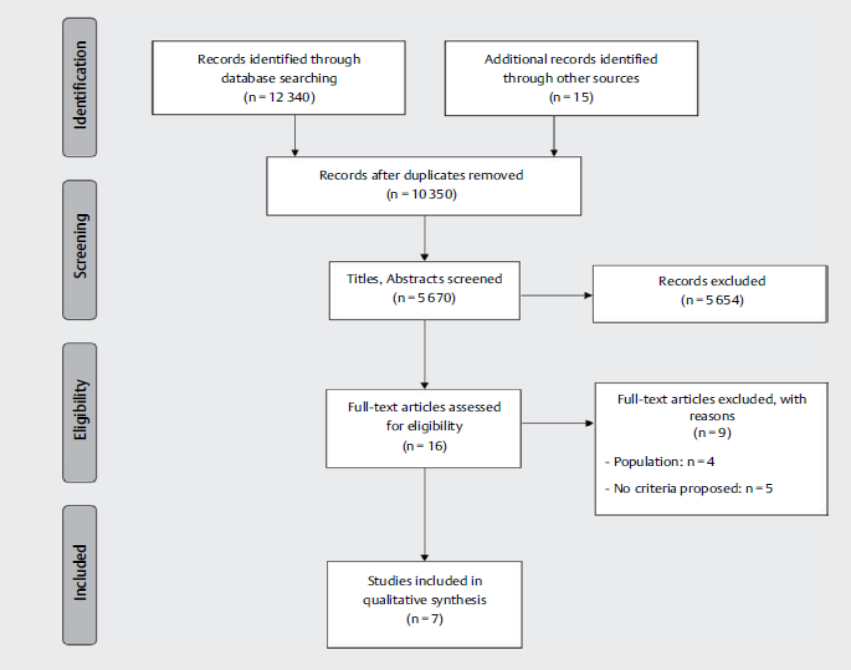


Figura 3: Diagrama de flujo del estudio.

Dos de los trabajos más reconocidos en la definición de artrosis precoz de rodilla son los ya mencionados de **Luyten *et al*.,** 2012 y 2018 (31,33). En estos trabajos, los autores crearon un comité de expertos formado por médicos, fisioterapeutas y cirujanos, estableciendo criterios de diagnóstico basados en un consenso común.

Más tarde, **Mahmoudian *et al*.,** 2021(34) llevaron a cabo un análisis de los criterios de Luyten et al., utilizando la base de datos de la *Osteoartritis Initiative*. Además, estos autores realizaron un análisis de regresión logística para evaluar el valor predictivo del conjunto de criterios, tanto para la progresión clínica como estructural.
Otros autores que debemos mencionar son **Runhaar *et al***., 2021 que realizaron un estudio CHECK basado en la selección de pacientes por expertos en el campo a través de un estudio de cohortes; que posteriormente se utilizó para crear modelos predictivos(45).

Por otro lado, **Migliore *et al.*,**2015,2017 realizaron una revisión sistemática acerca de la definición de la artrosis precoz de rodilla. Posteriormente, hicieron un análisis detallado utilizando tres grupos de enfoque, que incluyeron a clínicos expertos, investigadores y pacientes. También realizaron una revisión sistemática de la literatura y dos grupos de discusión, a los que siguió una encuesta Delphi(46,47).
Por último, **Emery *et al.,***2019 llevaron a cabo una revisión narrativa con criterios de consenso de expertos(35).

V.1.1. Criterios clínicos:

Los criterios de **Luyten *et al*.** en su primer trabajo en 2012, incluían gonalgia y la definían como al menos dos episodios de dolor de rodilla durante más de 10 días en el último año(31). En su posterior trabajo en 2018 incluyeron cuestionarios como el KOOS(32). Los criterios de **Luyten *et al.,*** 2018 **y Mahmoudian *et al*.**,2021 se describen en la introducción.

Migliore *et al.,* 2015 en su primer trabajo propusieron como criterio dolor de rodilla y rigidez articular de menos de 6 meses de duración e incluyeron los siguientes factores de riesgo: IMC >25, antecedentes familiares de artrosis, lesiones previas de rodilla, alteraciones en la alineación, dismetría de miembros inferiores, artrosis en otras articulaciones y síndrome metabólico.
Además, definieron la artrosis precoz de rodilla como:

a) 3 o más síntomas sin factores de riesgo asociados.
b) 2 o más síntomas con un factor de riesgo asociado.
c) 1 o más síntomas de duración menor a 6 meses más 2 o más factores de riesgo (47).

Posteriormente, en 2017 **Migliore *et al.*** definen la artrosis precoz de rodilla como una de las siguientes opciones:

a) La presencia de dos síntomas denominados "obligatorios": dolor de rodilla atraumática y rigidez articular de menos de 10 minutos de duración al iniciar el movimiento.
b) La presencia de dolor de rodilla asociado a uno o dos factores de riesgo de artrosis.
c) La presencia de tres o más factores de riesgo con al menos uno de los "síntomas obligatorios", con una duración de los síntomas de al menos 6 meses (46).

Por otro lado, **Runhaar *et al*.,** 2021 identificaron factores relacionados con el inicio de la artrosis precoz de rodilla, e incluyen el sexo femenino, la edad, dolor en la interlínea articular, derrame, IMC >25 kg/m^2 y crepitación. Además, hablan de la importancia de cuestionarios como el WOMAC. Estos autores no especifican el ritmo del dolor, de tal manera que puntúa como positivo tanto el dolor mecánico como el inflamatorio(45).

Por último, **Emery *et al.,*** 2019 sugieren tener en cuenta a la hora del diagnóstico de artrosis precoz de rodilla cuestionarios como el KOOS y también el Intermittent and Constant Assessment of Pain (ICOAP). Además, proponen incluir síntomas como el dolor en la interlínea articular, rigidez, crepitación y sensación de inestabilidad. En cuanto al ritmo del dolor, mencionan que en la artrosis precoz de rodilla, el dolor suele aparecer con las actividades, aunque no usan como criterio de exclusión el dolor inflamatorio.

Como pruebas funcionales le dan importancia al "*single leg hop test", "30-second chair sit-to-stand test*", "*star excursion balance test*", a las mediciones de la fuerza del cuádriceps, niveles de adiposidad y de los niveles de actividad física(35).

V.1.2. Criterios de imagen:

En su primer trabajo en 2012, **Luyten et al.** incluyen como criterio KL grado 0, 1 o 2 (31). Los criterios de **Luyten *et al*.,** 2012,2018 **y Mahmoudian *et al.,*** 2021 se describen en la introducción.

Migliore *et al.,*2015***,***2017 propusieron establecer como criterio para diagnosticar la artrosis temprana de rodilla KL de 0 (46,47).

Por otro lado, ***Runhaar et al.,***2021 propuso incluir hallazgos radiológicos como el estrechamiento del espacio articular, tumefacción ósea y estrechamiento del espacio articular patelofemoral sin valorar el KL(45).

Sin embargo**, Emery *et al*.,**2019 consideran que la radiografía simple no alcanza el mismo grado de sensibilidad que la resonancia magnética para detectar los cambios de la artrosis precoz de rodilla y que los hallazgos de la radiografía simple están asociados a etapas ya avanzadas de la artrosis(35).

V.1.3. Otros criterios:

Runhaar *et al*., 2021 en su estudio analizan el valor de la PCR en suero y Emery *et al.,*2019 también proponen valorar marcadores bioquímicos y biomecánicos(35,45).

V.1.4. Criterios comunes entre los diferentes autores:

La presencia de dolor articular es el criterio que incluyen todos los autores, aunque con diferentes duraciones como se muestra en la tabla 1:

	Luyten et al. 2012	Luyten et al. 2018	Mahmoudian et al. 2021	Migliore et al. 2015	Migliore et al. 2017	Runhaar et al. 2020	Emery et al. 2019
Pain	>2 episodes > 10 days in the last year	JLT	JLT	<6 months	< 6 months	JLT	JLT
Questionnaires	-	KOOS	KOOS	-	-	WOMAC	KOOS ICOAP
Crepitus	-	X	X	-	-	X	X
Effusion	-	-	X	-	-	X	-
Joint stiffness	-	-	-	<6months	<10 min, <6 months	-	x
BMI	-	-	-	>25	-	x	x

Tabla 1: Características clínicas del diagnóstico de la artrosis precoz de rodilla extraídas de los estudios incluidos. JLT: *Joint line tenderness.*

También coinciden en el uso de cuestionarios, aunque difieren en el tipo. En cuanto a los criterios radiológicos todos los autores menos Emery *et al.,*2019 están de acuerdo en usar la radiografía simple, aunque no coinciden en el grado de KL que se debe usar. Dado que los criterios de **Luyten *et al*.,** 2012,2018 **y Mahmoudian *et al.,***2021 son los más aceptados para la investigación clínica, son los que se han usado para clasificar a nuestra muestra de pacientes.

V.2. Early Knee Osteoarthritis Classification and Clinical Evolution: A Longitudinal Observational Pilot Study.

En este artículo los criterios de Luyten *et al.*,2018, y por otro lado, los de Mahmoudian *et al.,*2021, fueron aplicados a los participantes para clasificarlos en dos grupos:

- participantes sanos en riesgo de artrosis de rodilla (HS)
- pacientes con artrosis precoz de rodilla (EKOA)

Y posteriormente, tras hacerles un seguimiento longitudinal en dos revisiones clínicas, se obtuvieron los siguientes resultados:

V.2.1. Cambios en la clasificación:

Siguiendo tanto la clasificación de Luyten *et al.,*2018 como la de Mahmoudian *et al.,*2021, en cada revisión del seguimiento los pacientes fueron reclasificados. De tal manera que, algunos de aquellos pacientes que cumplían criterios de artrosis precoz en un momento dado, eran cambiados a pacientes sanos y viceversa. En las figuras 1 y 2, mostradas previamente, se expone con detalle esta variación en la clasificación.

V.2.2. Intensidad del dolor:

Según se evidencia en las tablas 2 y 3 no se encontraron diferencias estadísticamente significativas en la escala VAS (tanto en reposo como en la deambulación) al inicio del estudio en comparación con las dos revisiones posteriores del seguimiento, en ninguno de los dos grupos de pacientes. Estos resultados fueron similares tanto para los pacientes clasificados según los criterios de Luyten *et al.*, 2018, como de Mahmoudian *et al.,* 2021.

	Inicio	**9 meses**	**12 meses**
VAS Rest			
Luyten et al. [9]	2.04 ± 1.56	1.29 ± 2.05	2.21 ± 2.67
Mahmoudian et al. [10]	1.88 ± 2.31	1.50 ± 2.06	2.44 ± 2.78
VAS Walking			
Luyten et al. [9]	2.67 ± 2.73	2.42 ± 2.02	2.46 ± 2.40
Mahmoudian et al. [10]	2.69 ± 2.77	2.94 ± 2.11	2.63 ± 2.55

Tabla 2: Evolución de la escala VAS de los pacientes del grupo de EKOA.

	Inicio	9 meses	12 meses
VAS Rest			
Luyten et al. [9]	0.1 ± 0.29	0.74 ± 1.36	0.91 ± 1.41
Mahmoudian et al. [10]	0.68 ± 1.85	0.77 ± 1.54	1.13 ± 1.77
VAS Walking			
Luyten et al. [9]	0.52 ± 1.76	1.3 ± 2.01	1.52 ± 1.86
Mahmoudian et al. [10]	1.06 ± 2.23	1.32 ± 1.85	1.68 ± 1.92

Tabla 3: Evolución de la escala VAS de los pacientes del grupo de pacientes sanos.

V.2.3. Discapacidad:

Tal como se muestra en las tablas 4 y 5, tanto los pacientes del grupo de artrosis precoz de rodilla como los sujetos sanos en riesgo, presentaron a lo largo del seguimiento un empeoramiento de su dolor y de su discapacidad medida con la escala WOMAC.
Estas diferencias estadísticamente significativas están señaladas en las tablas 4 y 5 con un asterisco.

	Inicio	9 meses	12 meses
* WOMAC			
Luyten et al. [9]	18.55 ± 10.15	16.56 ± 15.66 *	22.47 ± 17.23 *
Mahmoudian et al. [10]	17.62 ± 9.47	22.04 ± 16.75 *	25.26 ± 18.75 *

Tabla 4: Evolución de la escala WOMAC de los participantes del grupo de EKOA.

	Inicio	9 meses	12 meses
* WOMAC			
Luyten et al. [9]	5.86 ± 4.3	9.57 ± 8.20 *	12.30 ± 10.30 *
Mahmoudian et al. [10]	9.32 ± 8.89	12.44 ± 8.45 *	12.77 ± 10.42 *

Tabla 5: Evolución de la escala WOMAC de los pacientes del grupo de HS.

V.3. Serum lipid biomarkers and inflammatory cytokines associated with onset and clinical status of patients with early knee osteoartritis.

V.3.1 Perfil lipídico:

Tras analizar los datos bioquímicos se encontraron diferencias estadísticamente significativas entre los dos grupos de pacientes, mostrando que los pacientes del grupo con artrosis precoz de rodilla tenían niveles más elevados de colesterol total y LDL en comparación con los sanos. Sin embargo, en cuanto al HDL y los triglicéridos no se encontraron diferencias entre los grupos.

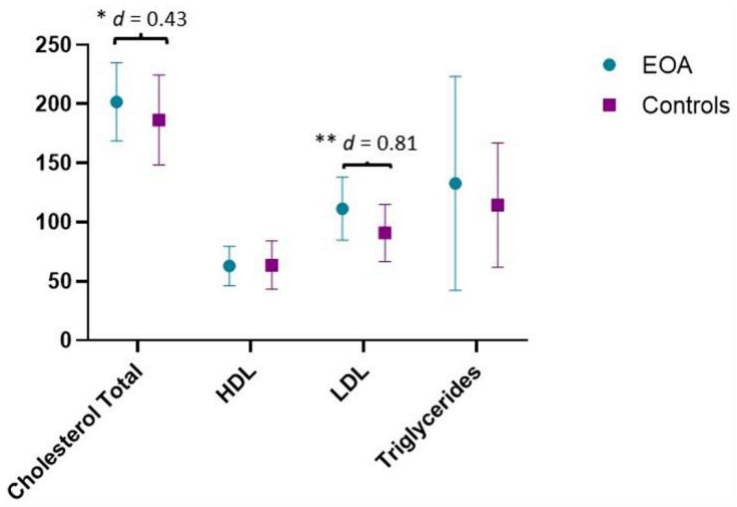


Figura 4: Resultados del análisis del perfil lipídico.

V.3.2. Parámetros inflamatorios:

En cuanto a los niveles de ácido úrico y PCR en sangre se vieron diferencias estadísticamente significativas entre ambos grupos, de manera que los pacientes con artrosis temprana de rodilla presentaban niveles más elevados de ambos parámetros en comparación con los sanos.

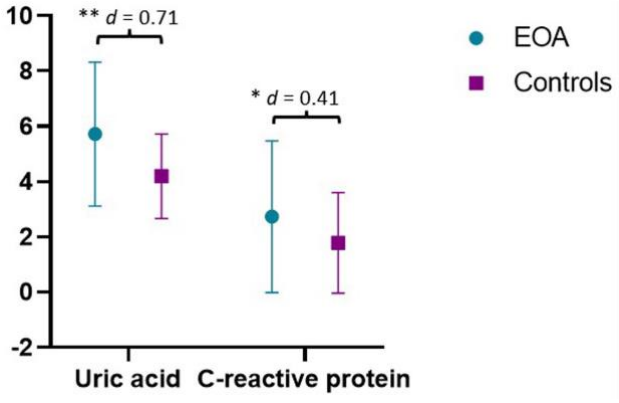


Figura 4: Resultados del análisis de los parámetros inflamatorios.

V.3.3. Relación entre variables:

Los resultados obtenidos mostraron que niveles más elevados de colesterol total estaban relacionados con niveles más elevados de dolor y discapacidad. También se observó que niveles elevados de LDL y PCR estaban relacionados con una mayor intensidad del dolor. Por último, se obtuvo que los niveles de ácido úrico y PCR estaban inversamente relacionados con la velocidad de la marcha y con "*5 sit-to-stand test".*

VI.DISCUSIÓN:

El primer objetivo de esta tesis era revisar el "estado del arte" de los criterios diagnósticos de artrosis precoz de rodilla con la hipótesis de que los criterios vigentes no se pueden considerar del todo fiables. Para afianzar esta suposición y valorar su viabilidad en la práctica clínica, se aplicaron los criterios a una muestra de pacientes reales y se les realizó un seguimiento. Por último, se analizaron nuevas herramientas diagnósticas posibles como los parámetros bioquímicos.
Teniendo esto en cuenta vamos a discutir las implicaciones que tienen los resultados de cada uno de los tres artículos publicados.

VI.1. Revisión de los criterios diagnósticos de la artrosis precoz de rodilla:

El objetivo de analizar las distintas propuestas de criterios diagnósticos de artrosis precoz de rodilla se cumple con la publicación del artículo "*Classification criteria for early knee osteoarthritis: a review article".*

Como ya se comentó en el apartado de resultados no existe un consenso claro para el diagnóstico de esta patología. Es cierto que la mayoría de los autores coinciden en usar como criterios diagnósticos la presencia de dolor con el apoyo de las imágenes de radiografía simple, aunque también existen discrepancias en cuanto al grado de KL o la duración del dolor.
La presencia de dolor es el factor con más peso para el diagnóstico de artrosis precoz de rodilla sintomática(33–35,46,47), a pesar de que se ha visto que no tiene correlación con las imágenes radiológicas, ya que podemos encontrar pacientes con dolor severo y hallazgos sutiles en la radiografía y viceversa(19,45). El dolor supone un desafío para el médico ya que se trata de un síntoma subjetivo y de difícil medición. Además, en estos casos cabe la posibilidad de que la causa del dolor de rodilla no sea la artrosis, sino otra patología o lesión. Conocer el ritmo del dolor nos puede ayudar a saber si la gonalgia del paciente es secundaria a artrosis o es debido a otras causas. Sin embargo, aunque típicamente el dolor de la artrosis establecida de rodilla es de ritmo mecánico (48), los autores no especifican el tipo de dolor, ni el ritmo del mismo, en la artrosis temprana de rodilla.
En cuanto a los criterios radiológicos destaca la utilización de la radiografía simple y la resonancia magnética. La mayoría de autores coinciden en el uso del KL para detectar a pacientes con artrosis precoz de rodilla, aunque son conscientes de que la radiografía simple tiene una menor sensibilidad que la resonancia para detectar lesiones precoces(33–35,45). De hecho, la resonancia magnética puede mostrar lesiones articulares en pacientes totalmente asintomáticos pudiendo dar lugar a un sobrediagnóstico de esta patología, por lo que se desaconseja su uso en la práctica clínica habitual(49,50).

Existe otra revisión en la literatura de los criterios diagnósticos de la artrosis precoz de rodilla que coincide con nuestros resultados, y también resalta la necesidad de crear una definición específica para esta patología(51). Por otro lado, destacan la falta de

diferenciación entre el diagnóstico de artrosis precoz y artrosis ya establecida de rodilla en algunos de los estudios analizados, defendiendo que en muchas ocasiones se habla de artrosis temprana, pero realmente ya hay cambios de artrosis establecida. Además, mencionan la discordancia clínico radiológica existente y la falta de un consenso acerca del tiempo, frecuencia, intensidad y duración del dolor(51).
Como ya se ha mencionado previamente, parte del trabajo de Migliore *et al*., 2015,2017 consistía en una revisión sistemática. Como resultado de esta revisión, se obtuvo que muchos de los estudios incluídos no hacían un diagnóstico como tal de artrosis temprana de rodilla, sino más bien, definían diferentes tipos de artrosis ya establecida, como la artrosis de rodilla de diagnóstico reciente, la artrosis de rodilla en pacientes jóvenes o la artrosis de rodilla detectada por RM(46,47).

En vista de estos resultados, algunos autores incluso sugieren que no se puede plantear un diagnóstico de artrosis en etapas tan tempranas. Sus argumentos se basan en que en estas fases no encontramos todavía signos en la radiografía, y además, a esto se le suma la heterogeneidad y el carácter fluctuante de los síntomas. Nuestro planteamiento es posibilista y se enfoca en conseguir aportar nuevos hallazgos, diferentes a los habitualmente contemplados, pero que sean objetivos y de fácil medición, como podría ser el análisis biomecánico de la marcha.

VI.2. <u>Aplicación de criterios diagnósticos de artrosis precoz de rodilla en pacientes reales:</u>

Con los resultados obtenidos de la revisión sistemática, que confirman la variabilidad de los criterios diagnósticos, se decide aplicar los criterios de Luyten *et al.,2018* y Mahmoudian *et al.,2021* a nuestra muestra de pacientes con el objetivo de ver cómo evolucionaban los pacientes en la clasificación durante el seguimiento. Esto se consigue en el artículo titulado: "*Early Knee Osteoarthritis Classification and Clinical Evolution: A Longitudinal Observational Pilot Study".*

Como era de esperar, durante el seguimiento de los casos hubo fluctuaciones en la clasificación tanto de Luyten *et al.*,2018 como de Mahmoudian *et al*.,2021 pasando algunos pacientes clasificados como pacientes con artrosis precoz a sujetos sanos y viceversa. Si bien es cierto que se encontraron menos fluctuaciones de grupo con la clasificación de Mahmoudian *et al*.,2021.
Esta variación en los grupos nos reafirma la falta de fiabilidad de estos criterios desde un punto de vista práctico y, dado que el dolor de rodilla es la única variable constante en todas las clasificaciones, nos planteamos que quizá, estos pacientes podrían presentar dolor de rodilla por otras causas, dando lugar a un diagnóstico erróneo en algunos casos. A esto hay que añadirle que el dolor de rodilla puede ser fluctuante en la artrosis, pudiendo suponer esto otra dificultad adicional para realizar el diagnóstico, lo que explicaría el trasvase de pacientes del grupo de artrosis precoz al grupo de sujetos sanos.

En la literatura existen pocos artículos que hayan hecho un estudio similar al nuestro. Cabe destacar el trabajo de Harkey *et al.,*2022 en el que en una muestra de pacientes operados de ligamento cruzado anterior, compararon los criterios de artrosis precoz, usando solo como criterio diagnóstico la escala KOOS de la clasificación de Luyten et al.,2018 y de Englund *et al.,* 2003(52). Estos autores encontraron que el número de pacientes con diagnóstico de artrosis precoz de rodilla según el KOOS, era mayor con los criterios de Luyten *et al.,*2018 que con los de Englund *et al.* ,2003 y que solo un 36% de los pacientes cumplía de manera simultánea los criterios de ambos autores, destacando de nuevo la discrepancia de criterios diagnósticos de artrosis precoz de rodilla(53).

Como hallazgo adicional, en nuestro artículo también se analizaron cómo evolucionaban las variables a lo largo del seguimiento, obteniendo que solo el WOMAC mostraba diferencias estadísticamente significativas durante el periodo de observación de los participantes. Es decir, hubo un empeoramiento a lo largo del seguimiento, en ambos grupos de pacientes, tanto en el dolor como en el grado de discapacidad, la cual se midió con la escala WOMAC.

Esto nos hace plantearnos que esta escala podría ser una herramienta válida para ayudarnos a establecer un diagnóstico más fiable de artrosis precoz de rodilla ya que lo esperable en esta patología es que se produzca un empeoramiento a lo largo del tiempo de la funcionalidad del paciente.

Nuestros hallazgos no coinciden con la revisión sistemática de Previtali *et al.,*2020 donde estudiaron factores predictivos de progresión del dolor, concluyendo que el WOMAC no cumplía criterios suficientes para ser un factor predictivo(54).

Por otro lado, Halilaj *et al.,* 2018 llevaron a cabo un estudio para relacionar la progresión radiológica, principalmente la disminución del espacio articular, con el WOMAC. Crearon dos grupos, los que tenían progresión radiológica y los que permanecían estables, y concluyeron que el WOMAC era similar en los dos grupos de pacientes. Tampoco encontraron relación entre un empeoramiento del WOMAC y la progresión radiológica(55). Debemos tener en cuenta que estos dos estudios fueron llevados a cabo en pacientes con artrosis ya establecida de rodilla, no con artrosis precoz. Por tanto, comparar sus resultados con los nuestros no sería del todo correcto.

Sin embargo, en un estudio biomecánico de la marcha en pacientes con artrosis de rodilla se encontró relación entre el WOMAC y algunos parámetros del análisis de la marcha. Por ejemplo, se observó que existía una relación inversamente proporcional entre la velocidad de la marcha, la cadencia y el tiempo de apoyo monopodal en el análisis de la marcha con la subescala de dolor del WOMAC de los pacientes con artrosis de rodilla. Estos autores concluyen que el análisis de la marcha y el cuestionario WOMAC proporcionan información del paciente desde diferentes perspectivas, lo que puede ofrecer información funcional integral de los pacientes y facilitar el diagnóstico de la artrosis de rodilla(42).

Con todo esto, cabe mencionar que los estudios que relacionan el WOMAC con la progresión de la artrosis, o que lo analizan como apoyo diagnóstico, no son concluyentes. Al tratarse de una herramienta de fácil manejo en consulta y que nos aporta información acerca de los síntomas y la funcionalidad del paciente, pensamos

que se podría valorar su utilidad para clarificar el diagnóstico de la artrosis precoz de rodilla.

Por lo tanto, es necesario encontrar un consenso internacional entre clínicos que indique cuál es el conjunto óptimo necesario para el diagnóstico de la artrosis temprana de rodilla, eligiendo los más adecuados entre los síntomas subjetivos, como el dolor, los hallazgos de exploración en el examen físico y otros criterios más objetivos que puedan aumentar la fiabilidad en el diagnóstico. Entre estos criterios más objetivos cabe mencionar los parámetros biomecánicos y/o bioquímicos.

VI.3. Relación de parámetros bioquímicos con la artrosis precoz de rodilla e implicaciones en el diagnóstico:

En esta búsqueda de parámetros objetivos para ayudarnos con el diagnóstico de la artrosis precoz de rodilla se realiza un estudio del perfil lipídico y de los parámetros inflamatorios de nuestra muestra de pacientes, con el objetivo de analizar su relación. Esto se muestra en el artículo titulado: *"Serum lipid biomarkers and inflammatory cytokines associated with onset and clinical status of patients with early knee osteoartritis"*

La relación entre los niveles de lípidos en suero y la artrosis es contradictoria en la evidencia científica actual. Una revisión sistemática y un metaanálisis encontraron que, en estudios de casos y controles y estudios transversales, había una clara relación entre la dislipidemia y la presencia de artrosis, especialmente en la rodilla. Sin embargo, esta misma revisión no encontró la misma relación al analizar solo estudios de cohortes(12).

Varios mecanismos que relacionan el metabolismo lipídico y la artrosis han sido propuestos. Por ejemplo, se ha visto que el colesterol desempeña un papel crucial en la condrogénesis y la osteogénesis endocondral(13). En este sentido, hay estudios que sugieren que niveles más altos de lipoproteínas de alta densidad (HDL) pueden tener un efecto protector en las articulaciones(56). Además, se ha visto que procesos inflamatorios pueden ser desencadenados por el aumento de lipoproteínas de baja densidad (LDL) en la matriz extracelular del cartílago(14). En la misma línea, existen estudios en la literatura que sugieren que la hipercolesterolemia puede llevar a la oxidación y a la deposición de lípidos en los tejidos, produciendo daño al cartílago(57).
Los resultados de nuestra investigación mostraron niveles más altos de colesterol total en pacientes con artrosis precoz en comparación con los pacientes sanos. Además, se evidenció una correlación entre estos niveles y una mayor intensidad del dolor y de la discapacidad. Todo esto nos reafirma en el planteamiento de una posible relación entre el colesterol total y LDL con el inicio de la artrosis.

Por otro lado, la proteína C reactiva (PCR) es una proteína de fase aguda sintetizada por los hepatocitos en respuesta a citocinas proinflamatorias durante procesos inflamatorios o infecciosos(15). Existe una tendencia actual a proponer que la PCR influye en la patogénesis de la artrosis(16). De hecho, existen estudios que refieren que

los niveles de PCR están significativamente elevados en pacientes con artrosis en comparación con controles sanos y además, plantean que existe una relación de la PCR con las características clínicas y el grado de severidad en la radiografía(58). Así mismo, hay autores que hablan de la relación entre los niveles de PCR , el dolor y la discapacidad, obteniendo resultados similares a los de nuestro estudio(59).

En cuanto al ácido úrico existen varias teorías que lo relacionan con la artrosis, aunque su mecanismo exacto se desconoce. Por ejemplo, los análisis in vitro mostraron que los cristales de urato aumentaron significativamente la expresión de mediadores catabólicos como el óxido nítrico(17,60). También se ha visto que el ácido úrico tiene efectos proinflamatorios y prooxidantes, y que la presencia de transportadores de ácido úrico en los condrocitos humanos sugiere que pueden internalizar el ácido úrico soluble e iniciar respuestas catabólicas(61).

Otra reflexión a destacar es que en nuestro trabajo se constató que la PCR y el ácido úrico estaban inversamente relacionados con la velocidad de la marcha y el "*sit-to-stand test*". Teniendo en cuenta que estos parámetros sirven para medir la funcionalidad del paciente, podríamos plantear que los marcadores inflamatorios podrían tener una relación directa con la capacidad funcional en pacientes con artrosis precoz.

Por último, quisiera expresar algunas reflexiones; una es ofrecer una propuesta de la opinión de nuestro grupo de investigación respecto a los criterios diagnósticos de la artrosis precoz de rodilla, la otra es respecto a las limitaciones y fortalezas de esta investigación, que se reflejan en el siguiente epígrafe.

Por tanto, nuestra sugerencia de criterios diagnósticos para la artrosis precoz de rodilla, teniendo en cuenta las propuestas de los autores y nuestros resultados, es la siguiente:

1. Dolor: gonalgia en ausencia de traumatismo previo. En cuanto a la duración, el paciente debe haber presentado al menos 2 episodios de dolor con una duración mayor de 10 días en el último año.
2. En la exploración física: al menos un criterio debe estar presente:
   - crepitación.
   - dolor en la interlínea articular.
3. En cuanto a los hallazgos radiográficos se incluiría un KL de grado 0-1.
4. Parámetros bioquímicos, como aumento de la PCR, LDL, colesterol total o ácido úrico.
5. En cuanto a los cuestionarios, recomendamos la escala WOMAC ya que consideramos que es más sencilla y rápida para la práctica clínica habitual en comparación con la escala KOOS; y aporta suficiente información acerca de los síntomas y la funcionalidad del paciente.

Con la aplicación de estos cinco criterios sugeridos, realizaríamos un diagnóstico "integral" que abarca la evaluación del dolor y la funcionalidad del paciente, junto con

la consideración de datos objetivos, tales como parámetros bioquímicos y resultados de imágenes como radiografías. En un futuro se podría plantear incluir un criterio objetivo adicional relacionado con la biomecánica de la marcha.

VI.4. Limitaciones y fortalezas:

Si bien esta tesis doctoral podría proporcionar valiosas aportaciones al campo del diagnóstico de la artrosis precoz de rodilla, es esencial reconocer las limitaciones de nuestra investigación para una interpretación adecuada de los resultados y para orientar futuras investigaciones. La principal limitación radica en que, a pesar de haber utilizado los criterios más aceptados por la comunidad científica en investigaciones de este tipo, la clasificación de los pacientes se ha llevado a cabo usando criterios que, según la revisión sistemática inicial, no tienen una alta fiabilidad para la práctica clínica. La otra limitación importante a mencionar es el reducido número de participantes en el estudio.

Por otro lado, esta tesis doctoral se sustenta en diversas fortalezas que contribuyen a la relevancia y aplicabilidad de los resultados. A continuación, se enumeran las principales fortalezas identificadas durante el desarrollo de este trabajo de investigación:

- Su rigor metodológico para contrarrestar la debilidad de la reducida muestra estudiada.

- Su doble confirmación de la falta de fiabilidad de los elementos diagnósticos actuales mediante una revisión del “estado del arte”, asociado a una puesta en práctica de dichos criterios con una muestra real de pacientes.

- Su utilidad clínica, ya que trata de una patología muy prevalente y que se encuentra en alza; proponiendo, además, criterios para poder establecer un diagnóstico válido. Esto engloba la oportunidad de poder mejorar, en un futuro, la investigación sobre su tratamiento al poder aplicarlo a una muestra de pacientes que sabemos, con seguridad, que tienen artrosis precoz de rodilla.

VII.CONCLUSIONES:

Con la revisión sistemática efectuada, tal como se planteaba en la hipótesis, evidenciamos que no hay consenso entre los autores respecto a los criterios de clasificación diagnóstica de artrosis precoz de rodilla.

Con el estudio piloto se demuestra, desde un punto de vista práctico, que los criterios actuales carecen de fiabilidad clínica y pueden conducir a un diagnóstico erróneo, dando lugar a variaciones a lo largo del seguimiento en el diagnóstico de nuestra muestra de pacientes.

Con el estudio transversal realizado entre los pacientes con artrosis precoz de rodilla y los parámetros bioquímicos se ha encontrado una relación novedosa entre la artrosis precoz de rodilla y una alteración del perfil lipídico e inflamatorio. Por lo tanto, la determinación de estos parámetros, podría ser una herramienta útil para el diagnóstico de la artrosis en las fases precoces, pudiendo ser útiles incluso como posible criterio diagnóstico.

VII.1. Futuras líneas de investigación:

Con el fin de encontrar criterios diagnósticos válidos nos planteamos el estudio de la biomecánica de la marcha como una herramienta útil, ya que se podrían objetivar alteraciones relacionadas con el dolor, o con alteraciones funcionales y/o estructurales de la artrosis precoz de rodilla.

Actualmente tenemos recogidos datos de la biomecánica de nuestros pacientes y en un futuro realizaremos su análisis. De hecho, ya existen algunos estudios que plantean usar el análisis de la biomecánica de la marcha para el diagnóstico de artrosis de rodilla bilateral(42).

La línea de investigación iniciada en esta tesis no ha culminado. Por su enorme interés, se pretende continuar para lograr que, una patología tan frecuente como la artrosis de rodilla disponga de criterios válidos y fiables para detectarla en sus fases precoces y de esta manera poder llevar a cabo un tratamiento conservador de la misma.

VIII.BIBLIOGRAFÍA:

1. Bijlsma JW, Berenbaum F, Lafeber FP. Osteoarthritis: an update with relevance for clinical practice. The Lancet. junio de 2011;377(9783):2115-26.

2. Steinmetz JD, Culbreth GT, Haile LM, Rafferty Q, Lo J, Fukutaki KG, et al. Global, regional, and national burden of osteoarthritis, 1990–2020 and projections to 2050: a systematic analysis for the Global Burden of Disease Study 2021. Lancet Rheumatol. septiembre de 2023;5(9):e508-22.

3. Orlowsky EW, Kraus VB. The Role of Innate Immunity in Osteoarthritis: When Our First Line of Defense Goes On the Offensive. J Rheumatol. marzo de 2015;42(3):363-71.

4. Loeser RF, Goldring SR, Scanzello CR, Goldring MB. Osteoarthritis: a disease of the joint as an organ. Arthritis Rheum. junio de 2012;64(6):1697-707.

5. Bruyère O, Cooper C, Arden N, Branco J, Brandi ML, Herrero-Beaumont G, et al. Can We Identify Patients with High Risk of Osteoarthritis Progression Who Will Respond to Treatment? A Focus on Epidemiology and Phenotype of Osteoarthritis. Drugs Aging. marzo de 2015;32(3):179-87.

6. Garriga XM. Definición, etiopatogenia, clasificación y formas de presentación. Aten Primaria. enero de 2014;46:3-10.

7. Sellam J, Berenbaum F. The role of synovitis in pathophysiology and clinical symptoms of osteoarthritis. Nat Rev Rheumatol. noviembre de 2010;6(11):625-35.

8. Bierma-Zeinstra SM, Koes BW. Risk factors and prognostic factors of hip and knee osteoarthritis. Nat Clin Pract Rheumatol. febrero de 2007;3(2):78-85.

9. Luppino FS, De Wit LM, Bouvy PF, Stijnen T, Cuijpers P, Penninx BWJH, et al. Overweight, Obesity, and Depression: A Systematic Review and Meta-analysis of Longitudinal Studies. Arch Gen Psychiatry. 1 de marzo de 2010;67(3):220.

10. Harwood HJ. The adipocyte as an endocrine organ in the regulation of metabolic homeostasis. Neuropharmacology. julio de 2012;63(1):57-75.

11. Zhuo Q, Yang W, Chen J, Wang Y. Metabolic syndrome meets osteoarthritis. Nat Rev Rheumatol. diciembre de 2012;8(12):729-37.

12. Xiong J, Long J, Chen X, Li Y, Song H. Dyslipidemia Might Be Associated with an Increased Risk of Osteoarthritis. BioMed Res Int. 17 de febrero de 2020;2020:1-9.

13. Wu S, De Luca F. Role of Cholesterol in the Regulation of Growth Plate Chondrogenesis and Longitudinal Bone Growth. J Biol Chem. febrero de 2004;279(6):4642-7.

14. Parthasarathy S, Raghavamenon A, Garelnabi MO, Santanam N. Oxidized Low-Density Lipoprotein. En: Uppu RM, Murthy SN, Pryor WA, Parinandi NL, editores. Free Radicals and Antioxidant Protocols [Internet]. Totowa, NJ: Humana Press; 2010 [citado 2 de noviembre de 2023]. p. 403-17. (Methods in Molecular Biology; vol. 610). Disponible en: http://link.springer.com/10.1007/978-1-60327-029-8_24

15. Luan Y yi, Yao Y ming. The Clinical Significance and Potential Role of C-Reactive Protein in Chronic Inflammatory and Neurodegenerative Diseases. Front Immunol. 7 de junio de 2018;9:1302.

16. Kozijn AE, Tartjiono MT, Ravipati S, Van Der Ham F, Barrett DA, Mastbergen SC, et al. Human C-reactive protein aggravates osteoarthritis development in mice on a high-fat diet. Osteoarthritis Cartilage. enero de 2019;27(1):118-28.

17. Chhana A, Callon KE, Pool B, Naot D, Gamble GD, Dray M, et al. The Effects of Monosodium Urate Monohydrate Crystals on Chondrocyte Viability and Function: Implications for Development of Cartilage Damage in Gout. J Rheumatol. diciembre de 2013;40(12):2067-74.

18. Felson DT, Hodgson R. Identifying and Treating Preclinical and Early Osteoarthritis. Rheum Dis Clin N Am. noviembre de 2014;40(4):699-710.

19. Malempati C, Jacobs CA, Lattermann C. The Early Osteoarthritic Knee. Clin Sports Med. julio de 2017;36(3):587-96.

20. Brockman BS, Maupin JJ, Thompson SF, Hollabaugh KM, Thakral R. Complication Rates in Total Knee Arthroplasty Performed for Osteoarthritis and Post-Traumatic Arthritis: A Comparison Study. J Arthroplasty. febrero de 2020;35(2):371-4.

21. Beswick AD, Wylde V, Gooberman-Hill R, Blom A, Dieppe P. What proportion of patients report long-term pain after total hip or knee replacement for osteoarthritis? A systematic review of prospective studies in unselected patients. BMJ Open. 2012;2(1):e000435.

22. Dowsey MM, Nikpour M, Dieppe P, Choong PFM. Associations between pre-operative radiographic changes and outcomes after total knee joint replacement for osteoarthritis. Osteoarthritis Cartilage. octubre de 2012;20(10):1095-102.

23. Niinimäki TT, Murray DW, Partanen J, Pajala A, Leppilahti JI. Unicompartmental knee arthroplasties implanted for osteoarthritis with partial loss of joint space have high re-operation rates. The Knee. diciembre de 2011;18(6):432-5.

24. Kanamoto T, Mae T, Yokoyama T, Tanaka H, Ebina K, Nakata K. Significance and definition of early knee osteoarthritis. Ann Jt. enero de 2020;5:4-4.

25. Mahmoudian A, Lohmander LS, Mobasheri A, Englund M, Luyten FP. Early-stage symptomatic osteoarthritis of the knee — time for action. Nat Rev Rheumatol. octubre de 2021;17(10):621-32.

26. Madry H, Luyten FP, Facchini A. Biological aspects of early osteoarthritis. Knee Surg Sports Traumatol Arthrosc. marzo de 2012;20(3):407-22.

27. Rondanelli M, Braschi V, Gasparri C, Nichetti M, Faliva MA, Peroni G, et al. Effectiveness of Non-Animal Chondroitin Sulfate Supplementation in the Treatment of Moderate Knee Osteoarthritis in a Group of Overweight Subjects: A Randomized, Double-Blind, Placebo-Controlled Pilot Study. Nutrients. 29 de agosto de 2019;11(9):2027.

28. Im GI. The Concept of Early Osteoarthritis and Its Significance in Regenerative Medicine. Tissue Eng Regen Med. junio de 2022;19(3):431-6.

29. Tognolo L, Maccarone MC, De Trane S, Scanu A, Masiero S, Fiore P. Therapeutic Exercise and Conservative Injection Treatment for Early Knee Osteoarthritis in Athletes: A Scoping Review. Medicina (Mex). 3 de enero de 2022;58(1):69.

30. Sun SF, Hsu CW, Lin HS, Liou IH, Chou YC, Wu SY, et al. A single intraarticular platelet-rich plasma improves pain and function for patients with early knee osteoarthritis: Analyses by radiographic severity and age. J Back Musculoskelet Rehabil. 12 de enero de 2022;35(1):93-102.

31. Luyten FP, Denti M, Filardo G, Kon E, Engebretsen L. Definition and classification of early osteoarthritis of the knee. Knee Surg Sports Traumatol Arthrosc. marzo de 2012;20(3):401-6.

32. Favero M, Ramonda R, Goldring MB, Goldring SR, Punzi L. Early knee osteoarthritis: Figure 1. RMD Open. agosto de 2015;1(Suppl 1):e000062.

33. Luyten FP, Bierma-Zeinstra S, Dell'Accio F, Kraus VB, Nakata K, Sekiya I, et al. Toward classification criteria for early osteoarthritis of the knee. Semin Arthritis Rheum. febrero de 2018;47(4):457-63.

34. Mahmoudian A, Lohmander LS, Jafari H, Luyten FP. Towards classification criteria for early-stage knee osteoarthritis: A population-based study to enrich for progressors. Semin Arthritis Rheum. febrero de 2021;51(1):285-91.

35. Emery CA, Whittaker JL, Mahmoudian A, Lohmander LS, Roos EM, Bennell KL, et al. Establishing outcome measures in early knee osteoarthritis. Nat Rev Rheumatol. julio de 2019;15(7):438-48.

36. Mündermann A, Dyrby CO, Andriacchi TP. Secondary gait changes in patients with medial compartment knee osteoarthritis: Increased load at the ankle, knee, and hip during walking. Arthritis Rheum. septiembre de 2005;52(9):2835-44.

37. Wikstrom EA, Tillman MD, Chmielewski TL, Borsa PA. Measurement and Evaluation of Dynamic Joint Stability of the Knee and Ankle After Injury: Sports Med. 2006;36(5):393-410.

38. Riemann BL, Lephart SM. The Sensorimotor System, Part II: The Role of Proprioception in Motor Control and Functional Joint Stability. J Athl Train. enero de 2002;37(1):80-4.

39. Williams GN, Buchanan TS, Barrance PJ, Axe MJ, Snyder-Mackler L. Quadriceps Weakness, Atrophy, and Activation Failure in Predicted Noncopers after Anterior Cruciate Ligament Injury. Am J Sports Med. marzo de 2005;33(3):402-7.

40. Suter E, Herzog W. Does muscle inhibition after knee injury increase the risk of osteoarthritis? Exerc Sport Sci Rev. enero de 2000;28(1):15-8.

41. Hubley-Kozey CL, Deluzio KJ, Landry SC, McNutt JS, Stanish WD. Neuromuscular alterations during walking in persons with moderate knee osteoarthritis. J Electromyogr Kinesiol. agosto de 2006;16(4):365-78.

42. Li H, Hu S, Zhao R, Zhang Y, Huang L, Shi J, et al. Gait Analysis of Bilateral Knee Osteoarthritis and Its Correlation with Western Ontario and McMaster University Osteoarthritis Index Assessment. Med Kaunas Lith. 9 de octubre de 2022;58(10):1419.

43. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JPA, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. PLoS Med. 21 de julio de 2009;6(7):e1000100.

44. Von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. J Clin Epidemiol. abril de 2008;61(4):344-9.

45. Runhaar J, Kloppenburg M, Boers M, Bijlsma JWJ, Bierma-Zeinstra SMA, and the CREDO expert group. Towards developing diagnostic criteria for early knee osteoarthritis: data from the CHECK study. Rheumatology. 14 de mayo de 2021;60(5):2448-55.

46. Migliore A, Scirè CA, Carmona L, Beaumont GH, Bizzi E, Branco J, et al. The challenge of the definition of early symptomatic knee osteoarthritis: a proposal of criteria and

red flags from an international initiative promoted by the Italian Society for Rheumatology. Rheumatol Int. agosto de 2017;37(8):1227-36.

47. Migliore A, Bizzi E. THE CHALLENGE OF EARLY KNEE OSTEOARTHRITIS. Reumatizam, Suppl 1:14-17; 2015.

48. Vittecoq O, Rottenberg P, Lequerré T, Michelin P. Enfoque diagnóstico y terapéutico del dolor de rodilla en el adulto (en ausencia de traumatismo). EMC - Tratado Med. septiembre de 2018;22(3):1-10.

49. Sukerkar PA, Doyle Z. Imaging of Osteoarthritis of the Knee. Radiol Clin North Am. julio de 2022;60(4):605-16.

50. Lee LS, Chan PK, Fung WC, Chan VWK, Yan CH, Chiu KY. Imaging of knee osteoarthritis: A review of current evidence and clinical guidelines. Musculoskeletal Care. septiembre de 2021;19(3):363-74.

51. Liew JW, King LK, Mahmoudian A, Wang Q, Atkinson HF, Flynn DB, et al. A scoping review of how early-stage knee osteoarthritis has been defined. Osteoarthritis Cartilage. septiembre de 2023;31(9):1234-41.

52. Englund M, Roos EM, Lohmander LS. Impact of type of meniscal tear on radiographic and symptomatic knee osteoarthritis: A sixteen-year followup of meniscectomy with matched controls. Arthritis Rheum. agosto de 2003;48(8):2178-87.

53. Harkey MS, Baez S, Lewis J, Grindstaff TL, Hart J, Driban JB, et al. Prevalence of Early Knee Osteoarthritis Illness Among Various PATIENT-REPORTED Classification Criteria After Anterior Cruciate Ligament Reconstruction. Arthritis Care Res. marzo de 2022;74(3):377-85.

54. Previtali D, Andriolo L, Di Laura Frattura G, Boffa A, Candrian C, Zaffagnini S, et al. Pain Trajectories in Knee Osteoarthritis—A Systematic Review and Best Evidence Synthesis on Pain Predictors. J Clin Med. 1 de septiembre de 2020;9(9):2828.

55. Halilaj E, Le Y, Hicks JL, Hastie TJ, Delp SL. Modeling and predicting osteoarthritis progression: data from the osteoarthritis initiative. Osteoarthritis Cartilage. diciembre de 2018;26(12):1643-50.

56. Choi, Jo, Park, Kang, Park. NF-B Signaling Pathways in Osteoarthritic Cartilage Destruction. Cells. 17 de julio de 2019;8(7):734.

57. Su Z, Zong Z, Deng J, Huang J, Liu G, Wei B, et al. Lipid Metabolism in Cartilage Development, Degeneration, and Regeneration. Nutrients. 25 de septiembre de 2022;14(19):3984.

58. Hanada M, Takahashi M, Furuhashi H, Koyama H, Matsuyama Y. Elevated erythrocyte sedimentation rate and high-sensitivity C-reactive protein in osteoarthritis of the knee: relationship with clinical findings and radiographic severity. Ann Clin Biochem Int J Lab Med. septiembre de 2016;53(5):548-53.

59. Jin X, Beguerie JR, Zhang W, Blizzard L, Otahal P, Jones G, et al. Circulating C reactive protein in osteoarthritis: a systematic review and meta-analysis. Ann Rheum Dis. abril de 2015;74(4):703-10.

60. Hwang H, Yang C, Park S, Kim H. Monosodium Urate Crystal-Induced Chondrocyte Death via Autophagic Process. Int J Mol Sci. 8 de diciembre de 2015;16(12):29265-77.

61. Shi Y. Caught red-handed: uric acid is an agent of inflammation. J Clin Invest. 1 de junio de 2010;120(6):1809-11.

IX.ANEXOS:

IX.1 Escalas:

IX.1.1 WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index.

Instructions: Please rate the activities in each category according to the following scale of difficulty:

0 = None, 1 = Slight, 2 = Moderate, 3 = Very, 4 = Extremely

Circle one number for each activity.

Pain

1. Walking 0 1 2 3 4
2. Stair Climbing 0 1 2 3 4
3. Nocturnal 0 1 2 3 4
4. Rest 0 1 2 3 4
5. Weight bearing 0 1 2 3 4

Stiffness

1. Morning stiffness 0 1 2 3 4
2. Stiffness occurring later in the day 0 1 2 3 4

Physical Function

1. Descending stairs 0 1 2 3 4
2. Ascending stairs 0 1 2 3 4
3. Rising from sitting 0 1 2 3 4 4. Standing 0 1 2 3 4
5. Bending to floor 0 1 2 3 4
6. Walking on flat surface 0 1 2 3 4
7. Getting in / out of car 0 1 2 3 4
8. Going shopping 0 1 2 3 4
9. Putting on socks 0 1 2 3 4
10. Lying in bed 0 1 2 3 4
11. Taking off socks 0 1 2 3 4
12. Rising from bed 0 1 2 3 4
13. Getting in/out of bath 0 1 2 3 4
14. Sitting 0 1 2 3 4
15. Getting on/off toilet 0 1 2 3 4
16. Heavy domestic duties 0 1 2 3 4
17. Light domestic duties 0 1 2 3 4

Total Score: _____ / 96 = _____% Comments / Interpretation (to be completed by therapist only):

IX.1.2. KOOS: Knee Injury and Osteoarthritis Outcome Score

INSTRUCTIONS: This survey asks for your view about your knee. This information will help us keep track of how you feel about your knee and how well you are able to perform your usual activities. Answer every question by ticking the appropriate box, only one box for each question. If you are unsure about how to answer a question, please give the best answer you can.

Symptoms
These questions should be answered thinking of your knee symptoms during the last week.

S1. Do you have swelling in your knee?
Never ___ Rarely ___ Sometimes ___ Often ___ Always ___
S2. Do you feel grinding, hear clicking or any other type of noise when your knee moves?
Never ___ Rarely ___ Sometimes ___ Often ___ Always ___
S3. Does your knee catch or hang up when moving?
Never ___ Rarely ___ Sometimes ___ Often ___ Always ___
S4. Can you straighten your knee fully?
Always ___ Often ___ Sometimes ___ Rarely ___ Never ___
S5. Can you bend your knee fully?
Always ___ Often ___ Sometimes ___ Rarely ___ Never ___

Stiffness
The following questions concern the amount of joint stiffness you have experienced during the last week in your knee. Stiffness is a sensation of restriction or slowness in the ease with which you move your knee joint.

S6. How severe is your knee joint stiffness after first wakening in the morning?
None ___ Mild ___ Moderate ___ Severe ___ Extreme ___
S7. How severe is your knee stiffness after sitting, lying or resting later in the day?
None ___ Mild ___ Moderate ___ Severe ___ Extreme ___

Pain
P1. How often do you experience knee pain?
Never ___ Monthly ___ Weekly ___ Daily ___ Always ___

What amount of knee pain have you experienced the last week during the following activities?

P2. Twisting/pivoting on your knee
None ___ Mild ___ Moderate ___ Severe ___ Extreme ___
P3. Straightening knee fully

None ___ Mild ___ Moderate ___ Severe ___ Extreme ___
P4. Bending knee fully
None ___ Mild ___ Moderate ___ Severe ___ Extreme ___
P5. Walking on flat surface
None ___ Mild ___ Moderate ___ Severe ___ Extreme ___
P6. Going up or down stairs
None ___ Mild ___ Moderate ___ Severe ___ Extreme ___
P7. At night while in bed
None ___ Mild ___ Moderate ___ Severe ___ Extreme ___
P8. Sitting or lying
None ___ Mild ___ Moderate ___ Severe ___ Extreme ___
P9. Standing upright
None ___ Mild ___ Moderate ___ Severe ___ Extreme ___

Function, daily living

The following questions concern your physical function. By this we mean your ability to move around and to look after yourself. For each of the following activities please indicate the degree of difficulty you have experienced in the last week due to your knee.

A1. Descending stairs
None ___ Mild ___ Moderate ___ Severe ___ Extreme ___
A2. Ascending stairs
None ___ Mild ___ Moderate ___ Severe ___ Extreme ___
A3. Rising from sitting
None ___ Mild ___ Moderate ___ Severe ___ Extreme ___
A4. Standing
None ___ Mild ___ Moderate ___ Severe ___ Extreme ___
A5. Bending to floor/pick up an object
None ___ Mild ___ Moderate ___ Severe ___ Extreme ___
A6. Walking on flat surface
None ___ Mild ___ Moderate ___ Severe ___ Extreme ___
A7. Getting in/out of car
None ___ Mild ___ Moderate ___ Severe ___ Extreme ___
A8. Going shopping
None ___ Mild ___ Moderate ___ Severe ___ Extreme ___
A9. Putting on socks/stockings
None ___ Mild ___ Moderate ___ Severe ___ Extreme ___
A10. Rising from bed
None ___ Mild ___ Moderate ___ Severe ___ Extreme ___
A11. Taking off socks/stockings
None ___ Mild ___ Moderate ___ Severe ___ Extreme ___
A12. Lying in bed (turning over, maintaining knee position)

None ___ Mild ___ Moderate ___ Severe ___ Extreme ___
A13. Getting in/out of bath
None ___ Mild ___ Moderate ___ Severe ___ Extreme ___
A14. Sitting
None ___ Mild ___ Moderate ___ Severe ___ Extreme ___
A15. Getting on/off toilet
None ___ Mild ___ Moderate ___ Severe ___ Extreme ___ A16. Heavy domestic duties (moving heavy boxes, scrubbing floors, etc)
None ___ Mild ___ Moderate ___ Severe ___ Extreme ___
A17. Light domestic duties (cooking, dusting, etc)
None ___ Mild ___ Moderate ___ Severe ___ Extreme ___

Function, sports and recreational activities

The following questions concern your physical function when being active on a higher level. The questions should be answered thinking of what degree of difficulty you have experienced during the last week due to your knee.

SP1. Squatting
None ___ Mild ___ Moderate ___ Severe ___ Extreme ___
SP2. Running
None ___ Mild ___ Moderate ___ Severe ___ Extreme ___
SP3. Jumping
None ___ Mild ___ Moderate ___ Severe ___ Extreme ___
SP4. Twisting/pivoting on your injured knee
None ___ Mild ___ Moderate ___ Severe ___ Extreme ___
SP5. Kneeling
None ___ Mild ___ Moderate ___ Severe ___ Extreme ___

Quality of Life

Q1. How often are you aware of your knee problem?
Never ___ Monthly ___ Weekly ___ Daily ___ Constantly ___
Q2. Have you modified your life style to avoid potentially damaging activities to your knee?
Not at all ___ Mildly ___ Moderately ___ Severely ___ Totally ___
Q3. How much are you troubled with lack of confidence in your knee?
Not at all ___ Mildly ___ Moderately ___ Severely ___ Extremely ___
Q4. In general, how much difficulty do you have with your knee?
None ___ Mild ___ Moderate ___ Severe ___ Extreme ___

IX.2 Artículos publicados:

Article published online: 2023-10-24

Classification Criteria For Early Knee Osteoarthritis: A Review Article

Klassifikationskriterien für frühe Kniegelenksarthrose: ein Übersichtsartikel

OPEN ACCESS

Authors

Luz Herrero-Manley[1], Ana Alabajos-Cea[1], Luis Suso-Martí[2], Enrique Viosca-Herrero[1]

Affiliations

1 Rehabilitation, Hospital La Fe, Valencia, Spain

2 FISIOTHERAPY, Universidad de Valencia, Valencia, Spain

Key words

diagnosis criteria, early osteoarthritis, knee osteoarthritis

Schlüsselwörter

Diagnosekriterien, Arthrose im Knie, Arthrose im Frühstadium

published online 2023

Bibliography

Akt Rheumatol

DOI 10.1055/a-2173-1607

ISSN 0341-051X

Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany

Correspondence

Dr. Luz María Herrero-Manley
Hospital La Fe
Rehabilitation
calle navarra 5
46006 Valencia
Spain
Tel.: 626430138
luzherreromanley@gmail.com

ABSTRACT

Objective The aim of this systematic review (SR) was to define the "state of the art" on classification criteria for early knee osteoarthritis (EKOA).

Methods A systematic review was performed using MEDLINE (Pubmed), Web of Science, Scopus, EMBASE, PEDro, CINAHL and Google scholar databases. Two independent reviewers conducted the eligibility review. Any type of study that proposed diagnostic criteria of EKOA was included.

Results Seven articles were included according to the inclusion criteria. The evidence presented in this SR shows that there is still no consensus regarding definition and classification of EKOA. At present, there are seven different proposals in the scientific literature, and they only agree on including knee pain and radiographic evaluation in their criteria, but they do not even consider the same situations for including these two factors.

Conclusion There is still no consensus regarding definition and classification of EKOA. Knee pain and radiological assessment seem to be the most commonly used criteria, but due to the variability encountered, it is not possible to reach a consensus on a clear definition and diagnosis of EOKA.

Introduction

Knee Osteoarthritis (KOA) is a major cause of joint pain, resulting in a marked reduction of quality of life and relevant costs to societies worldwide [1]. It is heterogeneous in terms of risk factors and rates of progression. This poses the challenge of stratifying patients with KOA, and proper classification criteria are essential [1]. Altman and colleagues developed the "ACR criteria" for KOA, used as diagnostic outcome criteria in Osteoarthritis (OA) research [2]. However, patients who meet the ACR criteria, already have significant structural joint damage. Subsequently, EULAR and also the National Institute for Health and Care Excellence (NICE) published diagnostic criteria for KOA [3, 4].

Kanamoto et al. highlight that a shift in focus towards early diagnosis is needed, suggesting that KOA progression may be delayed through early diagnosis before the joint is irreversibly destroyed [5]. Therefore, early diagnosis of KOA could be of significant importance for both healthcare and research purposes. It has been suggested that treatments such as Chondroitin sulfate or regenerative medicine for early knee OA (EKOA) could help in delaying the progression of OA and in pain reduction [6, 7]. However, regenerative treatments seem to yield better results when the joint damage is minimal, hence the importance of defining a reliable diagnosis of EKOA [7].

In the last few years several diagnostic criteria and a specific definition of EKOA have been proposed for diagnosing patients with EKOA [8, 9]. Knee pain is one of the established criteria. Nevertheless, it is important to acknowledge that knee pain can arise from various causes apart from OA. Therefore, exclusion criteria such as generalized pain, inflammatory joint disease and recent trauma or injury were proposed by Migliore et al.[10]. The aim of this systematic review (SR) was to define the ''state of the art'' on classification criteria for EKOA.

Methods

This SR was performed in accordance with a predefined protocol based in the PRISMA statement [11]. The PRISMA statement is composed of a 27-item checklist and a four-phase flow diagram, which assists in reporting systematic reviews [11].

Inclusion Criteria of the Studies

The selection criteria used in this review are based on methodological aspects as follows:

Population: Patients with early knee OA.

Outcomes: Only articles that presented diagnostic criteria or specific aspects for EKOA classification were included. These criteria could refer to clinical and radiological aspects, as well as any other type of measurement that facilitates the diagnosis of these patients.

Study design: Any type of study that proposed diagnostic criteria was included. Studies without language restriction were included, and articles published in the last 10 years were selected.

Search Strategy

Two independent reviewers conducted a search of scientific articles generating an agreement for the initial selection of the studies, after which the concordances were searched. The search of scientific articles was performed using the Medline (Pubmed), Web of Science, Scopus, Embase, Pedro, Cinahl and Google scholar databases. This search phase was concluded on April, 2021.

In these databases we used the following search terms and combinations: "Early osteoarthritis" AND "Classification", "Early osteoarthritis" AND "diagnose", "Early osteoarthritis" AND "criteria", "Early osteoarthritis".

Selection Criteria and Data Extraction

First, an analysis of information was carried out by two independent reviewers who evaluated the relevance of the studies in relation to the question and the objective of the investigation. This first analysis was made based on the information of the title, summary, and keywords of each study. In case there was no consensus, or the abstracts did not contain the necessary information, the full text was accessed. In a second phase of analysis, considering the full text, it was checked whether the studies met the inclusion criteria. The differences between reviewers were resolved by moderate consensus by a third reviewer. The data described in the results were extracted by means of the structured protocol that guarantees obtaining the most relevant information of each study [12].

Results

The study search strategy is shown in the form of a flow chart (▶ **Fig. 1**). Seven articles that met the inclusion criteria were selected.

Characteristics of the included studies

All seven studies proposed diagnostic classifications of EKOA or criteria for its diagnosis. The main characteristics of the studies are explained in ▶ **Table 1**.

First, two of the most recognized are those of Luyten et al., 2012 and 2018. In these studies, the authors carried out teamwork through workshops in multidisciplinary teams of physicians, physiotherapists, and surgeons, making diagnostic criteria based on the consensus. Furthermore, Mahmoudian et al., 2021 performed an analysis of the Luyten criteria using data from the Osteoarthritis Initiative. In addition, these authors performed a logistic regression analysis to evaluate the predictive performance of the criteria set for structural as well as clinical progression. On the other hand, Runhaar et al., 2020 conducted a CHECK study based on the screening of patients by experts in the field through a cohort study, which was subsequently used to create predictive models. Migliore and his group of collaborators conducted in 2015 a systematic review and definition of EKOA from a committee of experts. Subsequently, in 2017 they conducted an in-depth analysis using three focus groups, including expert clinicians, researchers, and patients; a systematic literature review and two discussion groups followed by a Delphi survey. Finally, Emery et al. performed a narrative review with consensus expert criteria.

Clinical criteria

Luyten et al. included the criteria "pain in the knee" defined as at least two episodes of pain for more than 10 days in the last year, in their 2012 criteria, and then in 2018 criteria they made a wider clinical approach through the patient-based questionnaires, Knee Injury and Osteoarthritis Outcome score (KOOS), needing to score

"positive" (≤ 85 %) 2 out of the 4 KOOS subscales (Pain, Symptoms, Function or Knee-related quality of life), and patients should present joint line tenderness (JLT) or crepitus in the clinical examination. Mahmoudian et al, in their review of Luyten's 2018 criteria, proposed changing the assessment of KOOS to use a single KOOS4 score (the average of four of the five KOOS subscales: pain, symptoms, ADL and quality of life) as well as 5 scores below and above the known threshold (≤ 80, ≤ 85, and ≤ 90), finding the best predictive performance for structural progression and clinical progression in KOOS4 ≤ 90 % and KOOS4 ≤ 80 %, respectively. Also, they examined the predictive ability of two more clinical variables, the presence of "effusion" and "Heberden's nodes". Migliore et al. on their paper in 2015 identified two major signs/symptoms: knee pain and very short joint stiffness when starting a movement lasting for less than 6 months. Early symptomatic knee OA (ESKOA) was then defined by the presence of 3 or more symptoms in the absence of risk factors, 2 or more symptoms and 1 risk factor, or 2 or more risk factors and 1 or more symptoms with a symptom duration of less than 6 months. The risk factors included were overweight with a BMI over 25, family history of OA, previous knee injuries, malalignment, lower limbs dissymmetry, OA in other sites, metabolic syndrome, and hypermobility. They integrated the signs and symptoms in a single referral criterion in order to improve applicability: "The presence of knee pain, in the absence of any recent trauma or injury, with or without joint stiffness, with symptoms lasting for less than 6 months". In 2017 the authors refined these criteria defining ESKOA when (a) two mandatory symptoms (knee pain in the absence of any recent trauma or injury and very short joint stiffness, lasting for less than 10 min, when starting movement) even in the absence of risk factors, or (b) knee pain, and 1 or 2 risk factors or (c) three or more risk factors in the presence of at least one mandatory symptom, with symptoms lasting less than 6 months. Runhaar et al. identified different sets of factors related to the onset of EKOA including questionnaires (WOMAC pain—stairs, WOMAC pain—night, WOMAC function—rising, WOMAC function—descending, WOMAC morning stiffness), sex (female), age, JLT, effusion, BMI and crepitus. Emery et al. included in their suggestions of outcome measures for clinical practice and research settings the use of KOOS and the Intermittent and Constant Assessment of Pain (ICOAP) as patient-reported measures. They also suggested the assessment of the JLT in subjects with new-onset symptoms of knee pain, stiffness, crepitus, or a feeling of 'giving way'. These authors also included in their proposal physical function and modifiable lifestyle-related outcomes, such as the single leg hop test, the 30-second chair sit-to-stand test, the star excursion balance test, and measures of quadriceps strength in the first group, and the assessment of adiposity (through dual-energy X-ray absorptiometry or bioelectrical impedance analysis if available, or BMI other case) and levels of physical activity (through a validated physical activity monitor or a validated questionnaire) in the second one.

Imaging criteria

Luyten et al. 2012 criteria included two imaging aspects: standard radiographs Kellgren and Lawrence (KL) grade 0 or 1 or 2 (osteophytes only), and at least one of two structural criteria (Arthroscopic findings of cartilage lesions (ICRS grade I-IV in at least two compartments or grade II-IV in one compartment with surrounding softening and swelling) or at least two MRI findings demonstrating articular cartilage degeneration, and/or meniscal degeneration, and/or subchondral BMLs: Cartilage morphology WORMS 3–6, Cartilage BLOKS grade 2 and 3, Meniscus BLOKS grade 3 and 4, BMLs WORMS 2 and 3). In the 2018 criteria, the authors simplified this point to KL grade 0–1, gaining more importance the clinical aspects. Mahmoudian et al. proposed to limit these criteria to including only subjects with KL grade 1. Migliore et al. established in 2015 an applicability criterion for the presence of KL grade 0, and maintained it the same in their 2017 version of the criteria. Runhaar et al. included the radiographic factors lateral joint space narrowing (JSN), bony swelling, medial JSN, and patellofemoral JSN for consideration. Emery et al. considered that standardized measures of plain radiography does not reach the same degree of sensitivity to change in knee OA as MRI, and that the radiographic features are associated with late-stage OA and are detected earlier by MRI. Sukerkar et al. advocate the advantages of MRI in both detecting EKOA and in research. Also, Lee et al. argue that MRI is the most precise imaging modality for KOA as it can even differentiate between patients at risk of knee OA and those who are not.

However, they do not consider the use of MRI for routine clinical care appropriate because of its high cost, long scanning times, limited availability and potential risk of over-diagnosis, given the high prevalence of MRI findings in asymptomatic patients. Although, it could be useful in a research setting.

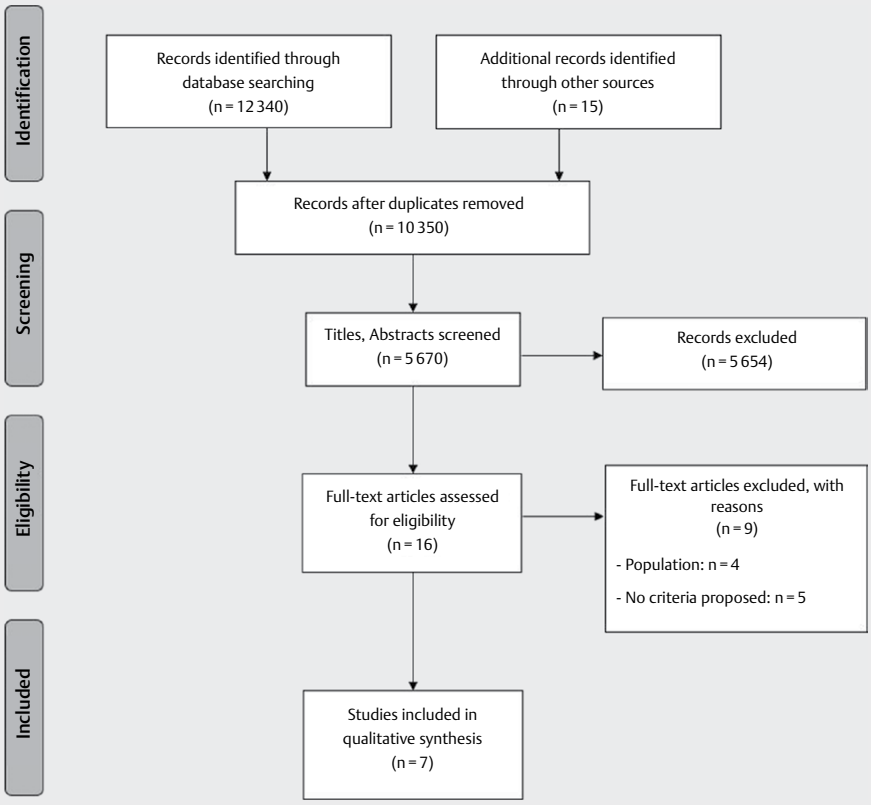
Other criteria

Runhaar et al. also included the hsCRP in one of their models, but they stated it did not add much value. Emery et al. suggested, for the research setting only, the use of biomechanical and biomarkers outcomes, although the last ones would need further validation. The rest of the authors did not include laboratory or biomechanical tests in their criteria.

Similarities and different between criteria

Analyzing the similarities between the different criteria, we find pain is the most constant factor, being included by all the authors, although in different ways, as ▶ **Table 2** summarizes. Questionnaires are present in Luyten's 2018 and Mahmoudian modification as KOOS, and in Runhaar's criteria as WOMAC. Emery et al. also include the KOOS, and add the ICOAP. Crepitus and effusion appear in Mahmoudian and Runhaar's, being the first one also present in Luyten's 2018 and Emery's. Joint stiffness is included in both Migliore's 2015 and 2017, and Emery's proposals, and BMI is present in Migliore's 2015, Runhaar's and Emery's criteria (▶ **Table 2**).

Regarding imaging criteria, all authors except Emery et al. agree in including radiograph features in their criteria, specifically 5 authors include the KL index, although they differ in the grade to consider. Runhaar et al. do not take into account KL as such, but some specific radiographic features. Only Luyten's 2012 include structural criteria through one of two of arthoscopic or MRI findings. Emery et al. only consider the use of MRI for research (▶ **Table 3**). And finally, Runhaar et al. consider a laboratory factor, and Emery et al. include biomarkers and biomechanical outcomes for research, as commented before.



▶ **Fig. 1** Study Flow chart.

Discussion

The evidence presented in this SR shows that there is still lacking a consensus regarding definition and classification of EKOA. In this review there are seven different proposals in scientific literature, and they only agree on including knee pain and radiographic evaluation in their criteria, but they do not even consider the same situations for including these two factors.

The main objective in defining the criteria for EKOA diagnosis is to be able to stop the evolution of this process. In addition, assessing EKOA is mandatory for OA reseach and is important as a clear-cut inclusion criteria for research to identify potential study participants.

However, if we consider that radiological findings should be included in the diagnosis, these are probably of limited use as EKOA progression has most likely already begun and it could be too late to carry out preventive measures for EKOA evolution. Therefore, we need to find a consensus between subjective symptoms such as pain, physical examination findings and a more objective criteria which could add reliability to the diagnosis of EKOA.

Regarding the therapeutic consequences, it is known that the initial treatment of symptoms of EKOA does not differ from other causes of knee pain as it is based on analgesic medication. However, an increasing number of studies suggest more specific treatments for knee pain secondary to OA, such as Chondroitin sulfate of non-animal origin or regenerative medicine [6, 7]. This again underlines the importance of identifying patients whose knee pain is caused by EKOA, as there are many other causes of knee pain where treatment differs. For instance, patellar tendinopathy could be treated with extra corporeal shock wave therapy [13], or knee pain due to anserine bursitis can be treated with aspiration, and corticosteroid injection [14]. In conclusion, for successful treatment of knee pain a specific diagnosis and course of treatment is required.

Clinical features

Experts agree that pain is the primary criteria for the classification of symptomatic EKOA [10, 15–17], despite pain and radiographic severity are not synonymous as there are subsets of OA patients with severe pain and mild radiographic changes, and those with mild or no pain despite severe radiographic changes [18, 19]. Joint line tenderness and crepitus are clinical features easy to examine, in clinical practice as well as for research purposes, and they might be associated with the development of OA in the future, even in the absence of radiological findings of OA [15–18].Effusion has also been considered by some authors, based on a study of the OAI cohort showing the association of joint effusion at baseline with future cartilage volume loss, progression of radiographic OA, and risk of total knee replacement over 4 years [16–18].

A systematic review showed a moderate level of evidence supporting a relationship between obesity (increasing weight, BMI or total body fat mass) and the presence of BMLs in the knee in individuals with OA [20], and total fat mass is also associated with the

presence of BMLs in healthy individuals and with knee cartilage defects [17, 21].

Functional features

It has been suggested that symptoms of EKOA might be not only pain but also the disturbance of ADLs because of a functional impairment [22]. This and the fact that early pre-radiographic OA is associated with intermittent symptoms and adaptive physical behavior support the incorporation of measures of physical function in the clinical evaluation of these patients. But no consensus exists regarding which measures are the most relevant for this end [17], being simple tests such as walking speed, chair rise, and simple muscle strength tests, among others, some of the suggested measures [15, 23].

Decary et al. made a SR on the reliability of physical examination tests for knee disorders. All OA tests demonstrated moderate intra-rater reliability, but tests that reached moderate inter-rater reliability came from low-quality evidence [23]. Due to the challenge of performing objective functional tests in primary care, and this low reliability of physical examination, the use of patient-reported outcomes, such as KOOS, WOMAC and ICOAP, has been suggested to assess functional features [15–18]. These patient-reported outcomes have been the subject of previous reviews in OA population, showing an acceptable reliability, validity, and ability to detect change. Although it should be taken into account that these tests seem to be responsive to change in patients with a variety of conditions, not only knee OA, and their ability to detect change has not been tested for healthy subjects in risk of developing OA or in EKOA [24, 25].

Imaging features

OA is a whole-joint disease involving multiple tissue pathologies. A number of different imaging modalities have been used to characterize the various structural components involved in OA, being radiography, and MRI the most used [17]. Almost all authors agree that radiography remains the primary imaging modality in OA research and in daily clinical practice, despite their known limitations, such as the detection of changes in a late-stage OA and a lower sensitivity than MRI [12, 15, 16, 18].Radiographic features of OA are generally classified using the KL grading system which includes JSN, osteophyte formation, sclerosis and deformity of bony contours [26]. But there is a serious lack of consensus regarding the KL grade to consider for early OA classification. Luyten et al. 2018 considered the variability of scoring of grade 2 across different centers and cohorts, and they agreed that, in the absence of obvious alternatives with significantly better performance, a KL grade of 0 or 1 should be used in the classification criteria [13]. Mahmoudian et al. limited these classification criteria to only subjects with KL grade 1, based on previous reports showing a strong association between this KL grade 1 and an increased risk of developing radiographic knee OA [16]. Migliore et al., for their part, established that any radiographic changes, in symptomatic patients, should be considered as an established disease rather than an early radiographic disease, and exclude the KL > 0 of their criteria [12].

On the other hand, preradiographic joint changes detectable on MRI may predict incident radiographic knee OA by several years, but MRI shows lesions in the tibiofemoral joint in most middle-aged and older people with no evidence of radiographic OA, regardless of pain [16]. Defining what changes are pathological and what changes are part of a normally ageing joint to avoid over-diagnosis because of incidental MRI findings, remains a challenge [17]. Luy-

▶ **Table 1** Main characteristics of the included studies.

Study	Type	Criteria
Luyten FP., 2018	Group of experts	Luyten's criteria for classifying EOA patients: (a) Patient-based questionnaires:Knee Injury and Osteoarthritis Outcome score: 2 out of the 4 KOOS subscales (Pain, Symptoms, Function or Knee-related quality of life) need to score "positive" (≤ 85 %); (b) Patients should present joint line tenderness or crepitus in the clinical examination; (c) X-rays: Kellgren and Lawrence (KL) grade 0–1 standing, weight bearing (at least 2 projections: PA fixed flexion and skyline for patellofemoral OA)
Luyten FP., 2012	Group of experts	1. Pain in the knee (at least two episodes of pain for more than 10 days in the last year) 2. Standard radiographs Kellgren–Lawrence grade 0 or I or II (osteophytes only). 3. 3. At least one of the two following structural criteria ▪ Arthroscopic findings of cartilage lesions (ICRS grade I-IV in at least two compartments or grade II-IV in one compartment with surrounding softening and swelling) ▪ MRI findings demonstrating articular cartilage degeneration and/or meniscal degeneration, and/or subchondral BMLs. At least two: Cartilage morphology WORMS 3–6 Cartilage BLOKS grade 2 and 3 Meniscus BLOKS grade 3 and 4 BMLs WORMS 2 and 3

▶ **Table 1** Continued.

Study	Type	Criteria
Mahmoudian, 2021	Test previous criteria using regression analysis	▪ X-ray examination: limiting inclusion to only subjects with KL grade 1. ▪ Clinical examination: examined the predictive ability of two more variables, the presence of "effusion" and "Heberden's nodes" ▪ Patient-based questionnaires: using a single KOOS4 score (the average of four of the five KOOS subscales: pain, symptoms, ADL and QoL) as well as 5 scores below and above the known threshold (≤ 80, ≤ 85, and ≤ 90)
		Ninety different combinations of the criteria, studying the best predictive performance for clinical and structural progression separately: ▪ Structural progression: the best predictive performance for the criteria set of: KL 1-only, KOOS4 ≤ 90 % and inclusion of (presence of) Heberden's nodes in the combination of clinical examinations (sensitivity of 42.0–43.9 and specificity of 84.0–84.6). (AUCs) for all prediction models ranged from 0.70 to 0.73 [CI, 0.700.75]. ▪ Clinical progression: the best predictive performance was found for KL 0–1, KOOS4 ≤ 80 % and presence of Heberden's nodes in addition to other clinical examinations. (AUCs) for all prediction models ranged from 0.66 to 0.69 [CI, 0.660.71].
Runhaar, 2020	Cohort Knee (CHECK) + Expert diagnosis	Questionnaire and physical examination items at baseline Odds ratio (95 % CI) WOMAC pain—stairs 1.99 (1.36, 2.92) WOMAC pain—night 1.52 (1.06, 2.20) WOMAC function—rising 1.61 (1.08, 2.39) Sex (female) 1.87 (1.20, 2.92) Joint line tenderness 2.36 (1.73, 3.22) Effusion 1.86 (1.09, 3.16) BMI 1.07 (1.03, 1.12) Pooled AUC (pooled S.D.) 0.746 (0.002) Questionnaire, physical examination and radiographic items at baseline Odds ratio (95 % CI) WOMAC pain—stairs 1.98 (1.34, 2.90) WOMAC pain—night 1.53 (1.06, 2.20) WOMAC function—rising 1.58 (1.06, 2.35) Sex (female) 1.81 (1.16, 2.83) Joint line tenderness 2.29 (1.68, 3.13) Effusion 1.85 (1.09, 3.15) BMI 1.07 (1.03, 1.12) Crepitus 1.32 (0.96, 1.81) Lateral JSN 5.32 (1.14, 24.88) Pooled AUC (pooled S.D.) 0.749 (0.002) Questionnaire, physical examination and radiographic items and hsCRP at baseline Odds ratio (95 % CI) WOMAC pain—stairs 2.05 (1.39, 3.03) WOMAC pain—night 1.55 (1.07, 2.24) WOMAC function—rising 1.67 (1.11, 2.49) Sex (female) 1.90 (1.22, 2.97) Joint line tenderness 2.43 (1.78, 3.32) Effusion 1.84 (1.08, 3.13) BMI 1.08 (1.03, 1.13) Lateral JSN 4.66 (1.01, 21.65) hsCRP 0.95 (0.90, 0.99) Pooled AUC (pooled S.D.) 0.756 (0.002

▶ **Table 1** Continued.

Study	Type	Criteria
Migliore, 2015	SR + focus groups + discussion groups + Delphi surveys + face-to-face meetings	**Exclusion criteria:** ▪ presence of generalized pain ▪ active inflammatory joint disease ▪ Kellgren-Lawrence radiologic degree above 0 ▪ any recent trauma or injury of the knee
		Two major signs/symptoms: ▪ knee pain ▪ very short joint stiffness when starting a movement. ▪ Lasting for less than 6 months.
		Applicability criteria: ▪ absence of inflammatory arthritis ▪ age of 50 years or older, or ▪ age of 40 years or older with the presence of at least 1 risk factor ▪ Kellgren Lawrence grade 0
		Definition: ▪ 3 or more symptoms in the absence of risk factors ▪ 2 or more symptoms and 1 risk factor ▪ 2 or more risk factors and 1 or more symptoms Symptom duration of less than 6 months.
		Risk factors: ▪ overweight with a BMI over 25 ▪ family history of OA ▪ previous knee injuries ▪ malalignment ▪ lower limbs dissymmetry ▪ OA in other sites ▪ metabolic syndrome ▪ hypermobility
		Referral criterion for the identification of patients affected by ESKOA: The presence of knee pain, in the absence of any recent trauma or injury, with or without joint stiffness, with symptoms lasting for less than 6 months.
Migliore, 2017	Expert consensus + review	**Applicability criteria:** ▪ Without active inflammatory arthritis or generalized pain ▪ More than 50 years ▪ More than 40 years if at least one risk factor present ▪ Kellgren and Lawrence = 0 ▪ Absence of any recent trauma or injury
		Definition: ▪ In the absence of risk factors 2 mandatory symptoms are necessary ▪ In the presence of 1 or 2 risk factors, presence of at least mandatory symptom number 1 is necessary ▪ In the presence of three or more risk factors, at least one mandatory symptom is necessary Mandatory (major) symptoms: (1) Any knee pain (in the absence of any recent trauma or injury) i. e. Pain when climbing up and/or down the stairs , Pain increasing with overload (2) Very short joint stiffness (less than 10 min) when starting the movement
		Risk factors: ▪ Overweight (body mass index > 25) ▪ Family history of OA ▪ Previous knee injury ▪ Malalignment ▪ Lower limbs dissymmetry ▪ OA in other sites ▪ Metabolic syndrome ▪ Not being ready to run or walk fast after a period of inactivity
		Symptoms duration: Less than 6 months

▶ **Table 1** Continued.

Study	Type	Criteria
		Referral criterion for the identification of patients affected by ESKOA: Knee pain, in the absence of any recent trauma or injury, with or without very short joint stiffness when starting a movement, with symptoms lasting for less than 6 months
Emery, 2019	Narrative review	**In clinical practice and research settings:** Patient-reported outcomes: ▪ KOOS can be used to measure pain during activity, other symptoms (for example, stiffness, grinding, catching, swelling, knee flexion and extension), function in daily life and during sport and recreational activities, and quality of life across different age and treatment groups. ▪ The Intermittent and Constant Assessment of Pain (ICoAP) questionnaire can be used to evaluate constant and intermittent pain. Clinical features: A clinical assessment including joint line tenderness should be performed in individuals with new-onset symptoms of knee pain, stiffness, crepitus or a feeling of 'giving way'. Physical function outcomes: single leg hop test, the 30-second chair sit-to-stand test, the star excursion balance test and measures of quadriceps strength. Modifiable lifestyle-related outcomes: Adiposity can be assessed by measuring body fat percentage or fat mass index (fat mass in kilograms/height in metres squared) using dual-energy X-ray absorptiometry or bioelectrical impedance analysis if available. BMI is more feasible in the clinical setting, although it has limitations for use in athletes. Levels of physical activity can be assessed using a validated physical activity monitor or a validated questionnaire if objective methods are not available. Nutrition outcomes are not currently suggested for use in routine clinical care; however, the 3-day dietary record provides reliable estimates of nutrient intake.
		In research setting only: Biomechanical outcomes: Measures of biomechanical outcomes require further research and are not currently suggested for use in routine clinical care. However, such outcomes are ideal for informing the underlying mechanisms of OA progression and informing treatment interventions in the research setting.
		Imaging features: The utility of plain radiography in early OA is limited. Although MRI has superior sensitivity to change, has validity in the context of early OA and is hence ideal in the research setting, MRI is not thought appropriate for the routine clinical care setting because of its high cost and potential risk of over-diagnosis.
		Biomarkers: No biomarkers are currently of use in routine clinical care; however, further validation of proteomic, lipidomic and metabolomic tools in the research setting could lead to informative cartilage and synovial fluid profiles and provide important insights into OA progression.

ten et al., who included MRI features in their 2012's criteria, reached the consensus in 2018 that, at present, MRI is not recommended as an aid to identify or define early OA in routine clinical practice or primary care, considering the lack of validated consensus criteria, and the high population prevalence of structural joint changes detected by this method.

Sukerkar et al. also defend the advantages of MRI in detecting EKOA. MRI is recognized for its exceptional cartilage imaging capabilities and its ability to identify initial biochemical alterations related to OA before any visible morphological changes occur [27]. Also, Lee et al. point out MRI notable specifity (82 %) and moderate sensitivity (61 %) in OA detection. Furthermore, MRI can quantify early degenerative cartilage changes in symptomatic patients [28].

However, there is inadequate evidence that MRI is superior to current diagnostic standards of clinical and radiographic evaluation [27, 28].

The arthroscopic evaluation, included in Luyten et al. 2012's criteria, was discarded in their 2018 review of the criteria. The arthroscopic evaluation remains the gold standard for assessing cartilage defects and their reparability, but it cannot determine the cause of the lesion, and is not generally useful in primary care because of its invasive nature [12, 16, 19].

▶ **Table 2** Clinical features of the EOA diagnosis extracted for the included studies.

	Luyten et al. 2012	Luyten et al. 2018	Mahmoudian et al. 2021	Migliore et al. 2015	Migliore et al. 2017	Runhaar et al. 2020	Emery et al. 2019
Pain	Knee pain ≥ 2 episodes > 10 days in the last year	JLT	JLT	Knee pain < 6 months	Knee pain < 10 min, < 6 months	JLT	JLT
Questionnaires	–	KOOS: 2 out of 4 ≤ 85 %	KOOS4 score ≤ 90 % (SP) and ≤ 80 % (CP)	–	–	WOMAC pain—stairs	KOOS
						WOMAC pain—night	ICOAP
						WOMAC function—rising	
						WOMAC function—descending	
						WOMAC morning stiffness	
Crepitus	–	x	x	–	–	x	x
Effusion	–		x	–	–	x	–
Joint stiffness	–	–	–	< 6 months	< 10 min, < 6 months	–	x
BMI	–	–	–	> 25	–	x	x

▶ **Table 3** Imaging features of the EOA diagnosis extracted for the included studies.

	Luyten et al. 2012	Luyten et al. 2018	Mahmoudian et al. 2021	Migliore et al. 2015	Migliore et al. 2017	Runhaar et al. 2020	Emery et al. 2019
Radiograph	KL grade 0–1–2 (osteophytes only)	KL grade 0–1	KL grade 1	KL grade 0	KL grade 0	Lateral JSN	–
						Bony swelling	
						Medial JSN	
						Patellofemoral JSN	
Arthroscopic	ICRS:	–	–	–	–	–	–
	- grade I-IV in ≥ 2 compartments						
	- grade II-IV in 1 compartment with surrounding softening and swelling						
MRI	≥ 2 of:	–	–	–	–	–	In research setting only
	Cartilage morphology WORMS 3–6						
	Cartilage BLOKS grade 2–3						
	Meniscus BLOKS grade 3–4						
	BMLs WORMS 2–3						

In the light of the above analysis of the current criteria, further efforts on the classification of EKOA are still needed, and maybe it should be considered if the classification in this early stage is even possible, given its nature of pre-radiographic stage and the heterogeneity and intermittence of symptoms.

Limitations

There are several limitations to be considered in the interpretation of the results of this systematic review. First, and although a systematic search strategy was followed, the risk of selection bias might still be present. Secondly, the disparity of criteria among the different proposals prevents us from being able to draw solid conclusions about the diagnosis of EKOA. Finally, most of the included studies made proposals based on expert opinion, but few of them evaluated these proposals in experimental studies. Regarding the importance of obtaining objective criteria to confirm EKOA diagnosis, using biomechanical gait parameters could be a point of interest.

Conclusions

There is still lacking a consensus regarding definition and classification of EKOA. Knee pain and radiological assessment seem to be the most commonly used criteria, but due to the variability encountered, it is not possible to reach a consensus on a clear definition and diagnosis of EKOA. Future experimental studies should evaluate these criteria to assess their clinical relevance, as well as to improve their research validity. In order to make reliable diagnoses of EKOA in our daily practice, several criteria could be established, such as pain and patient-reported outcomes.

Conflict of Interest

The authors declare that they have no conflict of interest.

References

[1] Iolascon G, Gimigliano F, Moretti A et al. Early osteoarthritis: How to define, diagnose, and manage. A systematic review. Eur Geriatr Med 2017; 8: 383–396

[2] Altman R, Asch E, Bloch D et al. Development of criteria for the classification and reporting of osteoarthritis: Classification of osteoarthritis of the knee. Arthritis Rheum [Internet] 1986; 29: 1039–1049. Available from: https://pubmed.ncbi.nlm.nih.gov/3741515/

[3] Zhang W, Doherty M, Peat G et al. EULAR evidence-based recommendations for the diagnosis of knee osteoarthritis. Ann Rheum Dis [Internet] 2010; 69: 483–489. Available from: https://pubmed.ncbi.nlm.nih.gov/19762361/

[4] Conaghan P, Birrel F, Porcheret M et al. Osteoarthritis: care and management in adults. Clinical guideline 177. Natl Clin Guidel Cent [Internet] 2014; 1–498. Available from: https://www.ncbi.nlm.nih.gov/books/NBK248069/

[5] Kanamoto T, Mae T, Yokoyama T et al. Significance and definition of early knee osteoarthritis. Ann Jt 2020; 5: 4–4

[6] Rondanelli M, Braschi V, Gasparri C et al Effectiveness of Non-Animal Chondroitin Sulfate Supplementation in the Treatment of Moderate Knee Osteoarthritis in a Group of Overweight Subjects: A Randomized, Double-Blind, Placebo-Controlled Pilot Study. Nutrients 2019; 11: 2027. DOI: 10.3390/nu11092027

[7] Im GI. The Concept of Early Osteoarthritis and Its Significance in Regenerative Medicine. Tissue Eng Regen Med. 2022; 19: 431–436. DOI: 10.1007/s13770-022-00436-6. Epub 2022 Mar 4PMID: 35244885; PMCID: PMC9130436.

[8] Luyten FP, Denti M, Filardo G et al. Definition and classification of early osteoarthritis of the knee. Knee Surgery, Sport Traumatol Arthrosc [Internet] 2012; 20: 401–406. Available from: https://pubmed.ncbi.nlm.nih.gov/22068268/

[9] Kanamoto T, Mae T, Yokoyama T et al. Significance and definition of early knee osteoarthritis. Ann Jt [Internet] 2020; 5: 4–4. Available from: http://aoj.amegroups.com/article/view/5432/html

[10] Migliore A, Scirè CA, Carmona L et al. The challenge of the definition of early symptomatic knee osteoarthritis: a proposal of criteria and red flags from an international initiative promoted by the Italian Society for Rheumatology. Rheumatol Int [Internet] 2017; 37: 1227–1236. Available from: https://pubmed.ncbi.nlm.nih.gov/28451793/

[11] Liberati A, Altman DG, Tetzlaff J et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. Ann Intern Med 2009; 151: W65–W94

[12] Higgins JP, Green S. Cochrane Handbook for Systematic Reviews of Interventions Cochrane Book Series 2008

[13] Muaidi QI. Rehabilitation of patellar tendinopathy. Journal of musculoskeletal & neuronal interactions 2020; 20: 535–540

[14] Hong E, Kraft MC. Evaluating anterior knee pain. The Medical clinics of North America 2014; 98: 697–xi. DOI: 10.1016/j.mcna.2014.03.001

[15] Luyten FP, Bierma-Zeinstra S, Dell'Accio F et al. Toward classification criteria for early osteoarthritis of the knee. Semin Arthritis Rheum [Internet] 2018; 47: 457–463. Available from: https://pubmed.ncbi.nlm.nih.gov/28917712/

[16] Mahmoudian A, Lohmander LS, Jafari H et al. Towards classification criteria for early-stage knee osteoarthritis: A population-based study to enrich for progressors. Semin Arthritis Rheum [Internet] 2021; 51: 285–291. Available from: https://pubmed.ncbi.nlm.nih.gov/33433364/

[17] Emery CA, Whittaker JL, Mahmoudian A et al. Establishing outcome measures in early knee osteoarthritis. Nat Rev Rheumatol [Internet] 2019; 15: 438–448. Available from: https://pubmed.ncbi.nlm.nih.gov/31201386/

[18] Runhaar J, Kloppenburg M, Boers M et al. Towards developing diagnostic criteria for early knee osteoarthritis: data from the CHECK study. Rheumatology [Internet] 2020; 60: 2448–2455. Available from: https://academic.oup.com/rheumatology/article/60/5/2448/6007761

[19] Malempati C, Jacobs CA, Lattermann C. The Early Osteoarthritic Knee: Implications for Cartilage Repair [Internet]. Vol. 36, Clinics in Sports Medicine.W.B. Saunders; 2017: 587–596. Available from: https://pubmed.ncbi.nlm.nih.gov/28577714/

[20] Lim YZ, Wang Y, Wluka AE et al. Association of obesity and systemic factors with bone marrow lesions at the knee: A systematic review. Semin Arthritis Rheum [Internet] 2014; 43: 600–612. Available from: https://pubmed.ncbi.nlm.nih.gov/24287353/

[21] Favero M, Ramonda R, Goldring MB et al. Early knee osteoarthritis [Internet]. Vol. 1, RMD Open.BMJ Publishing Group; 2015 Available from:pmc/articles/PMC4632144/

[22] Uchio Y. Early knee osteoarthritis – definition, pathogenesis, diagnosis, treatment, and prevention. Ann Jt [Internet] 2019; 4: 35–35. Available from: https://aoj.amegroups.com/article/view/5354/html

[23] Décary S, Ouellet P, Vendittoli PA et al. Reliability of physical examination tests for the diagnosis of knee disorders: Evidence from a systematic review [Internet]. Vol. 26, Manual Therapy.Churchill Livingstone; 2016: 172–182. Available from: https://pubmed.ncbi.nlm.nih.gov/27697691/

[24] Collins NJ, Prinsen CAC, Christensen R et al. Knee Injury and Osteoarthritis Outcome Score (KOOS): systematic review and meta-analysis of measurement properties [Internet]. Vol. 24, Osteoarthritis and Cartilage.W.B. Saunders Ltd; 2016: 1317–1329. Available from https://pubmed.ncbi.nlm.nih.gov/27012756/

[25] Baert IAC, Staes F, Truijen S et al. Weak associations between structural changes on MRI and symptoms, function and muscle strength in relation to knee osteoarthritis. Knee Surg Sports Traumatol Arthrosc [Internet] 2014; 22: 2013–2025. Available from: https://pubmed.ncbi.nlm.nih.gov/23377800/

[26] Kellgren JH, Lawrance JS. Radiological assessment of osteo-arthrosis. Ann Rheum Dis [Internet] 1957; 16: 494–502. Available from: https://pubmed.ncbi.nlm.nih.gov/13498

[27] Sukerkar PA, Doyle Z. Imaging of Osteoarthritis of the Knee. Radiologic clinics of North America 2022; 60: 605–616. DOI: 10.1016/j.rcl.2022.03.004

[28] Lee LS, Chan PK, Fung WC et al. Imaging of knee osteoarthritis: A review of current evidence and clinical guidelines. Musculoskeletal care 2021; 19: 363–374. DOI: 10.1002/msc.1536

biomedicines

MDPI

Article

Early Knee Osteoarthritis Classification and Clinical Evolution: A Longitudinal Observational Pilot Study

Luz Herrero-Manley [1,*], Ana Alabajos-Cea [1], Luis Suso-Martí [2], Enrique Viosca-Herrero [1] and Isabel Vazquez-Arce [1]

[1] Servicio de Medicina Física y Rehabilitación, Hospital La Fe, 46026 Valencia, Spain
[2] Exercise Intervention for Health Research Group (EXINH-RG), Department of Physiotherapy, University of Valencia, 46010 Valencia, Spain
* Correspondence: luzherreromanley8@gmail.com; Tel.: +34-626-430-138

Abstract: Knee osteoarthritis (KOA) is one of the main problems of an aging society in terms of incidence, impairment to the quality of daily living (QOL), and economics. The main aim of this study was to verify the usefulness, in practical terms, of applying the existing diagnostic criteria of early knee osteoarthritis (EKOA). The secondary objective of this project was to evaluate the clinical progression of healthy subjects (HS) at risk of osteoarthritis and of patients with diagnosed EKOA. A cross-sectional longitudinal pilot study was carried out, in which 105 participants were classified as EKOA patients or HS according to the diagnostic criteria. Measures of disability, pain, and self-reported variables were assessed. Two follow-ups were performed in order to assess the diagnoses and radiological progression, and the clinical progression was evaluated using self-reported measures. Following the current diagnostic criteria, the participants were divided into EKOA and HS. Most of the participants did not present changes in their classification, although some subjects were reclassified as EKOA or HS in the follow-ups which were performed. The current classification criteria for EKOA based on self-reported measures, radiological findings, and clinical conditions such as pain could lead to a misdiagnosis of this process, as fluctuations in the classifications of patients according to their conditions were found during follow up.

Keywords: osteoarthritis; knee osteoarthritis; early osteoarthritis; disability; diagnosis

Citation: Herrero-Manley, L.; Alabajos-Cea, A.; Suso-Martí, L.; Viosca-Herrero, E.; Vazquez-Arce, I. Early Knee Osteoarthritis Classification and Clinical Evolution: A Longitudinal Observational Pilot Study. *Biomedicines* **2023**, *11*, 1670. https://doi.org/10.3390/biomedicines11061670

Academic Editor: Elisa Belluzzi

Received: 2 May 2023
Revised: 5 June 2023
Accepted: 7 June 2023
Published: 9 June 2023

1. Introduction

Osteoarthritis (OA) is one of the most significant causes of disability, and knee OA (KOA) in particular is one of the main problems for the elderly in terms of incidence, impairment to the quality of daily living (QOL), and economics [1]. KOA is a degenerative disorder which includes pathology of a wide range of tissues. It also involves structural and qualitative abnormalities that interfere with joint function, motor function, and physical activity [2]. KOA is an unavoidable pathological process for humans which is linked to the aging process; therefore, early diagnosis, treatment, and prevention should be the main focuses for the aging population [3].

During the last two decades, the term "early osteoarthritis" has emerged in the medical literature, with scientific papers on early osteoarthritis being increasingly published, and there is growing awareness of the importance of identifying the early stages of the degenerative processes in KOA [4]. It has been suggested that KOA progression may be prevented or delayed through early diagnosis before the joint is irreversibly damaged. When OA is treated appropriately at an early stage, therapeutic treatment or exercise may be effective in halting the progression of or even healing KOA [2].

Many descriptions of treatments for the early stages of KOA are available. For instance, chondroitin sulfate of non-animal origins is said to improve pain and knee function in EKOA [5].

Therefore, the importance of closely analyzing the latest diagnosis criteria cannot be emphasized enough. This is essential in order to verify their accuracy and to establish

completely reliable criteria in the near future. With regard to prevention and treatment aspects, a clear definition of early knee OA (EKOA) is paramount for diagnosis [2].

In recent years, the definition of EKOA has begun to be discussed on a global scale, and various diagnostic criteria for identifying healthy subjects at risk of developing osteoarthritis have been put forward, in addition to criteria for detecting patients with EKOA [2,6]. The combination of the "symptoms" of joint pain; the "signs", such as joint stiffness and tenderness; various risk factors; and methods of diagnostic imaging such as radiographs have all been proposed as ways to define early OA [2,6]. However, the definition and identification of EKOA is a complicated matter, as the signs/symptoms may still be limited and sporadic, only manifesting under certain conditions [7,8].

For example, in the early phases of OA, pain is related to activity, whereas in the later stages, pain becomes more constant over time [8]. In addition, it has been suggested that synovitis increases the risk of joint pain. Moreover, it is common to find signs of OA in the MRI results of asymptomatic patients. This finding highlights the fact that EOA changes can be asymptomatic, and pain and stiffness may only occur when the OA pathological process is already established [7,8].

Therefore, procuring a 100% definite diagnosis of EKOA is a well-known challenge. If a way could be found to make an accurate diagnosis of EKOA, the development of this disease could be slowed down considerably and, therefore, patients could be treated more promptly. This pilot study is innovative in that it applies the most recently accepted criteria for EKOA to a sample group of patients in order to verify their reliability in daily practice.

The main objective of this study was to verify the relevance and accuracy of EKOA diagnoses according to the existing criteria. Therefore, a cross-sectional longitudinal pilot study was carried out. After recruiting the patients, they were classified as healthy subjects (HS) or EOA using two diagnostic criteria, with the aim of improving early and reliable detection of patients with EKOA.

The criteria utilized were those of Luyten et al. and Mahmoudian et al. [9,10]. Both references include self-reported measures such as knee injury and osteoarthritis outcome (KOOS), radiological findings based on Kellgren and Lawrence (KL) classification, and clinical examination findings [9,10]. In addition, the secondary objective was to evaluate the clinical progression of healthy subjects at risk of OA, as well as patients with EKOA.

2. Materials and Methods

2.1. Study Design

A cross-sectional longitudinal pilot study with a non-probabilistic sample was carried out. Our patients were recruited and classified as healthy subjects (HS) or EOA, following the criteria of Luyten et al. and the classification of Mahmoudian et al. in order to attempt to improve the detection of EOA patients [9,10].

The study design adhered to the international recommendations for Strengthening the Reporting of Observational Studies in Epidemiology [11]. All participants were duly informed about the study procedures, which were planned according to the ethical standards of the Declaration of Helsinki and approved by the Ethics Committee on Drug Research of the hospital (CEIm 2017/0147). Each patient provided written informed consent, and the purpose of the study and the specific tests they would undergo were clearly explained.

2.2. Participants

The patients included in the study were selected at a hospital in Valencia (Spain), within the H2020 project OACTIVE. The design of the data collection protocol started on November 2017. Once set up, the recruitment of participants began in the summer of 2018, with follow-ups lasting until the end of February 2021. A total of 105 participants were divided into 2 groups, namely, EKOA and HS at risk of developing OA. The classification of the patients was based on two separate criteria so as to ensure a reliable diagnosis of EKOA.

First, Luyten's criteria were applied [9], followed by those of Mahmoudian et al. [10]. All 105 participants were classified using both criteria, thus obtaining two separate samples per patient for follow-up (Figures 1 and 2).

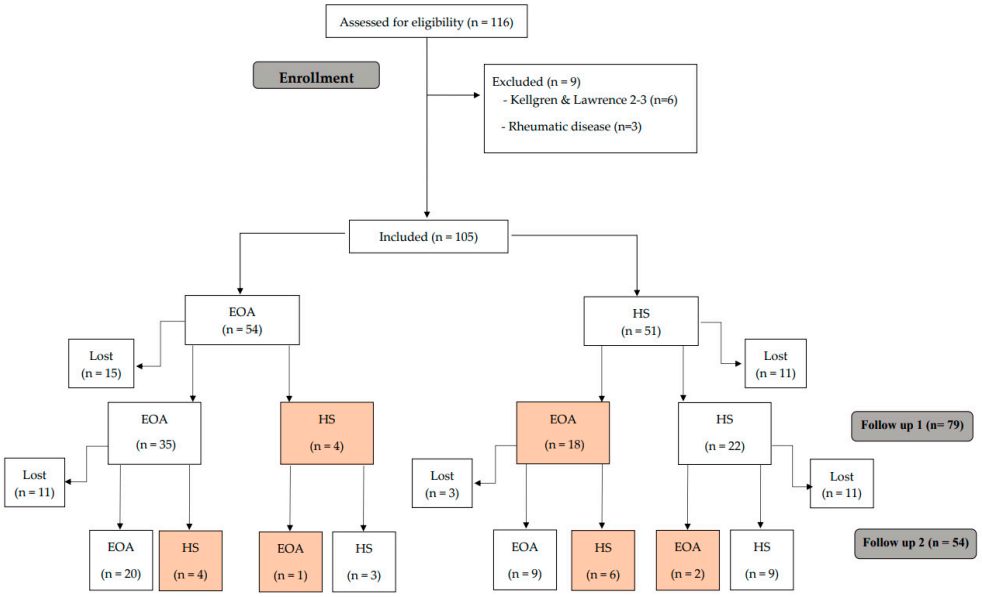


Figure 1. Study flow chart following the criteria of Luyten et al. [9].

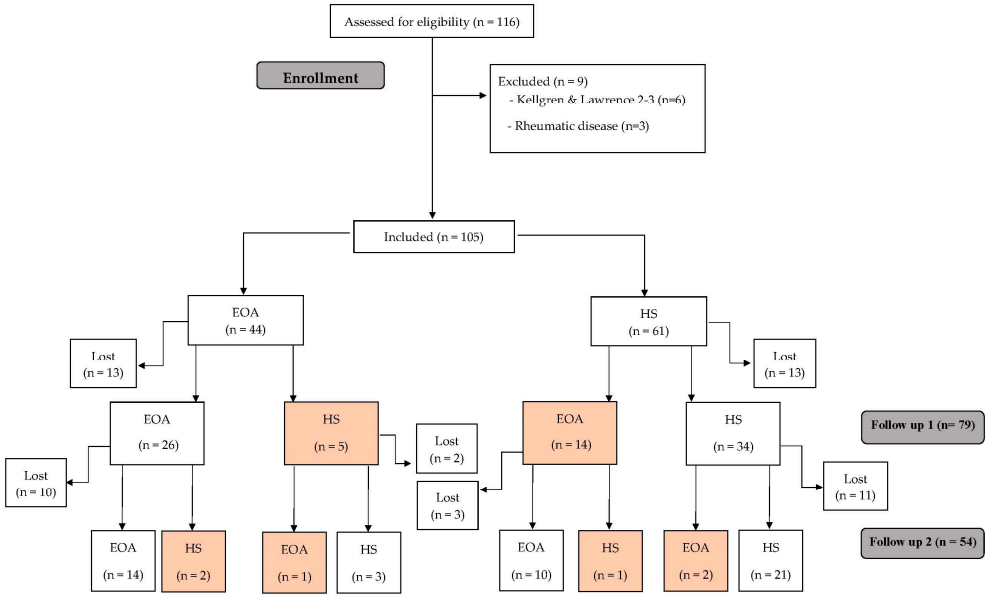


Figure 2. Study flow chart following the criteria of Mahmoudian et al. [10].

Luyten's criteria were used to classify EKOA patients in the following ways:

1. Patient-based questionnaires such as Knee Injury and Osteoarthritis Outcome score (KOOS) were used; 2 out of the 4 KOOS subscales (Symptoms, Knee pain, Function, and Knee-related quality of life) needed to score "positive" ($\leq$85%);
2. In the clinical examination, participants had to show crepitus or joint line tenderness;
3. Regarding X-rays, patients with Kellgren and Lawrence (KL) grade 0–1 on standing weight-bearing radiographs (AP, lateral, AP fixed flexion, and skyline for patellofemoral OA) were included [9].

For the second analysis, patients were reclassified using the criteria laid out by Mahmoudian et al. [10].

In order to be classified as EKOA, subjects had to fulfill the following criteria:

4. Patient-based questionnaires such as KOOS 4 score: the average of 4 of the 5 KOOS subscale averages, including pain, symptoms, ADL, and QOL (Pain, Symptoms, Function, and Knee-related quality of life) needed to score "positive" ($\leq$80%);
5. In the clinical examination, participants had to show crepitus or joint line tenderness.
6. Regarding X-rays, patients with KL grade 0–1 on standing weight-bearing radiographs (AP, lateral, AP fixed flexion, and skyline for patellofemoral OA) were included.

There were three inclusion criteria for HS at risk of OA:

- Kellgren and Lawrence grade 0–1.
- Regarding age limit, patients were required to be 40 years old or over.
- Participants had to be overweight, with a body mass index of at least 25.

The employed exclusion criteria were identical for EKOA and HS at risk of developing OA, and comprised autoimmune, rheumatic, and infectious conditions. Additionally, patients suffering from cognitive impairments which hindered their viewing of the audio–visual material and those with illiteracy, comprehension or communication issues, or insufficient knowledge of Spanish for following measurement instructions were also excluded.

2.3. Outcome Measures

2.3.1. Demographic Data and Control Variables

The study incorporated general demographic information obtained from extensive databases, along with well-established conventional predictors such as gender, age, educational level, and marital status [12,13]. Additionally, data regarding smoking and alcohol consumption habits were registered. In the case of women, hormonal status was also taken into account. Finally, measurements of weight, height, and QOL were also collected.

2.3.2. Pain and Disability Variables

Pain Intensity

In order to quantify pain intensity, the Visual Analogue Scale (VAS) was used. The VAS is a horizontal line 100 mm in length with verbal descriptors (word anchors) at each end to express the extremes of painful sensations (ranging from no pain to the maximum pain imaginable). Patients mark the point on the line that best corresponds to the severity of their symptoms. It has been shown to have good retest reliability ($r = 0.94$, $p < 0.001$) and a minimal detectable change of 15.0 mm [14,15]. The VAS scale was applied both at rest and while walking.

Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)

This questionnaire is widely used to evaluate the conditions of patients with osteoarthritis; it assesses the functional and symptomatic features.

The WOMAC questionnaire is self-administered and is used to assess patients with progressive hip and/or knee osteoarthritis. The questionnaire uses a multidimensional scale composed of 24 items divided into 3 aspects: functional pain (consisting of 5 items), stiffness (2 items), and difficulties in daily activities (17 items). Higher values indicate poorer scores for pain and physical function on the WOMAC subscales. The Spanish version of the WOMAC questionnaire has adequate psychometric properties, presenting an index of internal consistency (a) of 0.82 for pain and 0.93 for physical function [16].

Knee Injury and Osteoarthritis Outcome Score (KOOS)

The KOOS is a knee-specific questionnaire designed to assess short- and long-term patient-relevant opinions regarding their knee issues and other associated problems. The KOOS is self-administered and assesses five outcomes: Pain, other Symptoms, Function in daily living (ADL), Function in Sport and Recreation (Sport/Rec), and Knee-related Quality of Life (QOL). The psychometric properties and the ICC of the Spanish version have shown acceptable properties for both the total score and the subscales [17].

2.3.3. Psychological Variables

Anxiety and Depression Symptoms

The Spanish version of the Hospital Anxiety and Depression Scale was applied to identify depression and anxiety symptoms in the participants [18]. This scale includes 14 items, which are rated on a 4-point Likert-type scale. Two subscales assessed depression and anxiety independently. The internal consistency was 0.90 for the full scale; 0.84 for the depression subscale; and 0.85 for the anxiety subscale [18].

2.4. Procedures

Every participant was provided with an information sheet elucidating the procedure, together with a consent form to ensure that they were well-informed. Subsequently, participants were urged to express any inquiries pertaining to the nature of the study.

The subjects who agreed to participate then proceeded to fill in the sociodemographic questionnaire. Self-reported measures of disability, pain, and any variables were then assessed. The initial follow-up took place between July 2020 and September 2020, while the second follow-up occurred between January 2021 and February 2021.

2.5. Statistical Analysis

The statistical data analysis was conducted using statistical SPSS software, version 22.0 (SPSS Inc., Chicago, IL, USA). The normality of the variables was evaluated using the Shapiro–Wilk test. Descriptive statistics were used to summarize the data for continuous variables, and are presented as mean ± standard deviation, 95% confidence interval. A 2-way repeated measures analysis of variance (ANOVA) was conducted to study the effects of the between-participant "group" factor in each of the two categories (EOA and HS) and the within-participant "time" factor in each of the three categories (i.e., pre-, post-1, and post-2).

A post hoc analysis with Bonferroni correction was carried out in the case of significant ANOVA findings for multiple comparisons between variables. Effect sizes (d) were calculated in accordance with Cohen's method, in which the magnitude of the effect was classified as small (0.20–0.49), moderate (0.50–0.79), or large (0.8) [19].

3. Results

Altogether, 105 subjects were included (54 EKOA and 51 HS). A total of 11 HS group patients had been lost by the first follow-up, and 14 by the second round. As for the EKOA group, 15 subjects had dropped out by the first follow-up and 11 by the second (Figure 1). The main reason for this was the COVID-19 pandemic, but several patients did not wish to continue for personal reasons.

All the variables presented normal distribution. No statistically significant differences were found between groups for any of the primary variables, demographic data, or self-report variables at baseline (Table 1).

Table 1. Descriptive and demographic data, as well as control variables.

	EOA (*n* = 54)	**HS (*n* = 51)**	***p* Value**
Age (years)	51.85 ± 5.72	50.49 ± 6.21	0.46
BMI (kg/m^2)	27.40 ± 4.19	26.80 ± 3.68	0.43
Gender			0.17
Women	35 (64.8)	35 (68.6)	
Men	19 (35.2)	16 (31.4)	
Marital status			0.95
Single	5	7	
Married	31	30	
Widowed	2	2	
Divorced	6	6	

Table 1. *Cont.*

	EOA (n = 54)	HS (n = 51)	p Value
Level of formal education			0.18
Primary	6	9	
Secondary	20	12	
College	18	24	
Smoking			0.27
No	18	23	
Yes	9	4	
Ex	21	19	
Alcohol			0.65
Never	8	4	
Seldom	13	18	
1–2 times/month	11	9	
1–2 times/week	15	15	
1 time per day	2	2	
More than 1 per day	1	0	

3.1. Evolution Classification

Following the Luyten et al. [9] diagnostic criteria described above, participants were reclassified at each follow-up, which were between 9 to 12 months apart. In the EOA group, 4 participants at the first follow-up and another 4 participants at the second follow-up presented an improvement that caused their classification to change to HS. Conversely, 18 HS participants evolved to EOA at the first follow-up, but 6 of them were again classified as HS at the second follow-up (Figure 1). None of the participants progressed to advanced OA.

We also reclassified the patients during each follow-up according to the suggestions of Mahmoudian et al. [10]. Initially, the 105 subjects were classified as 44 EOA and 61 HS. In the EOA group, 5 subjects at the first follow-up and 2 at the second follow-up presented an improvement that changed their classification to HS. In addition, 14 HS evolved to EOA at the first follow-up (1 of them being classified as HS again at the second follow-up), and 2 at the second follow-up (Figure 2). None of the participants progressed to advanced OA.

3.2. Clinical Progression

3.2.1. Pain Intensity

The ANOVA did not reveal any statistically significant changes in VAS rest measurement overtime (F = 1.89, p = 0.16, η^2 = 0.79). It showed no differences between baseline, follow-up 1, and follow-up 2 for either the EOA or the HS group. Similar results were found using the classification of Mahmoudian et al. [10] (Tables 2 and 3).

Table 2. Clinical progression of OA patients.

	Baseline	Follow-Up 1	Follow-Up 2
VAS Rest			
Luyten et al. [9]	2.04 ± 1.56	1.29 ± 2.05	2.21 ± 2.67
Mahmoudian et al. [10]	1.88 ± 2.31	1.50 ± 2.06	2.44 ± 2.78
VAS Walking			
Luyten et al. [9]	2.67 ± 2.73	2.42 ± 2.02	2.46 ± 2.40
Mahmoudian et al. [10]	2.69 ± 2.77	2.94 ± 2.11	2.63 ± 2.55
* **WOMAC**			
Luyten et al. [9]	18.55 ± 10.15	16.56 ± 15.66 *	22.47 ± 17.23 *
Mahmoudian et al. [10]	17.62 ± 9.47	22.04 ± 16.75 *	25.26 ± 18.75 *
KOOS Pain			
Luyten et al. [9]	80.48 ± 13.44	78.62 ± 16.24	80.52 ± 19.97
Mahmoudian et al. [10]	86.17 ± 14.31	75.08 ± 19.40	74.25 ± 23.42

Table 2. *Cont.*

	Baseline	Follow-Up 1	Follow-Up 2
KOOS Symptoms			
Luyten et al. [9]	85.00 ± 12.71	79.62 ± 15.81	83.61 ± 12.45
Mahmoudian et al. [10]	85.92 ± 12.41	74.24 ± 16.58	77.67 ± 12.07
KOOS ADL			
Luyten et al. [9]	83.29 ± 16.94	79.62 ± 18.53	81.95 ± 18.67
Mahmoudian et al. [10]	86.83 ± 18.66	73.67 ± 21.62	73.92 ± 20.91
KOOS QQL			
Luyten et al. [9]	62.29 ± 26.56	51.86 ± 20.45	61.33 ± 24.59
Mahmoudian et al. [10]	65.17 ± 32.80	45.42 ± 18.64	50.08 ± 22.37
KOOS Sport			
Luyten et al. [9]	60.71 ± 30.83	55.71 ± 29.43	57.61 ± 26.77
Mahmoudian et al. [10]	58.75 ± 37.54	44.58 ± 30.63	46.25 ± 24.23
HAD Anxiety			
Luyten et al. [9]	5.42 ± 4.14	4.17 ± 3.81	5.29 ± 4.60
Mahmoudian et al. [10]	4.94 ± 3.35	4.75 ± 2.46	4.88 ± 3.20
HAD Depression			
Luyten et al. [9]	3.38 ± 3.07	3.13 ± 2.91	2.96 ± 3.32
Mahmoudian et al. [10]	2.81 ± 2.34	3.31 ± 2.85	2.50 ± 2.68

* Statistical significance. Data are presented as mean ± SD.

Table 3. Clinical progression of healthy subjects at risk of developing OA.

	Baseline	Follow-Up 1	Follow-Up 2
VAS Rest			
Luyten et al. [9]	0.1 ± 0.29	0.74 ± 1.36	0.91 ± 1.41
Mahmoudian et al. [10]	0.68 ± 1.85	0.77 ± 1.54	1.13 ± 1.77
VAS Walking			
Luyten et al. [9]	0.52 ± 1.76	1.3 ± 2.01	1.52 ± 1.86
Mahmoudian et al. [10]	1.06 ± 2.23	1.32 ± 1.85	1.68 ± 1.92
*** WOMAC**			
Luyten et al. [9]	5.86 ± 4.3	9.57 ± 8.20 *	12.30 ± 10.30 *
Mahmoudian et al. [10]	9.32 ± 8.89	12.44 ± 8.45 *	12.77 ± 10.42 *
KOOS Pain			
Luyten et al. [9]	88.80 ± 13.05	87.60 ± 9.65	88.96 ± 12.28
Mahmoudian et al. [10]	84.10 ± 14.31	86.90 ± 9.31	87.47 ± 11.61
KOOS Symptoms			
Luyten et al. [9]	90.24 ± 10.83	91.80 ± 6.79	92.60 ± 8.80
Mahmoudian et al. [10]	88.20 ± 12.20	90.53 ± 7.84	91.30 ± 8.51
KOOS ADL			
Luyten et al. [9]	89.88 ± 14.37	90.32 ± 7.84	92.01 ± 9.78
Mahmoudian et al. [10]	86.13 ± 15.54	89.83 ± 7.66	91.20 ± 9.06
KOOS QQL			
Luyten et al. [9]	76.88 ± 22.29	75.12 ± 20.62	79.64 ± 21.88
Mahmoudian et al. [10]	71.57 ± 22.72	71.97 ± 20.53	75.93 ± 20.81
KOOS Sport			
Luyten et al. [9]	71.40 ± 26.71	71.60 ± 22.16	72.60 ± 23.29
Mahmoudian et al. [10]	67.67 ± 25.72	71.33 ± 21.01	69.83 ± 22.03
HAD Anxiety			
Luyten et al. [9]	2.83 ± 3.34	3.04 ± 3.34	2.87 ± 2.79
Mahmoudian et al. [10]	3.74 ± 4.21	3.45 ± 4.09	3.71 ± 4.31
HAD Depression			
Luyten et al. [9]	1.17 ± 2.05	1.52 ± 2.27	1.26 ± 1.18
Mahmoudian et al. [10]	2.03 ± 3.04	1.84 ± 2.54	1.94 ± 2.62

* Statistical significance. Data presented as Mean ± SD.

The ANOVA did not reveal any statistically significant changes in the VAS walking measurement overtime ($F = 0.051$, $p = 0.61$, $\eta^2 = 0.02$). It showed no differences between

baseline, follow-up 1 and follow-up 2 for EOA or HS groups. Similar results were found using the classification of Mahmoudian et al. [10] (Tables 2 and 3).

3.2.2. Disability

The ANOVA revealed statistically significant changes in WOMAC measurement overtime ($F = 3.10$, $p = 0.048$, $\eta^2 = 0.181$), showing differences between the baseline and follow-up 2 for the EOA and HS groups. Similar results were found using the classification of Mahmoudian et al. [10] (Tables 2 and 3).

3.2.3. Psychological Variables

The ANOVA did not reveal any statistically significant changes in HAD Anxiety measurement overtime ($F = 0.14$, $p = 0.86$, $\eta^2 = 0.01$), nor in HAD Depression ($F = 0.66$, $p = 0.52$, $\eta^2 = 0.02$); no differences were found between baseline, follow-up 1, and follow-up 2 for the OA or the HS group.

Finally, the ANOVA did not reveal statistically significant changes in any of the KOOS subscale (pain, symptoms, QQL, ADL, and sport subscales) measurements overtime for the EOA or the HS group. Similar results were found using the classification of Mahmoudian et al. [10] (Tables 2 and 3).

4. Discussion

4.1. Diagnosis Criteria of EOA

With the objective of evaluating the reliability of EKOA diagnosis and the clinical progression of our patients, we used Luyten's criteria to classify them as HS or EOA. These classification criteria were intended only for research, as the authors declare, and showed a specificity of 76.5% for the detection of clinical progression [9,10].

At present, very few studies have evaluated the progression of patients with EKOA. In this regard, we found that some HS met the criteria for EKOA diagnosis at a certain moment in time who, afterwards, scored as HS again; we also found subjects classified as EKOA at the beginning who scored as HS at one or both follow-ups. It should be noted that these criteria are mainly based on clinical condition, so this finding made us wonder if it was possible that we were not actually detecting changes related to the onset of OA, but knee pain due to other reasons, leading to misdiagnoses. These findings may suggest that in order to diagnose EKOA in a more accurate way, new diagnostic criteria could be considered, such as biomechanical parameters, WOMAC criteria, or pain persistence, during a longer established period of time. This is to be the subject of a future study.

Recently, Mahmoudian et al., 2020, evaluated the classification criteria for EKOA, attempting to find some aspects that could refine the diagnosis [10]. Their results showed how these criteria can contribute to the prediction of structural and clinical progression (sensitivity of 29% and 43.5%, specificity of 73.1% and 76.5%, respectively). In addition, these authors noted that for the purpose of detecting structural evolution, a K&L grade I could be a better predictor. In relation to clinical evolution, it seems that adding more clinical aspects, such as effusion or Heberden's nodes, could increase the predictive value of the criteria, emphasizing the importance of physical examination. They found the best predictive performance for KOOS4 $\leq$ 80% [10]. We analyzed our sample again considering these suggestions, mainly the KOOS4 $\leq$ 80%, as we had a very small sample of subjects with K&L I, and none of our subjects had Heberden's nodes. After applying these modifications, we still found some changes from the EKOA to the HS group at the follow-ups, but they were fewer than the initial numbers.

These fluctuations between HS and EKOA patient classification in the follow-up using both criteria could point to a certain degree of unreliability in the diagnosis of EKOA, which raises doubts concerning the use of this classification in practice and highlights the clinical relevance of this pilot study.

4.2. Clinical Progression of OA

Our data are in keeping with previous results in the field of musculoskeletal pain and, specifically, in OA [20,21]. Regarding this, patients with OA were found to show fluctuations and exacerbations directly related to a linear progression of the disease or to the radiographic development of OA [22,23].

It is possible that EKOA may not be progressive for some time, and also that the clinical course depends on individual epigenetic, neurophysiological, or metabolic factors which need to be studied further [24,25]. In addition, there was no impairment of functional capacity due to pain or anticipation of pain, something that has been suggested previously [26,27]. In fact, our results also showed fluctuations in the functional statuses of OA patients, in agreement with some previous studies [28]. Only the WOMAC measurement showed fluctuations over time, showing differences between the baseline and follow-up for the EOA and HS groups.

Future studies with a longer period of follow-up, and even studies that include new factors such as, for example, biomechanical parameters, should address this question and determine whether there are indeed clinical variables that could determine EKOA. Nevertheless, in the interest of practicality, the follow-up period should not be overly extended.

5. Limitations

As this is a pilot study, there are certain limitations to be taken into consideration. Furthermore, due to the cross-sectional design of this study, it is not feasible to establish a causal relationship. In addition, a more extended period of follow-up is likely required in order to assess the progression of these patients and to validate our findings. In addition, as discussed above, we used the existing classification criteria to divide our patients into HS and EOA groups in order to evaluate their clinical progression. However, because of the variability in this classification overtime, we cannot be sure that this classification is correct.

6. Conclusions

The findings of the current study suggest that the existing classification criteria for EKOA based on self-reported measures, radiological findings, and clinical conditions such as pain could lead to misdiagnosis, as they raise doubts concerning practical viability. Furthermore, our results show that HS at risk of OA and patients diagnosed as EKOA according to the current classification criteria, did not show any significant changes in pain data, disability, or psychological variables for this follow-up period.

Author Contributions: Conceptualization, A.A.-C., L.H.-M., L.S.-M., I.V.-A. and E.V.-H.; data curation, A.A.-C. and E.V.-H.; formal analysis, A.A.-C. and L.S.-M.; funding acquisition, I.V.-A. and E.V.-H.; investigation, L.H.-M., L.S.-M. and A.A.-C.; methodology, L.H.-M. and A.A.-C.; project administration, A.A.-C., I.V.-A. and E.V.-H.; supervision, A.A.-C. and L.S.-M.; writing—original draft, A.A.-C., L.S.-M., L.H.-M. and E.V.-H.; writing—review and editing, A.A.-C., L.H.-M., E.V.-H. and L.S.-M. All authors have read and agreed to the published version of the manuscript.

Funding: This project received funding from the European Union's Horizon 2020 Research and Innovation Programme under grant agreement No. 777159. Línea de investigacion artrosis de rodilla. Referencia #00700409. La Fe Health Research Institute. Avinguda de Fernando Abril Martorell, 106, 46026, Valencia. Spain.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Uchio, Y.Y. Early knee osteoarthritis—Definition, pathogenesis, diagnosis, treatment, and prevention. *Ann. Jt.* **2019**, *4*, 35. [CrossRef]
2. Kanamoto, T.; Mae, T.; Yokoyama, T.; Tanaka, H.; Ebina, K.; Nakata, K. Significance and definition of early knee osteoarthritis. *Ann. Jt.* **2020**, *5*, 4. [CrossRef]
3. Chiba, D.; Nakamura, T.; Fu, F.H. Early osteoarthritis—Definition, pathogenesis, diagnosis, management and prevention: Management. *Ann. Jt.* **2019**, *4*, 5. [CrossRef]
4. Madry, H.; Kon, E.; Condello, V.; Peretti, G.M.; Steinwachs, M.; Seil, R.; Berruto, M.; Engebretsen, L.; Filardo, G. Early osteoarthritis of the knee. *Knee Surg. Sports Traumatol. Arthrosc.* **2016**, *24*, 1753–1762. [CrossRef]
5. Rondanelli, M.; Braschi, V.; Gasparri, C.; Nichetti, M.; Faliva, M.A.; Peroni, G.; Naso, M.; Iannello, G.; Spadaccini, D.; Miraglia, N.; et al. Effectiveness of Non-Animal Chondroitin Sulfate Supplementation in the Treatment of Moderate Knee Osteoarthritis in a Group of Overweight Subjects: A Randomized, Double-Blind, Placebo-Controlled Pilot Study. *Nutrients* **2019**, *11*, 2027. [CrossRef] [PubMed]
6. Luyten, F.P.; Denti, M.; Filardo, G.; Kon, E.; Engebretsen, L. Definition and classification of early osteoarthritis of the knee. *Knee Surg. Sport. Traumatol. Arthrosc.* **2012**, *20*, 401–406. [CrossRef] [PubMed]
7. Felson, D.T.; Hodgson, R. Identifying and treating preclinical and early osteoarthritis. *Rheum. Dis. Clin. N. Am.* **2014**, *40*, 699–710. [CrossRef]
8. Favero, M.; Ramonda, R.; Goldring, M.B.; Goldring, S.R.; Punzi, L. Early knee osteoarthritis. *RMD Open* **2015**, *1*, e000062. [CrossRef] [PubMed]
9. Luyten, F.P.; Bierma-Zeinstra, S.; Dell'Accio, F.; Kraus, V.B.; Nakata, K.; Sekiya, I.; Arden, N.K.; Lohmander, L.S. Toward classification criteria for early osteoarthritis of the knee. *Semin. Arthritis Rheum.* **2018**, *47*, 457–463. [CrossRef]
10. Mahmoudian, A.; Lohmander, L.S.; Jafari, H.; Luyten, F.P. Towards classification criteria for early-stage knee osteoarthritis: A population-based study to enrich for progressors. *Semin. Arthritis Rheum.* **2021**, *51*, 285–291. [CrossRef]
11. Von Elm, E.; Altman, D.G.; Egger, M.; Pocock, S.J.; Gøtzsche, P.C.; Vandenbroucke, J.P.; STROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: Guidelines for reporting observational studies. *J. Clin. Epidemiol.* **2008**, *61*, 344–349. [CrossRef] [PubMed]
12. Silverwood, V.; Blagojevic-Bucknall, M.; Jinks, C.; Jordan, J.L.; Protheroe, J.; Jordan, K.P. Current evidence on risk factors for knee osteoarthritis in older adults: A systematic review and meta-analysis. *Osteoarthr. Cartil.* **2015**, *23*, 507–515. [CrossRef]
13. Zhang, W.; McWilliams, D.F.; Ingham, S.L.; Doherty, S.A.; Muthuri, S.; Muir, K.R.; Doherty, M. Nottingham knee osteoarthritis risk prediction models. *Ann. Rheum. Dis.* **2011**, *70*, 1599–1604. [CrossRef]
14. Bijur, P.E.; Silver, W.; Gallagher, E.J. Reliability of the visual analog scale for measurement of acute pain. *Acad. Emerg. Med.* **2001**, *8*, 1153–1157. [CrossRef]
15. Ostelo, R.W.; Deyo, R.A.; Stratford, P.; Waddell, G.; Croft, P.; Von Korff, M.; Bouter, L.M.; de Vet, H.C. Interpreting Change Scores for Pain and Functional Status in Low Back Pain. *Spine* **2008**, *33*, 90–94. [CrossRef]
16. Escobar, A.; Quintana, J.M.; Bilbao, A.; Azkárte, J.; Güenaga, L.I. Validation of the Spanish version of the WOMAC questionnaire for patients with hip or knee osteoarthritis. *Clin. Rheumatol.* **2002**, *21*, 466–471. [CrossRef]
17. Vaquero, J.; Longo, U.G.; Forriol, F.; Martinelli, N.; Vethencourt, R.; Denaro, V. Reliability, validity and responsiveness of the Spanish version of the Knee Injury and Osteoarthritis Outcome Score (KOOS) in patients with chondral lesion of the knee. *Knee Surg. Sport. Traumatol. Arthrosc.* **2014**, *22*, 104–108. [CrossRef]
18. Herrero, M.J.; Blanch, J.; Peri, J.M.; De Pablo, J.; Pintor, L.; Bulbena, A. A validation study of the Hospital Anxiety and Depression Scale (HADS) in a Spanish population. *Gen. Hosp. Psychiatry* **2003**, *25*, 277–283. [CrossRef]
19. Cohen, J. *Statistical Power Analysis for the Behavioral Sciences*, 2nd ed.; Lawrence Erlbaum Associates, Publishers: Hillsdale, NJ, USA, 1988.
20. Holla, J.F.; van der Leeden, M.; Heymans, M.W.; Roorda, L.D.; Bierma-Zeinstra, S.M.; Boers, M.; Lems, W.F.; Steultjens, M.P.; Dekker, J. Three trajectories of activity limitations in early symptomatic knee osteoarthritis: A 5-year follow-up study. *Ann. Rheum. Dis.* **2014**, *73*, 1369–1375. [CrossRef] [PubMed]
21. Verkleij, S.P.; Hoekstra, T.; Rozendaal, R.M.; Waarsing, J.H.; Koes, B.W.; Luijsterburg, P.A.; Bierma-Zeinstra, S.M. Defining discriminative pain trajectories in hip osteoarthritis over a 2-year time period. *Ann. Rheum. Dis.* **2012**, *71*, 1517–1523. [CrossRef] [PubMed]
22. Allen, K.D.; Coffman, C.J.; Golightly, Y.M.; Stechuchak, K.M.; Keefe, F.J. Daily pain variations among patients with hand, hip, and knee osteoarthritis. *Osteoarthr. Cartil.* **2009**, *17*, 1275–1282. [CrossRef]
23. Hawker, G.A.; Stewart, L.; French, M.R.; Cibere, J.; Jordan, J.M.; March, L.; Suarez-Almazor, M.; Gooberman-Hill, R. Understanding the pain experience in hip and knee osteoarthritis—An OARSI/OMERACT initiative. *Osteoarthr. Cartil.* **2008**, *16*, 415–422. [CrossRef]
24. Lluch, E.; Torres, R.; Nijs, J.; Van Oosterwijck, J. Evidence for central sensitization in patients with osteoarthritis pain: A systematic literature review. *Eur. J. Pain* **2014**, *18*, 1367–1375. [CrossRef]
25. Villafañe, J.H.; Pedersini, P.; Berjano, P. Epigenetics in osteoarthritis related pain: An update. *Arch. Rheumatol.* **2020**, *35*, 456–457. [CrossRef]

26. Johnson, S.R.; Archibald, A.; Davis, A.M.; Badley, E.; Wright, J.G.; Hawker, G.A. Is self-reported improvement in osteoarthritis pain and disability reflected in objective measures? *J. Rheumatol.* **2007**, *34*, 159–164. [PubMed]
27. Massardo, L.; Watt, I.; Cushnaghan, J.; Dieppe, P. Osteoarthritis of the knee joint: An eight-year prospective study. *Ann. Rheum. Dis.* **1989**, *48*, 893–897. [CrossRef] [PubMed]
28. Nicholls, E.; Thomas, E.; van der Windt, D.A.; Croft, P.R.; Peat, G. Pain trajectory groups in persons with, or at high risk of, knee osteoarthritis: Findings from the Knee Clinical Assessment Study and the Osteoarthritis Initiative. *Osteoarthr. Cartil.* **2014**, *22*, 2041–2050. [CrossRef] [PubMed]

frontiers | Frontiers in Nutrition

TYPE Original Research
PUBLISHED 15 March 2023
DOI 10.3389/fnut.2023.1126796

OPEN ACCESS

EDITED BY
Paola De Luca,
Ospedale Galeazzi S.p.A, Italy

REVIEWED BY
Antonio Gigante,
Università Politecnica delle Marche, Italy
Enrico Ragni,
Ospedale Galeazzi S.p.A, Italy

*CORRESPONDENCE
Joaquín Calatayud
✉ joaquin.calatayud@uv.es

SPECIALTY SECTION
This article was submitted to Clinical Nutrition, a section of the journal Frontiers in Nutrition

RECEIVED 18 December 2022
ACCEPTED 24 February 2023
PUBLISHED 15 March 2023

CITATION
Herrero-Manley L, Alabajos-Cea A, Suso-Martí L, Cuenca-Martínez F, Calatayud J, Casaña J, Viosca-Herrero E, Vázquez-Arce I, Ferrer-Sargues FJ and Blanco-Díaz M (2023) Serum lipid biomarkers and inflammatory cytokines associated with onset and clinical status of patients with early knee osteoarthritis. *Front. Nutr.* 10:1126796. doi: 10.3389/fnut.2023.1126796

Serum lipid biomarkers and inflammatory cytokines associated with onset and clinical status of patients with early knee osteoarthritis

Luz Herrero-Manley[1], Ana Alabajos-Cea[1,2], Luis Suso-Martí[3], Ferran Cuenca-Martínez[4], Joaquín Calatayud[3]*, José Casaña[3], Enrique Viosca-Herrero[1], Isabel Vázquez-Arce[1], Francisco José Ferrer-Sargues[5] and María Blanco-Díaz[6]

[1]Servicio de Medicina Física y Rehabilitación, Hospital La Fe, Valencia, Spain, [2]Grupo de Investigación en Medicina Física y Rehabilitación, Instituto de Investigación Sanitaria La Fe (IISLAFE), Valencia, Spain, [3]Exercise Intervention for Health Research Group (EXINH-RG), Department of Physiotherapy, University of Valencia, Valencia, Spain, [4]Department of Physiotherapy, University of Valencia, Valencia, Spain, [5]Department of Physiotherapy, Universidad Cardenal Herrera-CEU, CEU Universities, Valencia, Spain, [6]Department of Surgery and Medical Surgical Specialties, Faculty of Medicine and Health Sciences, University of Oviedo, Oviedo, Spain

Introduction: Osteoarthritis (OA) is a common joint condition and one of the greatest causes of disability worldwide. The role of serum lipid and inflammatory biomarkers in the origin and development of the disease is not clear, although it could have important implications for diagnosis and treatment. The primary aim of this study was to evaluate differences of serum lipid and inflammatory biomarkers with knee EOA in comparison with matched controls, in order to determine the role of these factors in the origin of EOA.

Methods: For this proposal, a cross-sectional study with a non-randomized sample was performed. 48 subjects with early osteoarthritis (EOA) and 48 matched controls were selected and serum lipid levels (total cholesterol, LDL, HDL) and inflammatory biomarkers C-reactive protein (CRP), uric acid (UA) were analyzed. In addition, clinical (pain, disability) and functional (gait speed, sit-to-stand) variables were measured to establish their relationship to serum lipid levels and inflammatory biomarkers.

Results: Patients with EOA showed higher levels of total cholesterol LDL, UA, and CRP. Higher levels of total cholesterol, LDL and CRP were correlated with higher levels of pain intensity and higher disability ($p < 0.05$). In addition, UA and CRP were inversely correlated with gait speed and sit-to-stand tests ($r = -0.038$ to -0.5, $p < 0.05$).

Conclusion: These results highlight the relevance of metabolic and proinflammatory aspects in the early stages of knee OA and could be key to developing early diagnoses to prevent the onset and development of the disease.

KEYWORDS

osteoarthritis, early osteoarthritis, serum lipid, inflammatory biomarkers, cytokine

Introduction

Osteoarthritis (OA), one of the 10 main causes of physical disability today, has become a major public health problem worldwide, with knee osteoarthritis being the predominant form of this injury (1). Clinical presentation of knee OA includes degenerative changes due to the progressive loss of articular cartilage, subchondral bone changes, synovial inflammation, and meniscus degeneration (2, 3). All these manifestations lead to joint and multisite pain, stiffness, and loss of range of movement, affecting physical function and quality of life of patients (4).

A directly proportional relation between knee OA prevalence and demographic factors such as gender, aging and obesity rates has been found (5). However, these parameters, evaluated as isolated risk factors, are not the specific cause of OA in most cases (6). Currently, a new paradigm in OA has been proposed, shifting from a cartilage-specific disease toward that of an organ disease, in which synovitis and systemic pathology plays an important role (7, 8). Clustering of cardiovascular and metabolic factors can increase the risk of OA, causing a condition identified as metabolic syndrome (9, 10). This syndrome includes alterations of blood vessel function, decreased high-density lipoprotein (HDL) levels, increased low-density lipoprotein (LDL) and triglyceride levels, raised blood glucose levels and abdominal obesity, creating an archetype of low-grade chronic inflammation (11). The systemic nature of OA allows for potential future treatments that could improve the development of the disease and the quality of life of people suffering from the disease (12, 13).

Several theories have tried to explain the pathogenesis of OA and its relationship with the different components of metabolic syndrome. Despite underlying differences between them, a consensus has been reached that mechanical factors and humoral mediators are involved in the course of the disease (14, 15). The metabolic imbalance characteristic of metabolic syndrome, produced by the accumulation of adipose tissue, increased vascular resistance and insulin resistance, among other factors, produces alterations in protein concentrations, ultimately triggering these inflammatory processes (16).

Multifactorial causes of OA, and the combination of mechanical and metabolic variables, determine that the structural findings of the disease are a late phenomenon (17, 18) This process has a negative impact on patients, since non-surgical interventions normally have limited efficacy, since they are applied at an advanced stage of the pathology with severe joint and functional involvement (19, 20) In addition, the lack of control over the triggering factors translates into inaccurate forecasts, loss of functional independence and high costs for health services (21). It is for this reason that research has begun to focus on the concept of "early osteoarthritis" (EOA), with the aim of providing the patient a treatment in the early stages of the disease, which can prevent progression and structural changes in the joint, associated with later stages of OA (22, 23).

It is of prime importance that predictors for knee OA progression are found in order to improve treatment options and, moreover, to prevent this disabling disease (24, 25). However, even though a large number of potential risk factors have been studied, most of the findings should be approached with caution, because of the studies design or controversial results (26). In addition, it is appropriate to analyze whether or not the alteration of different metabolic markers, related to inflammatory processes present in knee OA patients, can help to obtain an early diagnose of the injury, and how their modification can influence its course. Therefore, the aim of this work was to study differences of serum lipid and inflammatory biomarkers with knee EOA in comparison with matched controls, in order to determine the role of these factors in the origin of EOA. The secondary objective is to determine the association of serum lipid and inflammatory biomarkers with pain intensity, disability, and functional variables in patients with knee EOA.

Methods

Study design

A cross-sectional study with a non-randomized sample was performed. The design followed the international recommendations for Strengthening the Reporting of Observational Studies in Epidemiology (27). All participants received an explanation of the study procedures, which were planned according to the ethical standards of the Declaration of Helsinki and approved by an Ethics Committee (CEIm La Fe 2017/0147). Written informed consent was obtained from all participants before their inclusion.

Participants

Subjects were recruited and followed at Hospital La Fe, Valencia, Spain, within the H2020 project OACTIVE. The design of the data collection protocol started in November 2017 and lasted until July 2018.

The subjects recruited were evaluated by a group of three experienced physical medicine and rehabilitation clinicians. The inclusion criteria for EOA patients were based on Luyten's proposal for EOA classification, as these criteria found a specificity of 76.5% for detection of clinical progression, being valid criteria for research use (28). Criteria were as follows: (a) Patient-based questionnaires: Knee Injury and Osteoarthritis Outcome score (KOOS): 2 out of the 4 KOOS subscales (Pain, Symptoms, Function or Knee-related quality of life) need to score "positive" ($\leq$85%); (b) Patients should present joint line tenderness or crepitus in the clinical examination; (c) X-rays: Kellgren and Lawrence (KL) grade 0–1 standing, weight bearing (at least 2 projections: PA fixed flexion and skyline for patellofemoral OA) (29). For matched controls the inclusion criteria were (a) Patient age greater than or equal to 40 years; (b) Kellgren & Lawrence 0–1.

Exclusion criteria were: (a) Any cognitive disability that hindered viewing of the audio-visual material; (b) Illiteracy; (c) Comprehension or communication difficulties, (d) Insufficient Spanish language comprehension to follow measurement instructions; (e) Presence of any rheumatic, autoimmune or infectious pathology; (f) other current knee injuries diagnosed by magnetic resonance image.

Outcome measures

Serum lipid and inflammatory biomarkers measurement

Serum lipid profile analysis (total cholesterol, triglyceride, HDL, and LDL) and inflammatory biomarkers C-Reactive protein (CRP),

and uric acid (UA) were measured in the biochemistry laboratory of the hospital. For the collection of blood we followed the rules proposed by the Standard Operating Procedures Internal Working Group (SOPIWG)/Early Detection Research Network (EDRN) for specimen collection. Four aliquots were sent on dry ice by courier to the Bionos Biotech La Fe and kept at −50°C until measurements of serum were taken using commercial ELISA kits (IDS Co., Bolden, United Kingdom), with intraassay coefficients of variation ranging from 5 to 15%.

Pain and disability variables

Pain intensity

Visual Analogue Scale (VAS) was used to measure pain intensity. The VAS is a 100-mm line with two endpoints representing the extreme states "no pain" (0) and "the maximal pain imaginable" (10). It has been shown to have good retest reliability ($r = 0.94$, $p < 0.001$) and a minimal detectable change of 15.0-mm (30, 31).

Western Ontario and McMaster universities osteoarthritis index (WOMAC)

This instrument is the most extensively used for the functional and symptomatic assessment of patients with OA. The WOMAC questionnaire is self-administered and is used to assess patients who progress with hip and/or knee OA. The questionnaire is a multidimensional scale composed of 24 items divided into three aspects: functional pain (consisting of 5 items), stiffness (2 items) and activities of daily life difficulties (17 items). Higher values mean poorer WOMAC subscales scores of pain and physical function. The Spanish version of the WOMAC questionnaire has adequate psychometric properties, presenting an index of internal consistency (a) of 0.82 for pain and 0.93 for physical function subscales (32).

Functional variables

Five times sit-to-stand test

To assess functional capacity, the sit-to-stand test was employed. The test was performed as follows: with the patient seated with their back against the back of the chair, the clinician counted each stand aloud so that the patient remained focused. The clinician stopped the test when the patient achieved the standing position on the 5th repetition (33). The amount of time needed to conduct the test was calculated in seconds. Relative inter-rater reliability results (ICC = 0.937) revealed excellent reliability (34).

Gait speed

The subject walked 10 m (32.8 feet) unaided and the time was measured for the intermediate 6 m (19.7 feet). Assistive devices could be used but had to be kept consistent and documented from test to test. It was performed at the fastest speed possible. There were three trials collected and the average of the three trials was calculated for the measurement (35, 36). Gait speed measurements were shown to have excellent test–retest reliability (ICC values of 0.96–0.98) (37).

Procedures

An information sheet with an explanation of the procedure and an informed consent form were given to all the participants. Once the subject had read the information regarding the study, they were allowed to ask any questions about its nature. Those subjects who agreed to participate proceeded to fill in the sociodemographic questionnaire. Their Self-reported measures of disability, pain and disability self-reported variables were then assessed. The study protocol lasted approximately 1 h. This procedure was identical for both groups.

Statistical analysis

The sociodemographic and clinical variables of the participants were analyzed. The data were summarized using frequency counts, descriptive statistics, summary tables and figures. The data analysis was performed using the Statistics Package for Social Sciences (SPSS 24, IBM Inc., United States). The categorical variables are shown as frequencies and percentages. The quantitative results are represented by descriptive statistics (confidence interval, mean, and standard deviation). Student's *t*-test was used for the group comparisons. Cohen's *d* effect sizes were calculated for multiple comparisons of the outcome variables. According to Cohen's method, the magnitude of the effect was classified as small (0.20–0.49), medium (0.50–0.79), or large (0.80).

The relationships between serum lipid measures with functional, pain and disability measurements in patients with EOA were examined using Pearson's correlation coefficients. A Pearson's correlation coefficient greater than 0.60 indicated a strong correlation, a coefficient between 0.30 and 0.60 indicated a moderate correlation and a coefficient below 0.30 indicated a low or very low correlation (38).

Results

A total of 96 participants were included in the study, with a mean age of 51.81 ± 5.59 (39 men and 58 women). 48 of the participants met the criteria to be classified as EOA and 48 participants as matched controls for sociodemographic characteristics. No abandonment of any participant was recorded, nor adverse effects were reported during the assessments. Also, there were no statistically significant differences between the groups in terms of descriptive and demographic variables (Table 1).

Main results

Regarding serum lipid profile analysis, statistically significant differences were found between groups. Patients with EOA showed higher levels of total cholesterol (201.78 ± 33.1 ng/mL) in comparison with matched controls (186.43 ± 38.03 ng/mL). Student's *t*-test showed statistically significant differences ($p < 0.05$), with medium effect size (MD: −15.36; $d = 0.43$). Similarly, patients with EOA showed higher levels of LDL (11.45 ± 26.59 ng/mL) in comparison with matched controls (90.86 ± 24.0.7 ng/mL). Student's *t*-test showed statistically

10.3389/fnut.2023.1126796

TABLE 1 Descriptive and demographic variables.

Measures	EOA (n=48)	HS (n=48)	p value
Age (years)	52.36 ± 5.02	50.72 ± 6.87	0.46
BMI (kg/m^2)	26.98 ± 4.36	27.50 ± 3.89	0.43
KL			0.65
0	19 (39.6)	20 (41.6)	
1	29 (60.4)	28 (58.4)	
Gender			0.17
Women	39 (81.3)	43 (89.6)	
Men	9 (18.7)	5 (10.4)	
Economic status			0.86
Easy	8 (16.7)	3 (6.3)	
Fairly easy	35 (72.9)	38 (79.2)	
With some difficulties	3 (6.2)	7 (14.5)	
With great difficulties	2 (4.2)	0 (0)	
Alcohol			0.65
Never	10 (22.2)	8 (16.7)	
Seldom	20 (41.7)	18 (37.5)	
1–2 times/month	4 (8.3)	8 (16.7)	
1–2 times/week	7 (14.3)	12 (25)	
1 time day	5 (10.3)	2 (4.1)	
More than 1 a day	2 (4.1)	0 (0)	
Smoking			0.27
Yes	3 (6.25)	6 (12.5)	
No	10 (22.2)	20 (41.7)	
Ex	35 (72.9)	22 (45.8)	

Data are expressed as mean ± standard deviation or n (%). BMI, Body Mass Index; KL, Kellgren & Lawrence; EOA, Early osteoarthritis.

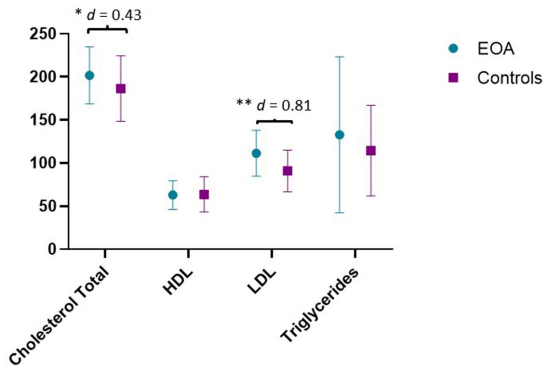


FIGURE 1
Results of serum lipid profile analysis. Results are expressed in ng/mL. HDL, high-density lipoprotein; LDL, low-density lipoprotein; EOA, Early Osteoarthritis. **p<0.01; *p<0.05; d=Effect size.

significant differences (p < 0.05), with large effect size (MD: −20.59; d = 0.81). However, no significant differences were found between groups in HDL and triglycerides (Figure 1). Serum lipid profile was compared to reference values according to the Adult Treatment Panel III (ATP III) (39) (Table 2).

In relation to inflammatory biomarkers, patients with EOA present higher levels of UA and CRP, and Student's t-test showed statistically significant differences for both variables (p < 0.05), with medium effect size (MD: 1.53; d = 0.71 and MD: −0.95, d = 0.41, respectively) (Figure 2). Inflammatory biomarkers were compared to reference values previously established (40, 41) (Table 2).

Correlation analysis

Correlation analysis showed that higher levels of total cholesterol were correlated with higher levels of pain intensity and higher disability, with low to moderate correlation strength (r = 0.25 and 0.37; p < 0.05). In addition, LDL and CRP levels were correlated with higher pain intensity (r = 0.44 and 0.34; p < 0.05). Finally, UA and CRP were inversely correlated with gait speed and sit-to-stand tests, with moderate strength (r = −0.038 to −0.5, p < 0.05) (Table 3).

Discussion

The main aim of this work was to study differences of serum lipid and inflammatory biomarkers with knee EOA in comparison with matched controls, in order to determine the role of these factors in the origin of EOA. The main results showed that patients with EOA have higher levels of total cholesterol, LDL, UA, and CRP compared to matched controls.

The relationship between serum lipid levels is contradictory in the current scientific evidence. A systematic review and meta-analysis found that in case–control and cross-sectional studies, there was a clear relationship between dyslipidemia and the presence of OA (case–control: OR = 1:37; 95%; CI = 1:27–1.46; cross-sectional: OR = 1:33; 95%CI = 1:21–1.46), especially in the knee. However, this same review did not find the same relationship when analyzing only cohort studies (RR = 1:00; 95%; CI = 0:85–1.14) (42).

Several mechanisms have been proposed in relation to lipid metabolism and OA. Cholesterol has a crucial role in chondrogenesis and endochondral osteogenesis (43). In this regard, it has been shown that higher levels of HDL may have a protective effect on joints (44). However, inflammatory processes can be triggered by the accumulation of persistent LDLs in the cartilage extracellular matrix. Oxidized LDL ligands to chondrocyte LOX-1 stimulate the production of ROS in chondrocytes, resulting in the expression of catabolic genes (45, 46). Several previous studies show relationships between inflammation and disequilibrium in cholesterol homeostasis, as osteoarthritic cartilage presents remarkable down-regulation of the expression of the cholesterol efflux gene compared to normal cartilage (47, 48). In addition, when there is an aggregation of joint cholesterol, vascular injury is at risk, resulting in impaired blood flow to the subchondral bone. When cartilage loses oxygen and nutrients, this can result in histopathology and contribute to the development of OA (48, 49). Additionally, hypercholesterolemia can also lead to oxidation and lipid deposition in tissues, resulting in cartilage damage (49). Our results showed higher levels of total cholesterol in patients with EOA and a correlation between these levels and a greater intensity of pain and disability, showing a possible relationship between cholesterol and

10.3389/fnut.2023.1126796

TABLE 2 Differences between groups.

Measures	EOA	Controls	Reference values	Mean difference (95% CI)	Effect size (*d*)
Uric acid	5.72 ± 2.6	4.19 ± 1.53	<6.0	−1.53** (−2.37 to −0.7)	0.7135
Cholesterol Total	201.78 ± 33.1	186.43 ± 38.03	<200	−15.36* (−29.49 to −1.22)	0.4313
HDL	62.96 ± 16.51	63.65 ± 20.46	>40	0.69 (−6.80 to 8.17)	0.0370
LDL	111.45 ± 26.59	90.86 ± 24.07	<100	−20.59** (−30.67 to −10.51)	0.8111
Triglycerides	132.71 ± 90.48	114.43 ± 52.63	<150	18.28 (−11.48 to 48.04)	0.2476
C-reactive protein	2.73 ± 2.74	1.78 ± 1.82	<1	−0.95* (−1.88 to −0.02)	0.4098

Data are expressed as mean (mg/dL) ± standard deviation. HDL, high-density lipoprotein; LDL, low-density lipoprotein; EOA, Early Osteoarthritis; CI, Confidence Interval. **$p < 0.01$; *$p < 0.05$.

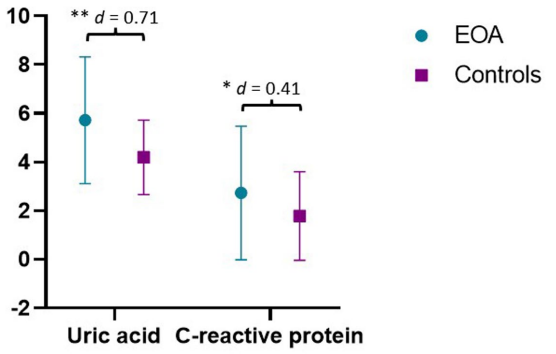


FIGURE 2
Results of inflammatory biomarkers. Results are expressed in ng/mL. EOA, Early Osteoarthritis. **$p<0.01$; *$p<0.05$; d=Effect size.

TABLE 3 Correlation analysis.

	WOMAC	Pain intensity	Walking speed	Sit-to-stand
Uric acid	0.04	0.04	−0.48*	−0.39*
Cholesterol total	0.25*	0.37*	0.09	0.02
HDL	0.03	−0.1	0.04	0.08
LDL	0.33*	0.44*	0.05	0.2
Triglycerides	0.1	0.04	0.2	0.15
C-reactive protein	0.23	0.34*	−0.5*	−0.38*

HDL, high-density lipoprotein; LDL, low-density lipoprotein; EOA, Early Osteoarthritis. *$p < 0.05$.

the genesis of OA (metabolic OA phenotype). Furthermore, these results suggest the need to further investigate the relationship between cholesterol levels, inflammation, and clinical symptoms in these patients, so that new therapies take into account pro-inflammatory nutritional aspects that appear to be linked.

CRP is an acute-phase protein synthesized by hepatocytes in response to pro-inflammatory cytokines during inflammatory/infectious processes (50). Low levels of CRP can be measured accurately, and it is thus possible to identify individuals with low-grade inflammation, that is associated with an increased risk of several diseases (51, 52). The involvement of CRP in the pathogenesis of OA in humans has been suggested (53). Systemic CRP levels are significantly elevated in OA patients compared to healthy controls and have been reported to be related to clinical features and radiographic severity (54). In addition, similar to our results, the population-based Chingford study confirmed these findings and the authors suggested that CRP levels in EOA can be used as a predictive marker of disease progression (55). Similarly, the meta-analysis performed by Jin et al. showed that CRP levels were significantly associated with pain and decreased physical function, but not with radiographic OA, similar to our results (56).

In relation to UA, an association between UA and OA has been proposed due to a shared pathogenetic mechanism related to MS. *In vitro* analyses of the effects of monosodium urate crystals on catabolic and proinflammatory signaling in chondrocytes revealed a strong dose-and time-dependent reduction in the viability of primary human chondrocytes and cartilage explants, together with a decrease in cartilage matrix proteins (57). Also, urate crystals significantly increased the expression of catabolic mediators such as nitric oxide (58, 59). In addition to urate crystals, soluble UA has various proinflammatory and prooxidant effects, and the presence of UA transporters in human chondrocytes suggests that they can internalize soluble UA and initiate catabolic responses (60). However, the specific role of uric acid during autophagy is currently unknown, but cell death could result in local supersaturation of uric acid as cytolysis generates large quantities of purines from RNA and DNA (61). As suggested by Matzinger's theories, the release of uric acid could provide an inflammatory danger signal which is responsible for activating a chronic immune inflammatory response, being the result of activation of IL-18 and IL-1β (62).

Finally, UA and CRP were inversely correlated with gait speed and sit-to-stand tests, these being clinical measures of functionality. Thus, the sit-to-stand test has been directly related to leg strength, a measure of functional status and ability (63). Furthermore, decline in gait speed has been associated with an increased risk of all-cause mortality and other markers of health in well-functioning individuals (64). This finding is interesting given that already in patients with EOA, inflammatory biomarkers have a direct relationship with functionality.

In this sense, these functional tests are quick, easy, and low-cost to use in clinical practice, so it may be relevant to assess them for early detection of inflammatory changes and to try to prevent physical decline and disease progression.

Limitations

Due to the nature of the study (cross-sectional), it is not possible to assess any cause-and-effect relationship neither temporal relationship between inflammatory and serum lipid biomarkers and the clinical variables assessed. In addition, it is not possible to determine the direction of the relationship (e.g., if inflammatory and serum lipid biomarkers levels are the result of the presence of OA or if they are responsible of its incidence). Finally, results should be interpreted with caution due to the low sample size included and the lack of the possibility to calculate the sample size in advance.

Conclusion

Patients with EOA have higher levels of total cholesterol, LDL, UA, and CRP compared to matched controls. In addition, higher levels of total cholesterol, LDL and CRP were correlated with higher levels of pain intensity and higher disability, and UA and CRP were inversely correlated with functional status. These results highlight the relevance of metabolic and proinflammatory aspects in the early stages of knee OA and could be key to developing early diagnoses to prevent the onset and development of the disease.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by the La Fé Hospital. The patients/participants provided their written informed consent to participate in this study.

Author contributions

LH-M, AA-C, EV-H, and IV-A contributed to conception and design of the study. LH-M organized the database. JCl performed the statistical analysis. FC-M wrote the first draft of the manuscript. LS-M, FF-S, JCs, and MB-D wrote sections of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

Funding

This project has received funding from the European Union's Horizon 2020 Research and Innovation Program under grant agreement no. 777159.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

1. Bijlsma JWJ, Berenbaum F, Lafeber FPJG. Osteoarthritis: An update with relevance for clinical practice. *Lancet*. (2011) 377:2115–26. doi: 10.1016/S0140-6736(11)60243-2

2. Mora JC, Przkora R, Cruz-Almeida Y. Knee osteoarthritis: Pathophysiology and current treatment modalities. *J Pain Res*. (2018) 11:2189–96. doi: 10.2147/JPR.S154002

3. Salaffi F, Carotti M, Stancati A, Grassi W. Health-related quality of life in older adults with symptomatic hip and knee osteoarthritis: A comparison with matched healthy controls. *Aging Clin Exp Res*. (2005) 17:255–63. doi: 10.1007/BF03324607

4. Neogi T. The epidemiology and impact of pain in osteoarthritis. *Osteoarthritis Cartilage*. (2013) 21:1145–53. doi: 10.1016/j.joca.2013.03.018

5. Nelson AE. Osteoarthritis year in review 2017: Clinical. *Osteoarthritis Cartilage*. (2018) 26:319–25. doi: 10.1016/j.joca.2017.11.014

6. Velasquez MT, Katz JD. Osteoarthritis: Another component of metabolic syndrome? *Metab Syndr Relat Disord*. (2010) 8:295–305. doi: 10.1089/met.2009.0110

7. Orlowsky EW, Kraus VB. The role of innate immunity in osteoarthritis: When our first line of defense goes on the offensive. *J Rheumatol*. (2015) 42:363–71. doi: 10.3899/jrheum.140382

8. Sellam J, Berenbaum F. The role of synovitis in pathophysiology and clinical symptoms of osteoarthritis. *Nat Rev Rheumatol*. (2010) 6:625–35. doi: 10.1038/nrrheum.2010.159

9. Bierma-Zeinstra SMA, Koes BW. Risk factors and prognostic factors of hip and knee osteoarthritis. *Nat Clin Pract Rheumatol*. (2007) 3:78–85. doi: 10.1038/ncprheum0423

10. Luppino FS, de Wit LM, Bouvy PF, Stijnen T, Cuijpers P, Penninx BWJH, et al. Overweight, obesity, and depression: A systematic review and meta-analysis of longitudinal studies. *Arch Gen Psychiatry*. (2010) 67:220–9. doi: 10.1001/archgenpsychiatry.2010.2

11. Festa A, D'Agostino R, Howard G, Mykkänen L, Tracy RP, Haffner SM. Chronic subclinical inflammation as part of the insulin resistance syndrome: The insulin resistance atherosclerosis study (IRAS). *Circulation*. (2000) 102:42–7. doi: 10.1161/01.cir.102.1.42.

12. Farinelli L, Aquili A, Mattioli-Belmonte M, Manzotti S, D'Angelo F, Ciccullo C, et al. Synovial mast cells from knee and hip osteoarthritis: Histological study and clinical correlations. *J Exp Orthop*. (2022) 9:13–8. doi: 10.1186/s40634-022-00446-2

13. Aquili A, Farinelli L, Bottegoni C, Antonicelli L, Gigante A. The effect of anti-IgE therapy in knee osteoarthritis: A pilot observational study. *J Biol Regul Homeost Agents*. (2017) 31:1–5.

14. Harwood HJ. The adipocyte as an endocrine organ in the regulation of metabolic homeostasis. *Neuropharmacology*. (2012) 63:57–75. doi: 10.1016/j.neuropharm.2011.12.010

15. Zhuo Q, Yang W, Chen J, Wang Y. Metabolic syndrome meets osteoarthritis. *Nat Rev Rheumatol*. (2012) 8:729–37. doi: 10.1038/nrrheum.2012.135

16. Kluzek S, Newton JL, Arden NK. Is osteoarthritis a metabolic disorder? *Br Med Bull*. (2015) 115:111–21. doi: 10.1093/bmb/ldv028

17. Loeser RF, Goldring SR, Scanzello CR, Goldring MB. Osteoarthritis: A disease of the joint as an organ. *Arthritis Rheum*. (2012) 64:1697–707. doi: 10.1002/art.34453

18. Chen D, Shen J, Zhao W, Wang T, Han L, Hamilton JL, et al. Osteoarthritis: Toward a comprehensive understanding of pathological mechanism. *Bone Res*. (2017) 5:16044. doi: 10.1038/boneres.2016.44

19. Felson DT, Hodgson R. Identifying and treating preclinical and early osteoarthritis. *Rheu. Dis. Clin. North Am.* (2014) 40:699–710. doi: 10.1016/j.rdc.2014.07.012

20. Malempati C, Jacobs CA, Lattermann C. The early osteoarthritic knee: Implications for cartilage repair. *Clin Sports Med*. (2017) 36:587–96. doi: 10.1016/j.csm.2017.02.011

21. Oliviero F, Ramonda R, Punzi L. New horizons in osteoarthritis. *Swiss Med Wkly*. (2010) 140:w13098. doi: 10.4414/smw.2010.13098

22. Mahmoudian A, Lohmander LS, Mobasheri A, Englund M, Luyten FP. Early-stage symptomatic osteoarthritis of the knee — time for action. *Nat Rev Rheumatol*. (2021) 17:621–32. doi: 10.1038/s41584-021-00673-4

23. Madry H, Luyten FP, Facchini A. Biological aspects of early osteoarthritis. *Knee Surg Sports Traumatol Arthrosc*. (2012) 20:407–22. doi: 10.1007/s00167-011-1705-8

24. Chiba D, Nakamura T, Fu FH. Early osteoarthritis—definition, pathogenesis, diagnosis, management and prevention: Management. *Ann Jt*. (2019) 4:5. doi: 10.21037/aoj.2019.01.03

25. Neogi T, Zhang Y. Osteoarthritis prevention. *Curr Opin Rheumatol*. (2011) 23:185–91. doi: 10.1097/BOR.0b013e32834307eb

26. Cooper C, Snow S, Mcalindon TE, Kellingray S, Stuart B, Coggon D, et al. Risk factors for the incidence and progression of radiographic knee osteoarthritis. *Arthritis Rheum*. (2000) 43:995–1000. doi: 10.1002/1529-0131

27. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP, et al. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: Guidelines for reporting observational studies. *J Clin Epidemiol*. (2008) 61:344–9. doi: 10.1016/j.jclinepi.2007.11.008

28. Mahmoudian A, Lohmander LS, Jafari H, Luyten FP. Towards classification criteria for early-stage knee osteoarthritis: A population-based study to enrich for progressors. *Semin Arthritis Rheum*. (2021) 51:285–91. doi: 10.1016/j.semarthrit.2020.11.002

29. Luyten FP, Denti M, Filardo G, Kon E, Engebretsen L. Definition and classification of early osteoarthritis of the knee. Knee surgery, sports traumatology. *Arthroscopy*. (2012) 20:401–6. doi: 10.1007/s00167-011-1743-2

30. Bijur PE, Silver W, Gallagher EJ. Reliability of the visual analog scale for measurement of acute pain. *Acad Emerg Med*. (2001) 8:1153–7. doi: 10.1111/j.1553-2712.2001.tb01132.x

31. Ostelo RWJG, Deyo RA, Stratford P, Waddell G, Croft P, Von Korff M, et al. Interpreting change scores for pain and functional status in low Back pain. *Spine*. (2008) 33:90–4. doi: 10.1097/BRS.0b013e31815e3a10

32. Escobar A, Quintana JM, Bilbao A, Azkárte J, Güenaga LI. Validation of the Spanish version of the WOMAC questionaire for patients with hip or knee osteoarthritis. *Clin Rheumatol*. (2002) 21:466–71. doi: 10.1007/s100670200117

33. Paul SS, Canning CG. Five-repetition sit-to-stand. *J Physiother Aust Physiother Assoc*. (2014) 60:168. doi: 10.1016/j.jphys.2014.06.002

34. Muñoz-Bermejo L, Adsuar JC, Mendoza-Muñoz M, Barrios-Fernández S, Garcia-Gordillo MA, Pérez-Gómez J, et al. Test-retest reliability of five times sit to stand test (FTSST) in adults: A systematic review and meta-analysis. *Biology*. (2021) 10:510. doi: 10.3390/biology10060510

35. Bohannon RW, Andrews AW, Thomas MW. Walking speed: Reference values and correlates for older adults. *J Orthopaed Sports Phys Therapy*. (1996) 24:86–90. doi: 10.2519/jospt.1996.24.2.86

36. Bohannon RW. Comfortable and maximum walking speed of adults aged 20-79 years: Reference values and determinants. *Age Ageing*. (1997) 26:15–9. doi: 10.1093/ageing/26.1.15

37. Peters DM, Fritz SL, Krotish DE. Assessing the reliability and validity of a shorter walk test compared with the 10-meter walk test for measurements of gait speed in healthy, older adults. *J Geriatr Phys Ther*. (2013) 36:24–30. doi: 10.1519/JPT.0b013e318248e20d

38. Hinkle DE, Wiersma W, Jurs SG. Applied statistics for the behavioral sciences. *Source J Educ Stat*. (1990) 15:84–7.

39. Cleeman JI. Executive summary of the third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment panel III). *JAMA*. (2001) 285:2486–97. doi: 10.1001/jama.285.19.2486

40. Nehring SM, Goyal A, Bansal P, Patel BC. C Reactive Protein. *Stat Pearls*. (2022) 65:237–44.

41. Desideri G, Castaldo G, Lombardi A, Mussap M, Testa A, Pontremoli R, et al. Is it time to revise the normal range of serum uric acid levels? *Eur Rev Med Pharmacol Sci*. (2014) 18:1295–306.

42. Xiong J, Long J, Chen X, Li Y, Song H. Dyslipidemia might be associated with an increased risk of osteoarthritis. *Biomed Res Int*. (2020) 2020:1–9. doi: 10.1155/2020/3105248

43. Wu S, de Luca F. Role of cholesterol in the regulation of growth plate chondrogenesis and longitudinal bone growth. *J Biol Chem*. (2004) 279:4642–7.

44. Oliviero F, Sfriso P, Baldo G, Dayer JM, Giunco S, Scanu A, et al. Apolipoprotein A-I and cholesterol in synovial fluid of patients with rheumatoid arthritis, psoriatic arthritis and osteoarthritis. *Clin Exp Rheumatol*. (2009) 27:79–83.

45. Choi MC, Jo J, Park J, Kang HK, Park Y. NF-κB signaling pathways in osteoarthritic cartilage destruction. *Cells*. (2019) 8:734. doi: 10.3390/cells8070734

46. Parthasarathy S, Raghavamenon A, Garelnabi MO, Santanam N. Oxidized low-density lipoprotein. *Methods Mol Biol*. (2010) 610:403–17. doi: 10.1007/978-1-60327-029-8_24

47. Papathanasiou I, Anastasopoulou L, Tsezou A. Cholesterol metabolism related genes in osteoarthritis. *Bone*. (2021) 152:116076. doi: 10.1016/j.bone.2021.116076

48. Farnaghi S, Crawford R, Xiao Y, Prasadam I. Cholesterol metabolism in pathogenesis of osteoarthritis disease. *Int J Rheum Dis*. (2017) 20:131–40. doi: 10.1111/1756-185X.13061

49. Su Z, Zong Z, Deng J, Huang J, Liu G, Wei B, et al. Lipid metabolism in cartilage development, degeneration, and regeneration. *Nutrients*. (2022) 14:3984. doi: 10.3390/nu14193984

50. Luan YY, Yao YM. The clinical significance and potential role of C-reactive protein in chronic inflammatory and neurodegenerative diseases. *Front Immunol*. (2018) 9:1302. doi: 10.3389/fimmu.2018.01302

51. Pepys MB, Hirschfield GM. C-reactive protein: A critical update. *J Clin Investig*. (2003) 111:1805–12. doi: 10.1172/JCI200318921

52. Dinh KM, Kaspersen KA, Mikkelsen S, Pedersen OB, Petersen MS, Thørner LW, et al. Low-grade inflammation is negatively associated with physical health-related quality of life in healthy individuals: Results from the Danish blood donor study (DBDS). *PLoS One*. (2019) 14:e0214468. doi: 10.1371/journal.pone.0214468

53. Kozijn AE, Tartjiono MT, Ravipati S, van der Ham F, Barrett DA, Mastbergen SC, et al. Human C-reactive protein aggravates osteoarthritis development in mice on a high-fat diet. *Osteoarthr Cartil*. (2019) 27:118–28. doi: 10.1016/j.joca.2018.09.007

54. Hanada M, Takahashi M, Furuhashi H, Koyama H, Matsuyama Y. Elevated erythrocyte sedimentation rate and high-sensitivity C-reactive protein in osteoarthritis of the knee: Relationship with clinical findings and radiographic severity. *Ann Clin Biochem*. (2016) 53:548–53. doi: 10.1177/0004563215610142

55. Spector TD, Hart DJ, Nandra D, Doyle DV, Mackillop N, Gallimore JR, et al. Low-level increases in serum C-reactive protein are present in early osteoarthritis of the knee and predict progressive disease. *Wiley Online Library*. (1997) 40:723–7. doi: 10.1002/art.1780400419

56. Jin X, Ruiz Beguerie J, Zhang W, Blizzard L, Otahal P, Jones G, et al. Circulating C reactive protein in osteoarthritis: A systematic review and meta-analysis. *Ann Rheum Dis*. (2015) 74:703–10. doi: 10.1136/annrheumdis-2013-204494

57. Go DJ, Kim DH, Kim JY, Guermazi A, Crema MD, Hunter DJ, et al. Serum uric acid and knee osteoarthritis in community residents without gout: A longitudinal study. *Rheumatology*. (2021) 60:4581–90. doi: 10.1093/rheumatology/keab048

58. Hwang H, Yang C, Park S, Kim HA. Monosodium urate crystal-induced chondrocyte death via autophagic process. *Int J Mol Sci*. (2015) 16:29265–77. doi: 10.3390/ijms161226164

59. Chhana A, Callon K, Pool B, Naot D, Gamble GD, Dray M. The effects of monosodium urate monohydrate crystals on chondrocyte viability and function: Implications for development of cartilage damage in gout. *J Rheumatol*. (2013) 40:2067–74. doi: 10.3899/jrheum.130708

60. Mobasheri A, Neama G, Bell S, Richardson S, Carter SD. Human articular chondrocytes express three facilitative glucose transporter isoforms: GLUT1, GLUT3 and GLUT9. *Cell Biol Int*. (2002) 26:297–300. doi: 10.1006/cbir.2001.0850

61. Shi Y. Caught red-handed: Uric acid is an agent of inflammation. *J Clin Invest*. (2010) 120:1809–11. doi: 10.1172/JCI43132

62. Martinon F, Pétrilli V, Mayor A, Tardivel A, Tschopp J. Gout-associated uric acid crystals activate the NALP3 inflammasome. *Nature*. (2006) 440:237–41. doi: 10.1038/nature04516

63. Foldvari M, Clark M, Laviolette LC, Bernstein MA, Kaliton D, Castaneda C, et al. Association of muscle power with functional status in community-dwelling elderly women. *J Gerontol A Biol Sci Med Sci*. (2000) 55:M192–9. doi: 10.1093/gerona/55.4.M192

64. Master H, Neogi T, Callahan LF, Nelson AE, LaValley M, Cleveland RJ, et al. The association between walking speed from short-and standard-distance tests with the risk of all-cause mortality among adults with radiographic knee osteoarthritis: Data from three large United States cohort studies. *Osteoarthritis Cartilage*. (2020) 28:1551–8. doi: 10.1016/j.joca.2020.08.009