Facultad de Medicina y Odontología

Universitat de València

Programa de Doctorado en Medicina 3139

Departamento de Medicina

"INVESTIGACIÓN DE FACTORES DE RIESGO RELACIONADOS CON LA ARTROSIS PRECOZ DE RODILLA"

TESIS DOCTORAL POR COMPENDIO DE PUBLICACIONES

Presentada por: Dña. Ana Alabajos Cea
Licenciada en Medicina
Tesis realizada en Hospital La Fe

Director: Enrique Viosca Herrero
Tutora: Mª Carmen Gómez Cabrera

Valencia. Septiembre 2023

PRÓLOGO

Los Doctores D. Enrique Viosca Herrero y Dña. Mª Carmen Gómez Cabrera, como director y tutora de la tesis "**INVESTIGACIÓN DE FACTORES DE RIESGO RELACIONADOS CON LA ARTROSIS PRECOZ DE RODILLA**",

EXPONEN:

Que los tres artículos que se recogen en la tesis están publicados en revistas indexadas con los siguientes factores de impacto e índices de calidad:

I. Alabajos-Cea A, Herrero-Manley L, Suso-Martí L, Sempere-Rubio N, Cuenca-Martínez F, Muñoz-Alarcos V, Pérez-Barquero JA, Viosca-Herrero E, Vázquez-Arce I. Screening Clinical Changes for the Diagnosis of Early Knee Osteoarthritis: A Cross-Sectional Observational Study. Diagnostics (Basel). 2022 Oct 30;12(11):2631.
DOI: 10.3390/diagnostics12112631
PMID: 36359475; PMCID: PMC9689265
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Q2 MEDICINE, GENERAL & INTERNAL

II. Alabajos-Cea A, Herrero-Manley L, Suso-Martí L, Alonso-Pérez-Barquero J, Viosca-Herrero E. Are Psychosocial Factors Determinant in the Pain and Social Participation of Patients with Early Knee Osteoarthritis? A Cross-Sectional Study. Int J Environ Res Public Health. 2021 Apr 26;18(9):4575.
DOI: 10.3390/ijerph18094575
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Q2 ENVIRONMENTAL SCIENCES; Q2 PUBLIC, ENVIRONMENTAL & OCCUPATIONAL HEALTH

III. Alabajos-Cea A, Herrero-Manley L, Suso-Martí L, Viosca-Herrero E, Cuenca-Martínez F, Varangot-Reille C, Blanco-Díaz M, Calatayud J, Casaña J. The Role of Vitamin D in Early Knee Osteoarthritis and Its Relationship with Their Physical and Psychological Status. Nutrients. 2021 Nov 12;13(11):4035.
DOI: 10.3390/nu13114035
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Otras publicaciones relacionadas con los datos obtenidos en la investigación en los que la doctoranda no es primera autora:

IV. Papaneophytou C, Alabajos-Cea A, Viosca-Herrero E, Calvis C, Costa M, Christodoulides AE, Kroushovski A, Lapithis A, Lapithi VM, Papayiannis I, Christou A, Messeguer R, Giannaki C, Felekkis K. Associations between serum biomarkers of cartilage metabolism and serum hyaluronic acid, with risk factors, pain categories, and disease severity in knee osteoarthritis: a pilot study. BMC Musculoskelet Disord. 2022 Mar 2;23(1):195.
DOI: 10.1186/s12891-022-05133-y
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Q3 ORTHOPEDICS

V. 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, Blanco-Díaz M. Serum lipid biomarkers and inflammatory cytokines associated with onset and clinical status of patients with early knee osteoarthritis. Front Nutr. 2023 Mar 15;10:1126796.
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2021 JOURNAL IMPACT FACTOR (Web of Science): 6.590
Q1 NUTRITION & DIETETICS

VI. 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 Jun 9;11(6):1670.
DOI: 10.3390/biomedicines11061670
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Revista: Biomedicines (EISSN: 2227-9059)
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Artículos realizados a partir de los datos y resultados obtenidos en el presente trabajo de investigación que han sido aceptados para su publicación:

VII. Herrero-Manley L, Alabajos-Cea A, Suso-Martí L, Viosca-Herrero E., Vázquez-Arce I. Classification criteria for early knee osteoarthritis: a systematic review. En revisión. *Aceptado en* Aktuelle Rheumatologie, ISSN 0341-051X. Manuscript ID: Manuscript ID: AktRheum-2023-03-0907-OA.R3

Así mismo, EXPONEN:

Que la Doctoranda, Ana Alabajos Cea, ha participado en cada uno de los 3 artículos que se recogen en esta tesis planificando el estudio, escribiendo el proyecto y solicitando su aceptación por el comité ético. Ana Alabajos Cea evaluó a todos los pacientes y recogió todos los datos clínicos, junto con los coautores de los trabajos. Del mismo modo, junto a los coautores de los artículos, revisó y analizó todos los datos obteniendo los resultados descritos y escribió el borrador de los artículos. Todos los autores aceptaron la versión final de los manuscritos.
Los datos incluidos en los 3 artículos expuestos en esta tesis han sido explícitamente recogidos para esta Tesis Doctoral y no han sido utilizados para otros proyectos ni estudios.

Para la realización de la Tesis Doctoral presentada, la investigadora Ana Alabajos Cea ha disfrutado de un contrato de investigación del programa H2020 de la CE, dentro del proyecto europeo H2020 “OACTIVE: Advanced personalised, multi-scale computer models preventing OsteoArthritis”, *Grant Agreement* No 777159.

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de D/Dña. Ana Alabajos Cea,

estudiante del Programa de Doctorado **3139 Medicina** (RD99/2011) en Medicina de la Universitat de València, emiten informe FAVORABLE *(favorable/desfavorable)* para la realización del depósito y la defensa de la tesis doctoral.

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“Los hombres de ciencia sospechan algo sobre ese mundo, pero lo ignoran casi todo.
Los sabios interpretan los sueños, y los dioses se ríen.”

— H. P. Lovecraft

“Sin datos, no eres más que otra persona con una opinión”

— W. Edwards Deming

ÍNDICE

RESUMEN

El objetivo general de esta tesis fue determinar factores que pudiesen ayudar a establecer un diagnóstico precoz de la artrosis de rodilla, permitiendo un abordaje temprano del proceso.

Para ello, se realizó un análisis extenso de multitud de variables en 55 sujetos con artrosis precoz de rodilla, clasificados según los criterios vigentes validados para la investigación en este campo, y 51 controles sanos, y se interpretaron los resultados cotejándolos con la literatura científica existente.

Las principales conclusiones han sido que variables como dolor, discapacidad, inestabilidad, debilidad muscular, test *sit-to-stand* y test de marcha, pueden contribuir al establecimiento de un diagnóstico precoz de la artrosis de rodilla; el abordaje temprano de la ansiedad y la depresión en sujetos con artrosis precoz de rodilla puede contribuir a una mayor participación social, y prevenir un empeoramiento del cuadro; la valoración y abordaje del déficit de vitamina D y niveles de PTH puede ser crucial en el diagnóstico precoz y en la prevención de la artrosis de rodilla.

ABREVIATURAS

- 25-(OH)D: 25-hidroxivitamina D
- ACR: American College of Rheumatology
- AEMPS: Agencia Española de Medicamentos y Productos Sanitarios
- CEIm: Comité de Ética de la investigación con medicamentos
- COMP: Cartilage oligomeric matrix protein
- EKOA: Early Knee Osteoarthritis
- EOA: Early Osteoarthritis
- EULAR: European Alliance of Associations for Rheumatology
- EVA: Escala Visual Analógica
- GAD: Goldberg Anxiety and Depression Inventory
- HADS: Hospital Anxiety and Depression Scale
- HDL: lipoproteínas de alta densidad
- KOA: Knee Osteoarthritis
- KOOS: Knee Injury and Osteoarthritis Outcome Score
- LDL: lipoproteínas de baja densidad
- MMII: miembros inferiores
- NHANES: National Health and Nutrition Examination Survey
- NICE: National Institute for Health and Care Excellence
- OA: Osteoarthritis
- OAI: Osteoarthritis Initiative
- PIICP: Procollagen type II C-terminal propeptide
- PTH: Hormona paratiroidea
- 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

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ÍNDICE DE TABLAS

I. INTRODUCCIÓN

La artrosis (OA por sus siglas en inglés, *Osteoarthritis*) es una de las diez causas principales de discapacidad, por lo que constituye un problema primordial de salud pública a nivel mundial[1, 2, 3].

Esta entidad 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[4].

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[5].

Se trata de un proceso caracterizado por cambios degenerativos progresivos[6, 7, 8] que pueden ocurrir como consecuencia de una gran variedad de factores (postraumáticos, genéticos, metabólicos, biomecánicos…), aunque el mecanismo exacto de su patogénesis se desconoce[9]. Típicamente, cursa con dolor crónico y provoca una disminución de la calidad de vida de los pacientes, constituyendo una causa fundamental de consumo de recursos sanitarios[10].

La artrosis de rodilla (KOA por sus siglas en inglés, *Knee Osteoarthritis*) es la forma más prevalente de artrosis. Es heterogénea en cuanto a factores de riesgo y grados de progresión y no existe tratamiento efectivo para ella[11]. Se ha asociado típicamente con cambios degenerativos resultantes de la pérdida progresiva de cartílago articular, así como con cambios en el hueso subcondral, inflamación sinovial y degeneración meniscal[12, 13]. Estas manifestaciones conducen a dolor articular, rigidez y disminución del rango articular, afectando la función física y la calidad de vida de los pacientes[14, 15].

En la literatura podemos encontrar mucha información relativa a los factores fisiopatológicos que condicionan la existencia de artrosis o que influyen en su desarrollo y progresión. Sin embargo, la mayor parte de estos factores y relaciones se han encontrado en fases avanzadas de artrosis, y los procesos involucrados en la aparición precoz de la KOA no se comprenden todavía en profundidad[9].

La artrosis precoz de rodilla (EKOA, *Early Knee Ostearthritis*) ha suscitado interés desde siempre, en un intento de encontrar predictores para su progresión y mejorar las opciones de tratamiento. Se han publicado distintas definiciones y clasificaciones[10, 16, 17, 18, 19, 20, 21, 22] para esta entidad, pero sin llegar a establecerse unos criterios diagnósticos claros y válidos.

Se trata de un tema de especial interés en los servicios de Rehabilitación. Por un lado, debido a que la mayoría de los pacientes remitidos con diagnóstico de KOA llegan en fases avanzadas, con escasas opciones de tratamiento y, en ocasiones, habiendo sido

sometidos a cirugías, tal vez evitables. Por otro lado, también vemos el otro extremo de la situación cuando nos remiten pacientes con dolor de rodilla sin estudiar completamente, bien porque se trata de EKOA, o bien porque debido a su gran prevalencia, se abusa de este diagnóstico.

I. 1. Definición EKOA

En 1986, Altman y colaboradores desarrollaron los "criterios ACR (*American College of Rheumatology*)[16]" (Figura 1) para la KOA, que se presentaron inicialmente como criterios de clasificación, pero fueron usados rápidamente como criterios diagnósticos en investigación.

Table 1. Classification for subsets of osteoarthritis*

I. Idiopathic
- A. Localized
  1. Hands: e.g., Heberden's and Bouchard's nodes (nodal), erosive interphalangeal arthritis (non-nodal), scapho-metacarpal, scaphotrapezial
  2. Feet: e.g., hallux valgus, hallux rigidus, contracted toes (hammer/cockup toes), talonavicular
  3. Knee
     a. Medial compartment
     b. Lateral compartment
     c. Patellofemoral compartment (e.g., chondromalacia)
  4. Hip
     a. Eccentric (superior)
     b. Concentric (axial, medial)
     c. Diffuse (coxae senilis)
  5. Spine (particularly cervical and lumbar)
     a. Apophyseal
     b. Intervertebral (disc)
     c. Spondylosis (osteophytes)
     d. Ligamentous (hyperostosis [Forestier's disease, or DISH])
  6. Other single sites: e.g., shoulder, temporomandibular, sacroiliac, ankle, wrist, acromioclavicular
- B. Generalized: includes 3 or more areas listed above (Kellgren-Moore, see ref. 18)
  1. Small (peripheral) and spine
  2. Large (central) and spine
  3. Mixed (peripheral and central) and spine

II. Secondary
- A. Post-traumatic
- B. Congenital or developmental diseases
  1. Localized
     a. Hip diseases: e.g., Legg-Calvé-Perthes, congenital hip dislocation, slipped capital femoral epiphysis, shallow acetabulum
     b. Mechanical and local factors: e.g., obesity (?), unequal lower extremity length, extreme valgus/varus deformity, hypermobility syndromes, scoliosis
  2. Generalized
     a. Bone dysplasias: e.g., epiphyseal dysplasia, spondylo-apophyseal dysplasia
     b. Metabolic diseases: e.g., hemochromatosis, ochronosis, Gaucher's disease, hemoglobinopathy, Ehlers-Danlos disease
- C. Calcium deposition disease
  1. Calcium pyrophosphate deposition disease
  2. Apatite arthropathy
  3. Destructive arthropathy (shoulder, knee)
- D. Other bone and joint disorders: e.g., avascular necrosis, rheumatoid arthritis, gouty arthritis, septic arthritis, Paget's disease, osteopetrosis, osteochondritis
- E. Other diseases
  1. Endocrine diseases: e.g., diabetes mellitus, acromegaly, hypothyroidism, hyperparathyroidism
  2. Neuropathic arthropathy (Charcot joints)
  3. Miscellaneous: e.g., frostbite, Kashin-Beck disease, Caisson disease

* DISH = diffuse idiopathic skeletal hyperostosis.

Figura 1.- Criterios ACR. Figura extraída de Altman et al., 1986.

Pero los pacientes que cumplían los criterios ACR clínicos y radiológicos ya tenían un daño estructural significativo.

El grupo *European Alliance of Associations for Rheumatology* (EULAR)[17], en 2009, publicó recomendaciones basadas en la evidencia, que incluían 3 síntomas (dolor persistente de rodilla, rigidez matutina autolimitada y función reducida) y 3 signos (crepitación, movilidad limitada y engrosamiento óseo).

En 2014, el *National Institute for Health and Care Excellence* (NICE)[18] publicó criterios para el diagnóstico clínico de KOA (edad mayor de 45, dolor articular relacionado con la actividad, rigidez articular matutina 30 min).

En ambos casos, nuevamente, el diagnóstico tiene lugar en fases tardías, cuando ya existen cambios estructurales en la articulación. Recientemente, hay un consenso general en la necesidad de cambiar el foco hacia un diagnóstico y tratamiento temprano, sugiriendo que la progresión de la KOA podría prevenirse y retrasarse con el diagnóstico precoz, antes de que la articulación esté irreversiblemente destruida[19].

Durante los últimos años se han formulado varios criterios de clasificación para identificar a sujetos sanos en riesgo de padecer artrosis, así como para reconocer a

pacientes con EKOA. Se ha propuesto la definición de EKOA como una combinación de síntomas de dolor articular, signos, presencia de factores de riesgo y alteraciones en pruebas complementarias de imagen[19, 20, 21, 22, 23].

Dos de los trabajos más reconocidos en este sentido son los de Luyten et al., 2012[22] y 2018[20]. En estas publicaciones los autores elaboran unos criterios de clasificación (Tabla 1) basados en las conclusiones de un consenso multidisciplinar de expertos. Mahmoudian et al.[21] publicaron en 2021 un análisis de estos criterios de Luyten testeándolos en población de la extensa base de datos *Osteoarthritis Initiative (OAI)*. Estos criterios presentan una especificidad del 76.5% para la detección de la progresión clínica, y están validados para su uso en investigación. Pero, aunque constituyen los criterios de clasificación más aceptados en el momento actual, no han podido establecerse como criterios diagnósticos y se encuentran bajo revisión por sus propios autores.

Table
Draft proposal for classification criteria for early OA of the knee

A. Patient-based questionnaires: Knee Injury and Osteoarthritis Outcome score: 2 out of the 4 KOOS subscales need to score "positive" (≤85%)
1. Pain (9 items, including information on pain intensity, frequency, and duration)
2. Symptoms, stiffness (7 items)
3. Function, daily living (short version: 7 items)
4. Knee-related quality of life (QOL: 4 items)
B. Clinical examination: at least 1 criterion needs to be present
• Joint line tenderness
• Crepitus
C. X-rays: KL grade 0-I standing, weight bearing (at least 2 projections: PA fixed flexion and skyline for patellofemoral OA)

Tabla 1. Criterios de Luyten para la clasificación de EKOA. Tabla extraída de Luyten et al.[20], 2018.

I. 2. Factores de riesgo relacionados con la KOA

I. 2. 1. Factores clínicos

Como se ha comentado, la artrosis se caracteriza por una pérdida de cartílago, cambios en el hueso subcondral, inflamación sinovial y degeneración de los meniscos[8]. La literatura existente con relación a los cambios estructurales observados, tanto en radiografías como en resonancia magnética (RM), establece que estos cambios aparecen de forma tardía, cuando ya existe una progresión considerable del proceso[23, 24]. Se sugiere, de hecho, que una posible explicación a la falta de efectividad de los tratamientos no quirúrgicos se deba a esta detección en estadios tardíos, cuando los cambios estructurales ya son avanzados[24].

Dado, por tanto, que las pruebas de imagen no son la mejor alternativa para realizar un diagnóstico temprano, se ha sugerido el estudio de otros factores para intentar lograr ese diagnóstico en fases precoces, tales como variables físicas, motoras y funcionales[25, 26].

I. 2. 2. Factores psicosociales

Por otra parte, la KOA se presenta con multitud de síntomas que provocan interferencias con la vida diaria, afectando la función y la calidad de vida global de aquellos sujetos que la padecen[15].

En la percepción del dolor pueden influir diversos mecanismos, como la nocicepción, los síntomas neuropáticos, los factores psicológicos y la personalidad, factores genéticos, experiencias dolorosas pasadas, afecciones comórbidas y expectativas referentes al dolor futuro[27, 28].

Se ha especulado, por tanto, sobre la relación existente entre los factores psicosociales, tales como síntomas depresivos o niveles elevados de ansiedad, con el dolor y la discapacidad de la OA[29, 30].

I. 2. 3. Factores metabólicos

La vitamina D tiene un papel importante sobre el estado de diversas estructuras articulares, tales como el cartílago, el hueso subcondral o los tejidos musculares, todos ellos implicados en la progresión de la OA[31].

Del mismo modo, los niveles de PTH intervienen en la pérdida y formación de hueso, y se han relacionado con el remodelado del hueso subcondral y, por tanto, con la progresión clínica y radiográfica de la KOA. En algunos trabajos se ha sugerido la relación entre vitamina D y PTH con causa y progresión de la KOA[32].

II. HIPÓTESIS

El estudio holístico de diversas variables clínicas, analíticas, biomecánicas, funcionales y de imagen, puede conducirnos a la determinación de un conjunto de factores que contribuyan al diagnóstico precoz de la artrosis de rodilla, favoreciendo de este modo un abordaje temprano que ayudaría a prevenir la progresión de la enfermedad.

III. OBJETIVOS

Los objetivos planteados en esta investigación son los siguientes:

1) Evaluar las variables clínicas, motoras y funcionales relacionadas con la aparición de EKOA.

   Este objetivo se ha estudiado en la publicación original:

   Alabajos-Cea A, Herrero-Manley L, Suso-Martí L, Sempere-Rubio N, Cuenca-Martínez F, Muñoz-Alarcos V, Pérez-Barquero JA, Viosca-Herrero E, Vázquez-Arce I. Screening Clinical Changes for the Diagnosis of Early Knee Osteoarthritis: A Cross-Sectional Observational Study. Diagnostics (Basel). 2022 Oct 30;12(11):2631. doi: 10.3390/diagnostics12112631. PMID: 36359475; PMCID: PMC9689265.

2) Identificar la relación entre el dolor y los factores psicosociales, así como la participación social en pacientes con EKOA.

   Este objetivo se ha estudiado en la publicación original:

   Alabajos-Cea A, Herrero-Manley L, Suso-Martí L, Alonso-Pérez-Barquero J, Viosca-Herrero E. Are Psychosocial Factors Determinant in the Pain and Social Participation of Patients with Early Knee Osteoarthritis? A Cross-Sectional Study. Int J Environ Res Public Health. 2021 Apr 26;18(9):4575. doi: 10.3390/ijerph18094575. PMID: 33925879; PMCID: PMC8123481.

3) Estudiar la asociación entre las concentraciones séricas de vitamina D y PTH y la EKOA, así como su relación con las variables clínicas y motoras y con la intensidad del dolor, discapacidad y aspectos funcionales y psicológicos en la EKOA.

   Este objetivo se ha estudiado en la publicación original:

   Alabajos-Cea A, Herrero-Manley L, Suso-Martí L, Viosca-Herrero E, Cuenca-Martínez F, Varangot-Reille C, Blanco-Díaz M, Calatayud J, Casaña J. The Role of Vitamin D in Early Knee Osteoarthritis and Its Relationship with Their Physical and Psychological Status. Nutrients. 2021 Nov 12;13(11):4035. doi: 10.3390/nu13114035. PMID: 34836290; PMCID: PMC8622912.

IV. MATERIAL Y MÉTODOS

IV. 1. Diseño del estudio

Se ha realizado un estudio transversal con una muestra no probabilística, siguiendo para su diseño las recomendaciones internacionales STROBE[33] (*Strengthening the Reporting of Observational Studies in Epidemiology*). Todos los participantes recibieron una explicación del procedimiento del estudio, que cumple los estándares éticos de la Declaración de Helsinki, y que ha sido aprobado por el Comité de Ética de la investigación con medicamentos (CEIm) La Fe, con referencia 2017/0147. Todos los participantes firmaron un consentimiento informado previo a su inclusión.

IV. 2. Participantes

Los sujetos fueron reclutados y seguidos en el Hospital La Fe, Valencia, España, en el marco del proyecto internacional H2020 "OACTIVE: *Advanced personalised, multi-scale computer models preventing OsteoArthritis*", *Grant Agreement* No 777159. El diseño y el protocolo para la recogida de datos se inició en noviembre de 2017 y el reclutamiento y seguimiento de los pacientes se inició en julio de 2018 y duró hasta febrero de 2021.

Se reclutó un total de 115 sujetos. Se recogieron variables de la historia clínica, estado socioeconómico, participación social, escalas de dolor y de calidad de vida, radiografías, RM, estudio biomecánico de la marcha y pruebas de laboratorio. Se realizó también una entrevista clínica y exploración física a los sujetos, aunque los últimos 16 sujetos recogidos se vieron afectados por la pandemia de COVID-19, y su reclutamiento fue telemático siguiendo las instrucciones de la AEMPS aplicables a ensayos clínicos y estudios observacionales en situación de emergencia por COVID-19 (Referencia: MUH 04/2020). En estos sujetos se realizó la entrevista clínica mediante un formulario, en el cual se recogían también preguntas relacionadas con el estado físico, para obtener al menos una aproximación a la exploración física del paciente, aunque algunas de las pruebas y tests específicos no pudieron recogerse en dichos pacientes.

Tras analizar los resultados de todas las variables recogidas se clasificó a los sujetos en "Sanos" y "EKOA" siguiendo los criterios de Luyten (Tabla 1, sección I.1.) que, como se ha comentado, están validados para su uso en investigación clínica[20, 21, 34].

Mediante estos criterios los sujetos se clasificaron de la siguiente forma:

- n=51 Sanos (35 mujeres y 16 hombres)
- n=55 Artrosis Inicial (35 mujeres y 19 hombres)
- n=9 (4 mujeres y 5 hombres) fueron excluidos por no cumplir criterios:
    - Kellgren & Lawrence 2-3: n=6
    - Enfermedad Reumática: n=3

Por tanto, la n final fue de 106.

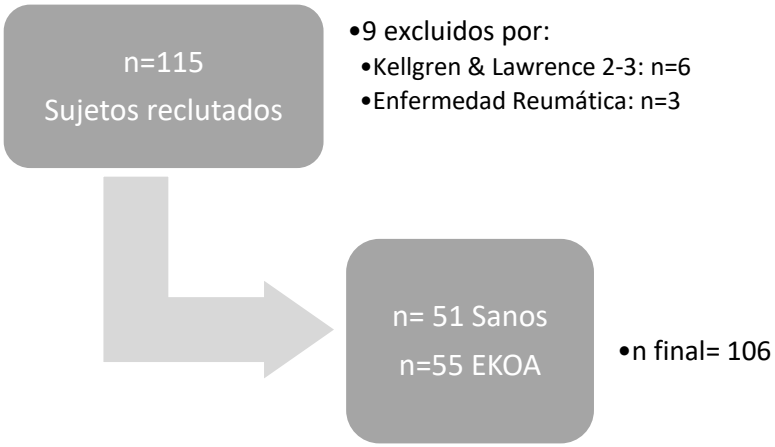

Figura 2.- Diagrama de flujo de la población de estudio.

Dentro de cada artículo publicado, el número de sujetos incluido varía ligeramente ya que, como se comenta anteriormente, en algunos sujetos no pudieron recogerse determinadas variables, y para cada estudio sólo se seleccionaron a aquellos sujetos de los que disponíamos de datos de todas las variables estudiadas.

Se realizaron seguimientos telemáticos anuales de los sujetos, evaluando las mismas variables recogidas inicialmente para poder valorar la evolución.

Los criterios de exclusión fueron los mismos para los dos grupos:
-impedimento físico o cognitivo para la comprensión o comunicación
-presencia de otra patología reumática, autoinmune o infecciosa

IV. 3. Variables

Las múltiples variables recogidas se incluyen listadas en el Anexo 1, así como en cada una de las publicaciones anexadas, y se describen en los distintos apartados de Resultados.

V. RESULTADOS

Los resultados obtenidos han quedado plasmados en las publicaciones que se recogen en esta tesis, y en otros trabajos que se encuentran actualmente en proceso de publicación y en revisión. Los resumo a continuación:

V.1. Alabajos-Cea A, Herrero-Manley L, Suso-Martí L, Sempere-Rubio N, Cuenca-Martínez F, Muñoz-Alarcos V, Pérez-Barquero JA, Viosca-Herrero E, Vázquez-Arce I. Screening Clinical Changes for the Diagnosis of Early Knee Osteoarthritis: A Cross-Sectional Observational Study. Diagnostics (Basel). 2022 Oct 30;12(11):2631. doi: 10.3390/diagnostics12112631. PMID: 36359475; PMCID: PMC9689265.

El objetivo de este trabajo fue evaluar qué variables clínicas, motoras y funcionales podrían estar relacionadas con la EKOA.

Para ello, se realizó la selección y clasificación de pacientes como se recoge en el apartado Material y Métodos.

De los 106 sujetos reclutados (n=51 Sanos; n=55 EKOA), 97 participaron en este estudio (n=43 Sanos; n=54 EKOA; n=9 faltaban datos de alguna variable).

V. 1. 1. Variables descriptivas y demográficas:

En esta sección se recogió información demográfica general incluida en otras grandes bases de datos y factores predictores existentes en la literatura, tales como sexo, edad, nivel educacional y estado civil[17, 26]. Se registró la existencia de historia personal de artrosis de mano y cadera, así como la historia familiar de artrosis, definida como padres, hermanos o abuelos diagnosticados de artrosis, sometidos a artroplastias de cadera o rodilla, o con presencia de nódulos de Heberden. Se recogieron el riesgo ocupacional, definido como necesidad de arrodillarse y levantarse frecuentemente, y hábitos de vida como fumar y beber alcohol. También se registró el estado hormonal en mujeres (pre o postmenopausia). Se recogió la frecuencia con que se realizaban actividades deportivas de ocio, y la presencia de lesiones previas de rodilla. Se recogió también el peso, altura e índice de masa corporal (IMC).

V. 1. 2. Variables clínicas:

Se midieron las siguientes variables:
- Morfología de rodilla: tumefacción, derrame articular, quiste de Baker u otros cambios.
- Flexo de rodilla[l]: se midió con goniómetro el ángulo formado entre el eje largo del muslo y el eje largo de la pierna, viendo al paciente desde un lado, posicionado en decúbito supino.

[l] Deep K., Nunag P., Willcox N., Deakin A.H., Picard F. A Comparison of Three Different Methods of Measurement of Knee Deformity in Osteoarthritis. J. Orthop. Rheumatol. Sports Med. 2016;1:107.

- Circometría[II]: se midió el perímetro del muslo a 10 cm del polo superior de la rótula, con un metro no elástico, con un nivel de sensibilidad de 0,1 cm.
- Inestabilidad ligamentosa[III]: se realizaron los tests pasivos tradicionales: Lachman, cajón anterior y posterior, estabilidad al forzar varo y valgo, etc.
- Propiocepción articular[IV]: con el paciente en sedestación al borde de la camilla y con los ojos tapados, el explorador le extendía la rodilla desde la posición de flexión hasta un ángulo aproximado de 30º a velocidad lenta. El paciente debía identificar la posición manteniéndola activamente durante 4 segundos, y posteriormente volver a la posición de inicio. Se pedía al paciente reproducir la posición anterior de forma activa.

V. 1. 3. Variables motoras y funcionales:

- Fuerza muscular[V]: se midió la fuerza isométrica del muslo con un dinamómetro de mano. Se utilizó el dinamómetro NedDFM/IBV y el software NedDiscapacidad/IBV. Se midió la fuerza de extensión y flexión de rodilla, solicitando a los participantes que efectuasen dichos movimientos con toda la fuerza posible aproximadamente durante unos 4 segundos. Se tomaron 3 medidas de cada movimiento y se calculó la media.
- Rango articular de rodilla[VI]: se midió localizando el trocánter mayor por palpación y alineando el brazo proximal del goniómetro al fémur. El brazo distal se situó paralelo a la tibia.
- Test *sit-to-stand*[VII]: con el paciente sentado con su espalda contra el respaldo de la silla, el explorador enumeraba en voz alta las veces en que el paciente pasaba a bipedestación, deteniendo el test al alcanzar la quinta repetición (ver en detalle en el Anexo 2).
- Velocidad de marcha[VIII]: el sujeto caminaba 10 metros sin ayudas, a la mayor velocidad posible, y el tiempo se midió para los 6 metros intermedios. Se realizaron 3 pruebas y se calculó la media (Anexo 2).

V. 1. 4. Variables de dolor y discapacidad:

- Intensidad del dolor: se utilizó la Escala Visual Analógica (EVA)[IX].

[II] Bakar Y., Özdemir Ö., Sevim S., Duygu E., Tuğral A., Sürmeli M. Intra-observer and inter-observer reliability of leg circumference measurement among six observers: A single blinded randomized trial. J. Med. Life. 2017;10:176–181.

[III] Malanga G.A., Andrus S., Nadler S.F., McLean J. Physical examination of the knee: A review of the original test description and scientific validity of common orthopedic tests. Arch. Phys. Med. Rehabil. 2003;84:592–603.

[IV] Lokhande M.V., Shetye J., Mehta A., Deo M.V. Assessment of Knee Joint Proprioception in Weight Bearing and in Non-Weight Bearing Positions in Normal Subjects. J. Krishna Inst. Med. Sci. Univ. 2013;2:94–101.

[V] Bohannon R.W., Bubela D.J., Magasi S.R., Gershon R.C. Relative reliability of three objective tests of limb muscle strength. Isokinet. Exerc. Sci. 2011;19:77–81.

[VI] Bhave A., Shabtai L., Woelber E., Apelyan A., Paley D., Herzenberg J.E. Muscle strength and knee range of motion after femoral lengthening: 2- to 5-year follow-up. Acta Orthop. 2017;88:179–184.

[VII] Paul S.S., Canning C.G. Five-repetition sit-to-stand. J. Physiother. 2014;60:168.

[VIII] Bohannon R.W. Comfortable and maximum walking speed of adults aged 20–79 years: Reference values and determinants. Age Ageing. 1997;26:15–19.

[IX] 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.

- Tipo de dolor: se evaluó con las preguntas NHANES (*National Health and Nutrition Examination Survey (NHANES)-type knee pain questions*)[X]: presencia de dolor de rodilla la mayoría de los días en un mes; presencia de dolor de rodilla al menos un mes en el último año; presencia de dolor de rodilla la mayoría de los días en el último mes.
- Escala *Western Ontario and McMaster Universities Osteoarthritis Index* (WOMAC)[XI]: recoge datos de dolor, rigidez y función mediante evaluación de dificultades en la vida diaria.
- Escala *Knee Injury and Osteoarthritis Outcome Score* (KOOS)[XII]: recoge datos sobre dolor, otros síntomas clínicos, función en la vida diaria, función en deporte, y calidad de vida en relación con la rodilla.

Las escalas pueden verse en detalle en el Anexo 2.

V. 1. 5. Variables de imagen:

- Alineación de rodilla[XIII]: se midió mediante radiografía bilateral en carga, en proyección anteroposterior, el ángulo formado por la intersección de la línea trazada del centro de la cabeza femoral al centro femoral intercondíleo y la línea trazada desde el centro del astrágalo al centro del área intercondílea tibial. Se definió varo de rodilla cuando el ángulo fue mayor a 0º en posición de varo, y el valgo cuando el ángulo fue mayor a 0º en dicha posición.
- Dismetría: en la misma proyección radiográfica descrita anteriormente se trazó una línea por encima de las cabezas femorales, viendo si una quedaba por encima de la otra y midiendo la diferencia entre ambas.

V. 1. 6. Resultados:

Los resultados fueron:

Se encontró una asociación estadísticamente significativa entre el dolor y la artrosis, siendo los valores de la EVA mayores en el grupo de sujetos con artrosis inicial. Niveles mayores de dolor se asocian también a disminución en el rango articular (Figura 3, Tabla 2).

Se encontró una mayor presencia, de forma estadísticamente significativa, de inestabilidad y varo de rodillas en el grupo de sujetos con artrosis inicial.

[X] Leyland K.M., Gates L.S., Nevitt M., Felson D., Bierma-Zeinstra S.M., Conaghan P.G., Engebretsen L., Hochberg M., Hunter D.J., Jones G., et al. Harmonising measures of knee and hip osteoarthritis in population-based cohort studies: An international study. Osteoarthr. Cartil. 2018;26:872–879.

[XI] Escobar A., Quintana J.M., Bilbao A., Azkárte J., Güenaga L.I. Validation of the Spanish version of the WOMAC questionaire for patients with hip or knee osteoarthritis. Clin. Rheumatol. 2002;21:466–471.

[XII] 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. Sports Traumatol. Arthrosc. 2014;22:104–108.

[XIII] Malanga G.A., Andrus S., Nadler S.F., McLean J. Physical examination of the knee: A review of the original test description and scientific validity of common orthopedic tests. Arch. Phys. Med. Rehabil. 2003;84:592–603.

En las variables motoras y funcionales, el grupo de sujetos con artrosis inicial presentó, de forma significativa, menor fuerza de flexión y extensión de rodilla, así como mayor tiempo para completar el "*sit to stand test*" (Figura 4, Tabla 2).

No se encontraron diferencias en variables tales como sexo, antecedentes personales de artrosis de mano y cadera, hábitos de vida, riesgo ocupacional o estado hormonal.

Se encontró relación estadísticamente significativa entre mayor IMC y disminución del rango articular, pero no con la intensidad del dolor.

En los pacientes con EKOA parece existir una tendencia al sedentarismo, pero las diferencias no fueron estadísticamente significativas.

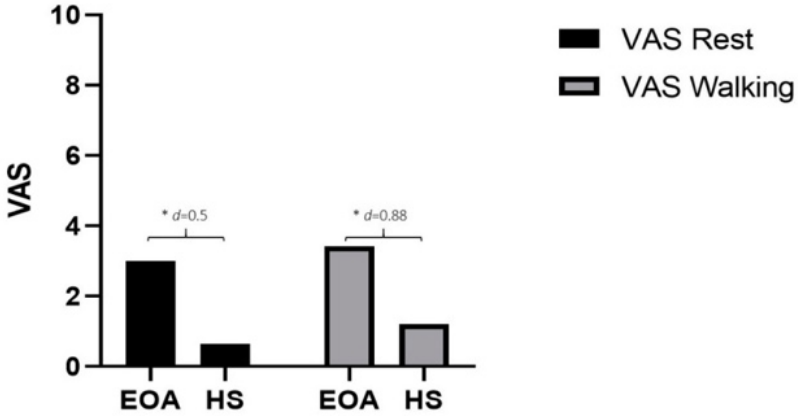

Figura 3. Diferencias en la variable dolor. p < 0,05. d=*Effect size*. VAS=*Visual Analogue Scale.* EOA=*Early Osteoarthritis.* HS= *Healthy subjects.* Figura extraída de Alabajos et al., 2022

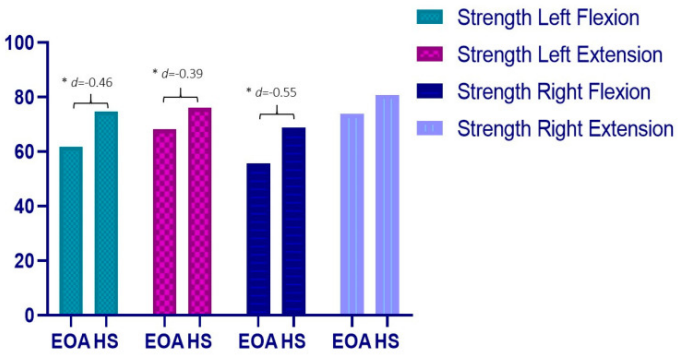

Figura 4. Diferencias en la variable fuerza. p < 0,05. d=*Effect size*. EOA=*Early Osteoarthritis.* HS= *Healthy subjects.* Figura extraída de Alabajos et al., 2022

Between-group comparisons regarding pain, disability, motor, and functional variables.

Measures	EOA ($n = 54$)	HS ($n = 43$)	Mean Difference (95% CI)	Effect Size (d)
VAS Rest	3.0 ± 6.44	0.65 ± 1.53	−2.35 * (−4.35 to −0.35)	0.5
VAS Walking	3.42 ± 2.75	1.21 ± 2.23	−2.21 * (−3.24 to −1.18)	0.88
WOMAC	0.25 ± 0.13	0.12 ± 0.13	−0.13 ** (−0.19 to −0.7)	1.01
KOOS				
Pain	73.5 ± 13.79	89.29 ± 14.56	15.79 ** (10.01 to 21.56)	−1.11
Symptoms	77.87 ± 12.66	90.79 ± 12.76	12.91 ** (7.73 to 18.1)	−1.01
ADL	77.7 ± 15.94	90.83 ± 10.56	13.13 ** (7.47 to 18.79)	−0.97
QQL	52.63 ± 24.86	76.17 ± 23.96	23.54 ** (13.58 to 33.49)	−0.96
Strength Left (Kg)				
Flexion	61.91 ± 21.57	74.83 ± 33.00	12.92 * (0.45 to 25.39)	−0.46
Extension	68.24 ± 21.47	76.05 ± 17.81	7.81 * (1.26 to 16.88)	−0.39
Strength Right (Kg)				
Flexion	55.71 ± 16.52	68.77 ± 28.85	13.06 * (2.59 to 23.52)	−0.55
Extension	73.89 ± 22.98	80.86 ± 22.21	6.97 (−3.34 to 17.29)	−0.31
ROM Left Leg (°)	132.39 ± 9.61	132.43 ± 12.75	0.04 (−4.91 to 5.00)	−0.01
ROM Right Leg (°)	132.61 ± 8.11	131.84 ± 12.19	−0.78 (−5.29 to 3.74)	0.07
Sit to stand (sec)	13.18 ± 4.27	11.26 ± 2.61	−1.91 * (−3.52 to −0.31)	0.54
Walking speed (sec)	3.54 ± 0.89	3.36 ± 0.63	−0.17 (−0.53 to 0.18)	0.23

Note: ** $p < 0.01$; * $p < 0.05$; CI: confidence interval; EOA: Early osteoarthritis; HS: Healthy subjects.

Tabla 2. Comparaciones entre grupos respecto a variables dolor, discapacidad, motoras y funcionales. Tabla extraída de Alabajos et al., 2022

V.2. Alabajos-Cea A, Herrero-Manley L, Suso-Martí L, Alonso-Pérez-Barquero J, Viosca-Herrero E. Are Psychosocial Factors Determinant in the Pain and Social Participation of Patients with Early Knee Osteoarthritis? A Cross-Sectional Study. Int J Environ Res Public Health. 2021 Apr 26;18(9):4575. doi: 10.3390/ijerph18094575. PMID: 33925879; PMCID: PMC8123481.

El objetivo principal de este trabajo fue determinar las diferencias psicosociales entre pacientes con dolor de rodilla, EKOA y sujetos sanos. El objetivo secundario fue identificar la relación entre el dolor, los factores psicosociales y la participación social en sujetos con EKOA.

Para ello, se realizó la selección y clasificación de pacientes como se recoge en el apartado Material y Métodos.

De los 106 sujetos reclutados (n=51 Sanos; n=55 EKOA), 105 participaron en este estudio (n=51 Sanos; n=54 EKOA; n=1 faltaban datos de alguna variable).

Para individualizar el estudio de las diferentes variables se realizaron dos grupos de análisis:

- Sujetos con dolor de rodilla y sujetos sin dolor de rodilla (independientemente de su clasificación como EKOA o sanos)
- Sujetos con EKOA y sujetos sanos

V. 2. 1. Variables descriptivas y demográficas:

De este apartado se recogieron las mismas variables enumeradas en la sección V. 1. 1.

V. 2. 2. Variables de dolor y discapacidad:

En este caso se estudiaron las variables EVA y WOMAC, descritas en la sección V. 1. 4.

V. 2. 3. Variables psicosociales:

- Se recogieron datos sobre síntomas de Ansiedad y Depresión según las escalas *Hospital Anxiety and Depression* (HADS) y *Goldberg Anxiety and Depression Inventory* (GAD).
Las escalas pueden verse en detalle en el Anexo 2.
- Participación social: se evaluó según el *Maastricht Social Participation Profile*, que incluye nueve preguntas para determinar la frecuencia y diversidad de la implicación social de personas con enfermedades crónicas (Mars et al., 2009)[XIV].

V. 2. 4. Resultados:

- Análisis del grupo Dolor de rodilla frente a No dolor de rodilla:

[XIV] Mars G.M.J., Kempen G.I.J.M., Post M.W.M., Proot I.M., Mesters I., van Eijk J.T.M. The Maastricht social participation profile: Development and clinimetric properties in older adults with a chronic physical illness. Qual. Life Res. 2009;18:1207–1218.

Se encontró relación estadísticamente significativa entre las variables psicológicas, ansiedad y depresión, y el dolor de rodilla, siendo mayor la incidencia de dichas variables en los sujetos que presentan dolor (Tabla 3).

Between-group comparisons.

Measures	Pain Group ($n = 64$)	No-Pain Group ($n = 41$)	Mean Difference (95% CI)	Effect Size (d)
WOMAC	0.18 ± 0.15	0.21 ± 0.19	0.03 (−0.05 to 0.11)	-
HAD Anxiety	5.62 ± 3.54	3.27 ± 3.55	−2.35 ** (−3.76 to −0.94)	0.66
HAD Depression	3.98 ± 3.12	1.54 ± 2.43	−2.45 ** (−3.59 to −1.31)	0.87
Social Participation	5.89 ± 3.44	5.68 ± 2.73	−0.21 (−1.47 to 1.05)	-

Note: ** $p < 0.01$.

Tabla 3. Comparaciones entre grupo Dolor de rodilla y No dolor de rodilla respecto a escalas. Tabla extraída de Alabajos et al., 2021

- Análisis del grupo EKOA frente a controles sanos:

Se halló también relación significativa con la artrosis inicial, encontrando mayor incidencia de las variables psicológicas en el grupo de sujetos con artrosis (Tabla 4).

Se ha encontrado también, de forma estadísticamente significativa, mayor puntuación en las escalas de depresión en el grupo de sujetos con artrosis inicial, respecto a los controles sanos.

Y, del mismo modo, se ha encontrado relación significativa entre mayor puntuación en las escalas de depresión y una menor participación social (Figura 5).

Between-group comparisons.

Measures	EOA ($n = 54$)	HS ($n = 51$)	Mean Difference (95% CI)	Effect Size (d)
WOMAC	0.21 ± 0.16	0.18 ± 0.17	−0.03 (−0.09 to 0.05)	-
VAS Rest	2.17 ± 2.53	0.78 ± 1.87	−1.38 * (−2.25 to −0.52)	0.62
VAS Walking	3.17 ± 2.86	0.75 ± 1.91	−2.42 ** (−3.37 to −1.48)	0.99
HAD Anxiety	5.80 ± 3.69	3.50 ± 3.39	−2.29** (−3.67 to −0.92)	0.65
HAD Depression	4.06 ± 3.19	1.90 ± 2.59	−2.15 ** (−3.29 to −1.02)	0.74
Social Participation	5.89 ± 3.23	5.73 ± 3.14	−0.16 (−1.39 to 1.07)	-

EOA: early osteoarthritis; healthy subjects. Note: ** $p < 0.01$; * $p < 0.05$.

Tabla 4. Comparaciones entre grupos EKOA y Sanos respecto a escalas. Tabla extraída de Alabajos et al., 2021

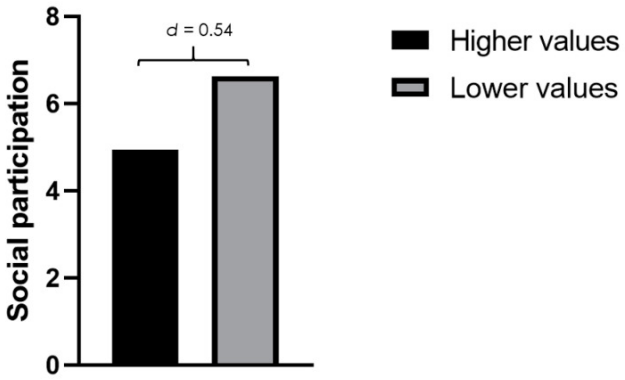

Figura 5. Participación social en relación a los niveles de depresión.

V.3. Alabajos-Cea A, Herrero-Manley L, Suso-Martí L, Viosca-Herrero E, Cuenca-Martínez F, Varangot-Reille C, Blanco-Díaz M, Calatayud J, Casaña J. The Role of Vitamin D in Early Knee Osteoarthritis and Its Relationship with Their Physical and Psychological Status. Nutrients. 2021 Nov 12;13(11):4035. doi: 10.3390/nu13114035. PMID: 34836290; PMCID: PMC8622912.

El objetivo principal de este trabajo fue estudiar la asociación de las concentraciones séricas de vitamina D en pacientes con EKOA. Los objetivos secundarios fueron determinar la asociación de las concentraciones séricas de PTH en rodillas con artrosis precoz, y estudiar la relación entre la deficiencia de vitamina D, el nivel de PTH, la intensidad del dolor, la discapacidad, factores psicológicos y variables funcionales en población EKOA.

Para ello, se realizó la selección y clasificación de pacientes como se recoge en el apartado Material y Métodos.

De los 106 sujetos reclutados (n=51 Sanos; n=55 EKOA), 96 participaron en este estudio (n=48 Sanos; n=48 EKOA; n=10 faltaban datos de alguna variable).

V. 3. 1. Variables analíticas: niveles de vitamina D y PTH

Se analizaron las concentraciones plasmáticas de 25-hidroxivitamina D [25-(OH)D] y PTH[XV].

Los niveles de vitamina D se clasificaron de la siguiente forma:

- Déficit de vitamina D: concentración sérica de 25-(OH)D < 20 ng/mL
- Insuficiencia de vitamina D: concentración sérica de 25-(OH)D 20–29 ng/mL
- Suficiencia de vitamina D: concentración sérica de 25-(OH)D ≥ 30 ng/mL

Respecto a la PTH, se buscaron relaciones entre el resto de variables con mayores o menores niveles de ésta.

V. 3. 2. Variables de dolor y discapacidad:

En este caso se estudiaron las variables EVA y WOMAC, descritas en la sección V. 1. 4.

V. 3. 3. Variables funcionales:

Se estudiaron el test *sit-to-stand* y la velocidad de marcha, descritas en la sección V. 1. 3.

V. 3. 4. Variables psicosociales:

[XV] Javadian Y., Adabi M., Heidari B., Babaei M., Firouzjahi A., Ghahhari B.Y., Hajian-Tilaki K. Quadriceps Muscle Strength Correlates With Serum Vitamin D and Knee Pain in Knee Osteoarthritis. Clin. J. Pain. 2017;33:67–70.

Se estudiaron la HADS y la participación social según el *Maastricht Social Participation Profile*, ambas descritas en la sección V. 2. 3.

V. 3. 5. Resultados:

En los pacientes con EKOA se halló mayor déficit estadísticamente significativo de vitamina D que en los controles sanos (Figura 6).

Se encontró también relación entre la deficiencia de vitamina D en artrosis precoz y mayor nivel de dolor, discapacidad, ansiedad y síntomas depresivos, menor participación social y menor actividad física, de forma estadísticamente significativa (Tabla 5).

Niveles más bajos de PTH se asociaron con mayor intensidad del dolor y con menor participación social.

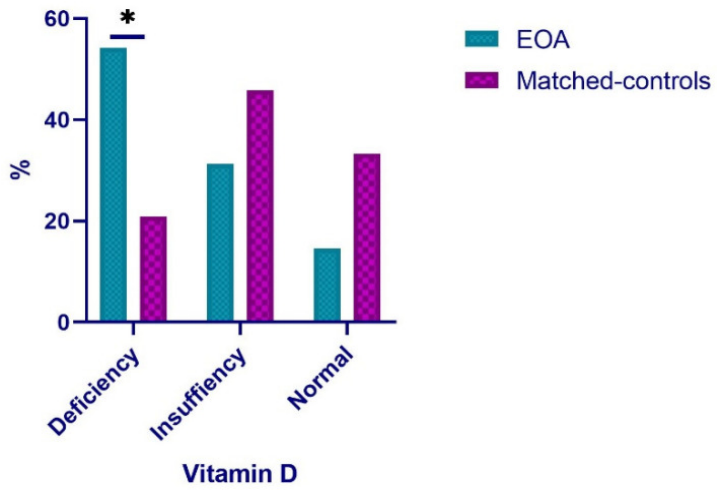

Figura 6. Niveles de vitamina D en sujetos con EKOA y sanos. p < 0,05. EOA= *Early Osteoarthritis*

Physical and psychological status in patients with EOA according to vitamin D levels.

Measures	EOA Deficiency (<20 ng/mL)	EOA Sufficiency (>20 ng/mL)	Mean Difference (95% CI)	Effect Size (*d*)
Pain intensity	4.95 ± 3.52	2.22 ± 2.59	2.73 ** (−3.39 to −0.76)	0.88
WOMAC Total	29.27 ± 12.45	23.76 ± 13.93	5.51 * (−14.65 to −6.64)	0.41
Sit-to-stand (s)	16.29 ± 3.44	10.53 ± 2.54	5.76 ** (−6.34 to −0.81)	1.90
Walking speed (km/h)	4.99 ± 1.38	3.07 ± 0.54	1.92 ** (−1.34 to −0.11)	1.83
Anxiety	7.36 ± 4.17	4.01 ± 3.05	4.35 * (−3.86 to −2.15)	0.88
Depression	6.21 ± 3.06	3.31 ± 3.06	2.9 * (−2.96 to −0.15)	0.94
Social participation	4.57 ± 3.61	8.73 ± 2.55	−4.16 ** (−2.82 to −1.14)	1.01

Data are expressed as mean ± standard deviation. ** $p < 0.01$; * $p < 0.05$.

Tabla 5. Relación entre las distintas variables estudiadas y los niveles de vitamina D. EOA= *Early Osteoarthritis*

VI. DISCUSIÓN

La hipótesis planteada en este trabajo consistía en que el estudio holístico de diversas variables clínicas, analíticas, biomecánicas, funcionales y de imagen, puede conducirnos a la determinación de un conjunto de factores que contribuyan al diagnóstico precoz de la artrosis de rodilla, favoreciendo de este modo un abordaje temprano que ayudaría a prevenir la progresión de la enfermedad.

En este sentido, analicemos los resultados obtenidos y sus implicaciones.

VI. 1. Identificación de factores clínicos y funcionales

El primer objetivo planteado era la evaluación de las variables clínicas, motoras y funcionales relacionadas con la aparición de EKOA, al que se ha respondido con la publicación "*Screening Clinical Changes for the Diagnosis of Early Knee Osteoarthritis: A Cross-Sectional Observational Study.*"[XVI]

En la literatura se ha considerado que factores no modificables, como la edad, el sexo, los antecedentes de artrosis o el estado hormonal, son factores ligados al desarrollo de KOA[35]; en este estudio, en cambio, no se han encontrado diferencias en variables tales como sexo, antecedentes personales de artrosis de mano y cadera o estado hormonal. Estas diferencias halladas entre la población de estudio y la literatura existente pueden deberse a varios motivos, como pueden ser el tamaño muestral o la propia clasificación de artrosis precoz, ya que, como se ha comentado, no hay un consenso claro a este respecto.

Clásicamente se han relacionado también con el desarrollo de KOA factores modificables como obesidad, riesgo ocupacional y hábitos de vida[36, 37]. Respecto a los hábitos de vida, el alcohol y el tabaco se han descrito como estadísticamente no significativos, tanto como factores de riesgo como protectores[26, 35]. Se ha descrito un riesgo ocupacional de desarrollar KOA en sujetos que trabajan en el suelo, o en aquellos que deben arrodillarse y levantarse con frecuencia[37]. En la población de este estudio, en la que se encontró un bajo porcentaje de sujetos que presentasen riesgo ocupacional o hábitos tóxicos, no hemos hallado diferencias significativas relativas a estas variables. Quizás habría que estudiar una muestra mayor, o seleccionar otro tipo de sujetos para obtener información relevante en este sentido.

El sobrepeso y la obesidad son dos de los factores modificables más estudiados. Se ha encontrado una asociación entre un IMC elevado con mayor dolor de rodilla en personas con KOA o en alto riesgo de padecerla[36], en datos de la OAI. En este trabajo se ha encontrado relación estadísticamente significativa entre mayor IMC y disminución del rango articular, pero no con la intensidad del dolor. Esta limitación articular podría tener

[XVI] Alabajos-Cea A, Herrero-Manley L, Suso-Martí L, Sempere-Rubio N, Cuenca-Martínez F, Muñoz-Alarcos V, Pérez-Barquero JA, Viosca-Herrero E, Vázquez-Arce I. Screening Clinical Changes for the Diagnosis of Early Knee Osteoarthritis: A Cross-Sectional Observational Study. Diagnostics (Basel). 2022 Oct 30;12(11):2631. doi: 10.3390/diagnostics12112631. PMID: 36359475; PMCID: PMC9689265.

su explicación en el aumento del volumen del miembro, o incluso con el mayor sedentarismo.

El sedentarismo[37, 38, 39, 40, 41] es otro de los factores estudiados, encontrándose menor riesgo de pérdida funcional en aquellos sujetos en riesgo de padecer KOA que presentaban mayores índices de marcha[41] y asociándose el menor sedentarismo con una funcionalidad global mejor[39, 40]. En cambio, las actividades deportivas regulares podrían estar asociadas a una progresión de la artrosis[37]. Una revisión de la Cochrane[38] concluyó que la gente no comprende la causa de su dolor, y si no existe una adecuada información proveniente de los profesionales de salud, evitan realizar actividad física por miedo a que les genere dolor. En los sujetos estudiados con EKOA en este trabajo parece existir una tendencia al sedentarismo, pero las diferencias no son estadísticamente significativas, quizá se necesita una muestra mayor para poder establecer dicha relación.

La debilidad de la musculatura de rodilla se ha asociado con la inestabilidad funcional y con mayor riesgo de padecer artrosis sintomática[25, 42, 43]. A su vez, la inestabilidad[44] por sí misma se ha relacionado también con el desarrollo de la artrosis. Los resultados de este estudio muestran que las variables motoras tales como la fuerza, o las variables funcionales, están alteradas significativamente en los pacientes con EKOA. La disminución de fuerza podría estar implicada en la inestabilidad hallada en estos sujetos, debiéndose ésta no sólo a causas ligamentosas.

Otro de los factores considerados es el varo/valgo de rodilla, tanto estático como dinámico, ya que tiene importantes implicaciones en la distribución de cargas de la rodilla. No hay suficiente evidencia para lanzar conclusiones respecto al efecto del mal alineamiento sobre el desarrollo de KOA, y es posible además que dicho mal alineamiento refleje la severidad de la enfermedad como consecuencia del estrechamiento del espacio articular[45]. Del mismo modo, la dismetría es un factor fácilmente modificable que puede afectar la biomecánica articular de funcionamiento de miembros inferiores (MMII). Se ha relacionado una diferencia de mínimo 2 cm entre MMII con una probabilidad del doble de presentar artrosis radiográfica[37]. En este trabajo se ha encontrado una mayor presencia, de forma estadísticamente significativa, de inestabilidad y deformidad en varo de rodillas en el grupo de sujetos con EKOA, sin hallar diferencias respecto a la dismetría. Cabe mencionar que no hubo dismetrías importantes en los sujetos de estudio.

Se han descrito también como factores asociados a la KOA la inestabilidad ligamentosa[44] y la presencia de lesiones previas en rodilla[26]. En este estudio se ha encontrado una tendencia a mayores niveles de inestabilidad ligamentosa y presencia de lesiones previas en los sujetos con EKOA, sin encontrar diferencias estadísticamente significativas. Nuevamente hay que mencionar que el índice de sujetos de estudio que presentaron inestabilidad ligamentosa y lesiones previas de rodilla fue bajo.

La literatura establece el dolor de rodilla como parte de los hallazgos en la artrosis establecida, y no como predictor de ésta[26, 35, 46]. En este trabajo se vio que los sujetos con EKOA mostraban mayores niveles de discapacidad (según el WOMAC) y de dolor

(según el VAS) tanto en reposo como durante la marcha, de forma estadísticamente significativa. Niveles mayores de dolor se asocian a disminución en el rango articular, tanto en sujetos con EKOA como en sujetos sanos. Podríamos considerar, por tanto, que el dolor tal vez sí tenga cierto valor predictivo cuando aparece como síntoma aislado, o unido a una limitación funcional precoz.

La relación del WOMAC con la EKOA se estudió tanto en el primer artículo recogido en esta tesis, *Screening Clinical Changes for the Diagnosis of Early Knee Osteoarthritis: A Cross-Sectional Observational Study*, como en el segundo, *Are Psychosocial Factors Determinant in the Pain and Social Participation of Patients with Early Knee Osteoarthritis? A Cross-Sectional Study*. Si observamos la tabla 2 (sección V.1.6) y la tabla 3 (sección V.2.4) podemos ver que existe una diferencia respecto a la significación del WOMAC. Esto puede ser debido a que, como se ha comentado, no todas las variables pudieron medirse en todos los sujetos, por lo tanto, el tamaño muestral incluido en cada estudio fue discretamente diferente, y esto pudo ocasionar pequeñas diferencias a nivel de significación estadística.

VI. 2. Influencia de los factores psicosociales

Se planteaba como segundo objetivo identificar la relación entre el dolor y los factores psicosociales, así como con la participación social en pacientes con EKOA. Se ha respondido a este objetivo con la publicación "*Are Psychosocial Factors Determinant in the Pain and Social Participation of Patients with Early Knee Osteoarthritis? A Cross-Sectional Study.*"[XVII]

En la comunidad científica se ha estudiado la relación existente entre factores tales como síntomas depresivos o niveles elevados de ansiedad, con el dolor y la discapacidad de la artrosis[29, 30]; el dolor y la alteración de la función en la artrosis se asocian con mayores síntomas depresivos, y la existencia de síntomas depresivos supone un fuerte predictor de empeoramiento del dolor de rodilla[47]. Se ha observado también una asociación entre la presencia de síntomas depresivos y una menor eficacia para el manejo de los síntomas propios de la artrosis, así como mayor dolor, catastrofismo y mayor miedo al movimiento[48, 49].

Por otra parte, los beneficios de un estilo de vida físicamente activo están bien descritos en personas mayores, y cómo el implicarse en actividades sociales puede promover mayor actividad física[50].

Del mismo modo que ocurría con los factores clínicos, estas relaciones comentadas entre los factores psicosociales y la KOA se han estudiado en fases avanzadas, pero están poco estudiadas en EKOA, antes de que los cambios estructurales y degenerativos se establezcan en la articulación[6, 7, 15].

[XVII] Alabajos-Cea A, Herrero-Manley L, Suso-Martí L, Alonso-Pérez-Barquero J, Viosca-Herrero E. Are Psychosocial Factors Determinant in the Pain and Social Participation of Patients with Early Knee Osteoarthritis? A Cross-Sectional Study. Int J Environ Res Public Health. 2021 Apr 26;18(9):4575. doi: 10.3390/ijerph18094575. PMID: 33925879; PMCID: PMC8123481.

En la población estudiada en este trabajo se ha encontrado una relación estadísticamente significativa entre las variables psicológicas, ansiedad y depresión, y el dolor de rodilla, de forma independiente al diagnóstico de EKOA. Se ha encontrado mayor incidencia de las variables psicológicas en el grupo de sujetos con artrosis inicial. No sabemos si esta relación es de contribución en la etiología de la artrosis (causa), si es una consecuencia de ésta, o si está relacionada con ambas (causa y consecuencia). Podemos especular que la aparición de estos síntomas psicosociales en la artrosis puede constituir un factor de confusión en su diagnóstico, así como en la prescripción de su tratamiento.

Se ha encontrado también, de forma estadísticamente significativa, mayor puntuación en las escalas de depresión en el grupo de sujetos con artrosis inicial respecto a controles sanos, y entre mayor puntuación en las escalas de depresión y una menor participación social. Por tanto, como cabría esperar de acuerdo a la literatura existente para KOA, la depresión podría ser un factor relevante en relación con la menor participación social de sujetos con EKOA.

VI. 3. Influencia de los factores metabólicos en la KOA

Por último, el tercer objetivo era estudiar la influencia de los factores metabólicos en la KOA, al que se ha respondido con el artículo "*The Role of Vitamin D in Early Knee Osteoarthritis and Its Relationship with Their Physical and Psychological Status.*"[XVIII]

La deficiencia de vitamina D es la deficiencia nutricional más común a nivel mundial, definida como nivel sérico de 25-(OH)D inferior a 20 nmol/L. Más de un 40% de la población adulta por encima de 50 años presenta esta deficiencia, y este porcentaje es todavía mayor entre las mujeres[51, 52].

En algunos trabajos se ha sugerido que la vitamina D podría estimular la síntesis de proteoglicanos en condrocitos maduros a través de una transformación metabólica mediada por receptores de vitamina D[53, 54]. Por tanto, la deficiencia de vitamina D podría obstaculizar el remodelado óseo, relacionándose con causa y progresión de KOA[55]. Por otra parte, otros estudios concluyen que los niveles bajos de vitamina D no se asocian con el riesgo de desarrollar KOA, aunque sí con el riesgo de progresión de ésta[54, 56].

En lo referente a la suplementación de vitamina D en los casos en que existe un déficit de ésta, hay controversia respecto a si puede ayudar a prevenir la progresión de la enfermedad o no, y se ha descrito que no interviene en el control del dolor[56, 57, 58].

La mayoría de los estudios que han reportado una conexión entre la vitamina D y la artrosis se han llevado a cabo en pacientes en fases avanzadas de la enfermedad, quedando de nuevo inexplorado qué ocurre en las fases precoces de esta entidad, y el

[XVIII] Alabajos-Cea A, Herrero-Manley L, Suso-Martí L, Viosca-Herrero E, Cuenca-Martínez F, Varangot-Reille C, Blanco-Díaz M, Calatayud J, Casaña J. The Role of Vitamin D in Early Knee Osteoarthritis and Its Relationship with Their Physical and Psychological Status. Nutrients. 2021 Nov 12;13(11):4035. doi: 10.3390/nu13114035. PMID: 34836290; PMCID: PMC8622912.

papel que la vitamina D y la PTH podrían desempeñar en el inicio y progresión de la EKOA.

En los sujetos con EKOA de este estudio se ha hallado mayor déficit estadísticamente significativo de vitamina D, sugiriendo que este déficit podría estar implicado en el desarrollo de la artrosis precoz. Podría considerarse, por tanto, un dato relevante a incluir en la formulación de los criterios diagnósticos de EKOA, así como un factor a considerar en la prevención de la artrosis de rodilla.

Se ha encontrado también relación entre la deficiencia de vitamina D en artrosis precoz y mayor nivel de dolor, discapacidad, ansiedad y síntomas depresivos, menor participación social y menor actividad física, de forma estadísticamente significativa. Niveles inferiores de PTH se han asociado con mayor intensidad del dolor y menor participación social. De nuevo, podría ser parte de la etiología o consecuencia del inicio de la artrosis precoz de rodilla. Como sabemos, la exposición solar es la mayor fuente de vitamina D. Holick et al.[59] advierten que sin la exposición solar suficiente no es posible producir la cantidad necesaria de vitamina D. Como se ha comentado en el apartado anterior, es probable que los sujetos con ansiedad y depresión, así como aquellos con dolor y discapacidad, disminuyan su participación social, y por tanto presenten una menor exposición solar, que podría afectar a sus niveles de vitamina D.

VI. 4. Reflexión final

Podemos afirmar que la KOA es una entidad con una fisiopatología muy compleja y todavía muy desconocida, en la que intervienen multitud de factores, mezclándose estos entre ellos y siendo en ocasiones tanto posibles causas como posibles consecuencias de la enfermedad. A la luz de los hallazgos obtenidos en este trabajo, se podría especular que las primeras manifestaciones clínicas de la EKOA son el dolor y la limitación funcional que éste genera, que unida al miedo a padecer más dolor asocia falta de actividad física y de participación social. Esto, a su vez, perpetuaría un círculo vicioso en el que el sujeto se siente peor a nivel afectivo, tanto por el dolor y la sensación de discapacidad como por la falta de participación social. Del mismo modo, otro círculo aberrante se genera al evitar la actividad física, lo que puede acarrear mayor debilidad, mayor inestabilidad articular, mayor dolor, y poco a poco va llevando a la progresión de la enfermedad y el establecimiento de los cambios estructurales (ilustrado en figura 7).

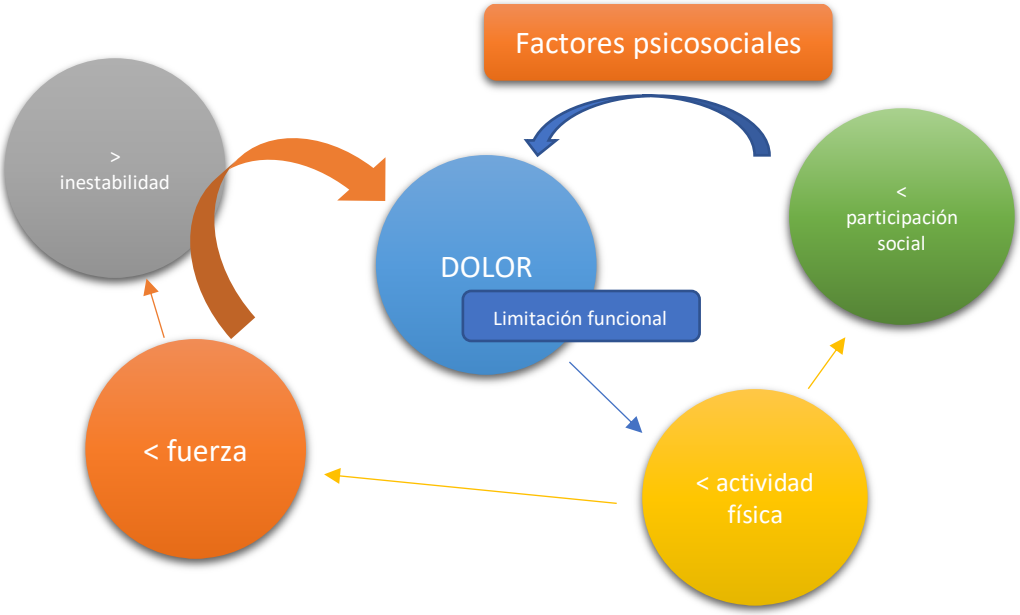

Figura 7. Posible mecanismo de establecimiento y progresión de la artrosis de rodilla.

Junto a esta teoría cabría recordar y tener presente la relación hallada con factores de riesgo modificables como el elevado IMC, y el déficit de vitamina D. Ambos podrían verse empeorados por el sedentarismo y la disminución en la participación social, agravando el cuadro.

Siguiendo la línea sugerida, de constituir el dolor la primera manifestación de la artrosis precoz de rodilla, habría que centrar el esfuerzo en confirmar dicha teoría, así como en el estudio del abordaje del mismo con la intención de cortar los circuitos aberrantes que perpetúan y llevan al progreso de la enfermedad.

Del mismo modo, habría que tener muy presentes los factores psicosociales, la participación social y la actividad física, y ahondar tanto en el estudio como en el abordaje de estos factores. Sería también interesante estudiar la relación entre dichos factores psicosociales, el dolor y la correcta indicación de cirugía de prótesis de rodilla, para determinar si estos factores psicosociales pueden constituir un factor de confusión, al introducir "ruido", tanto en el diagnóstico de la KOA como en la indicación de tratamientos agresivos en la artrosis establecida.

Por último, si bien este trabajo se ha llevado a cabo clasificando a los sujetos con artrosis precoz de rodilla bajo los criterios de clasificación validados actualmente para la investigación científica en este campo, como hemos comentado, estos criterios están bajo revisión, por lo que sería interesante comprobar los resultados obtenidos una vez bien establecidos los nuevos criterios.

VII. CONCLUSIONES

Tras el estudio de los factores clínicos y funcionales, tal como se planteaba en la hipótesis, se ha visto que las variables dolor, discapacidad, inestabilidad, debilidad muscular, test *sit-to-stand* y test de marcha pueden contribuir al establecimiento de un diagnóstico precoz de la artrosis de rodilla.

Respecto a los factores psicosociales, el abordaje temprano de la ansiedad y la depresión en sujetos con artrosis precoz de rodilla puede contribuir a una mayor participación social, y prevenir un empeoramiento del cuadro.

Del estudio de los factores metabólicos se deriva que la valoración y abordaje del déficit de vitamina D y niveles de PTH puede ser crucial en el diagnóstico precoz y en la prevención de la artrosis de rodilla.

Considero que esta tesis es de utilidad clínica y que aporta resultados que facilitan el cambio en el foco de la visión de la artrosis de rodilla. Este punto de vista podría ser el inicio del largo camino a recorrer para lograr una detección temprana y segura, así como un abordaje precoz amplio de la artrosis de rodilla, que englobaría desde la identificación de estos factores que pueden influir en fases iniciales, pasando por procurar consejos a los sujetos que se encuentren en esta fase, hasta el inicio de un tratamiento médico y rehabilitador precoz.

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ANEXO 1. TABLA DE VARIABLES

DEMOGRAPHICS:		
Sex		
Male		
Female		
Age (years)		
Birth country		
Spain		
Cyprus		
Greece		
Other European countries		
Other non-European countries		
Ethnicity		
White		
Black		
Hispanic American		
American Indian		
Asian		
Pacific Islander		
Other Race		
Two or More Races		
Level of education (level of studies completed)	Individual	Parents
Elementary school not completed		
Elementary school completed		
Vocational education or general secondary education		
College or university education		
Marital status		

Single	
Married/Civil partnership	
Separated/Divorced	
Widow	
Residency	
Living independently	
Living with family	
Living in institution	
Household income: Thinking of your household's total monthly income, would you say that your household is able to make ends meet?	
With great difficulty	
With some difficulty	
Fairly easily	
Easily	
Housing status	
Renting	
Owning	
Occupation	
MEDICAL & FAMILY HISTORY:	
Any Current Medication	
Family history of OA	
No	
Yes	
Personal history of hand OA	
No	
Yes	
Personal history of hip OA	
No	
Yes	
Do you have knee osteoarthritis?	

No	
Yes	
Have you ever been told that you have OA of your knee by a doctor?	
No	
Yes	
Occupational risk (Occupational kneeling and lifting)	
Never	
Seldom	
Once-twice/month	
Once-twice/week	
Once a day	
Always	
Alcohol	
Never	
Seldom	
Once-twice/month	
Once-twice/week	
Once a day	
> once a day	
Smoking	
No	
Yes (number of cigarettes per day or week)	
Ex-smoker	
Hormonal status (women)	
Premenopause	
Postmenopause	
Previous knee injuries (indicate L: Left; R: Right; B: Bilateral)	
No/Yes	
Ligament	

Meniscus		
Cartilage		
Bone		
Regular sport leisure activity		
No		
Yes: type of sport		
Once-twice/month		
Once-twice/week		
Once a day		
Knee pain (NHANES-type questions)	L	R
NHANES A: Knee pain on most days in the last month		
NHANES C: Knee pain lasting at least a month in the last year		
No pain		
Resting VAS (Visual Analogue Scale)		
Walking VAS		
Pain rhythm	L	R
Mechanical		
Inflammatory		
Neuropathic component	L	R
No		
Yes		
Time since pain start (months, ages)		
SOCIAL PARTICIPATION How often in the past four weeks…		
Have you taken part in a club, interest group or activity group, church or other similar activity?		
Not		
Less than once a week		

Once or twice a week	
More than twice a week	
Have you been to a cultural or educational event such as the cinema, theatre, museum, talk or course	
Not	
Less than once a week	
Once or twice a week	
More than twice a week	
Have you eaten out?	
Not	
Less than once a week	
Once or twice a week	
More than twice a week	
Have you been out to a pub, café or tearoom?	
Not	
Less than once a week	
Once or twice a week	
More than twice a week	
Have you been to a public event?	
Not	
Less than once a week	
Once or twice a week	
More than twice a week	
Have you taken part in an organised games afternoon or evening? For instance, bingo, quiz or card games	
Not	
Less than once a week	
Once or twice a week	
More than twice a week	
Have you been on a day trip organised by a club or society?	
Not	
Less than once a week	
Once or twice a week	
More than twice a week	
Have you carried out committee work for a club, society or other group?	
Not	

Less than once a week		
Once or twice a week		
More than twice a week		
Have you done any organised voluntary work?		
Not		
Less than once a week		
Once or twice a week		
More than twice a week		
PHYSICAL EXAMINATION:		
Mass (Kg)		
Height (cm)		
BMI		
Knee morphology	L	R
Normal		
Altered		
Joint effusion	L	R
No		
Yes		
Increased local temperature	L	R
No		
Yes		
Local redness	L	R
No		
Yes		
Baker's cyst	L	R
No		
Yes		
Muscle strength (MRC Manual Muscle Testing scale: 0-5)	L	R
Hip flexors (0-5)		

Hip abductors (0-5)		
Knee extensors (0-5)		
Knee flexors (0-5)		
Plantar flexors (0-5)		
Dynamometric/HHD evaluation of knee extension strength		
Dynamometric/HHD evaluation of knee flexion strength		
Leg-length inequality		
No		
Yes		
Knee alignment	L	R
Radiographic angle		
Flexion deformity (angle)		
Knee ROM	L	R
Flexion (angle)		
Extension (angle)		
Knee Instability (Buckling-Any knee buckling, shifting or giving away during the past 3 months)		
No		
Yes		
Knee Laxity	L	R
Anterior		
Posterior		
Varus		
Valgus		
Joint Proprioception (Joint Positioning Sense)	L	R
Normal		
Altered		
Joint line tenderness	L	R

No		
Yes		
Patellofemoral pain	L	R
No		
Yes		
Crepitus	L	R
No		
Yes		
Abdominal perimeter		
5 Sit-to-stand test: Time(sec)		
Walking Speed: 10 meter walk test (m/s)		
Muscle atrophy (difference of circumference between both thighs, in centimeters)		
High blood pressure		
No		
Yes		
Kellgren & Lawrence (KL)	L	R
0=0 points		
1=1-2 points		
2=3-4 points		
3=5-9 points		
4=10 points		
X-ray 30º view of patellofemoral compartment	L	R
Patellofemoral lateral angle		
Lateral deviation patella		
Congruence angle		
Synovitis (by complementary tests: radiograph/ MRI/ US)	L	R
No		

Yes		
Not applicable		
Cartilage damage (by complementary tests: radiograph/ MRI/ US)	L	R
No		
Yes		
Not applicable		
Meniscal damage (by complementary tests: radiograph/ MRI/ US)	L	R
No		
Yes		
Not applicable		
MRI Examination (Specify affected area: Tibia M/L Femur M/L, Patella, Overall Joint)		
MOAKS (MRI Osteoarthritis Knee Score)		
Gait Examination (3D Gait Analysis)	L	R
BLOOD TEST:		
PTH (pg/mL)		
Vitamine D (mg/L)		
Total cholesterol (mg/dL)		
HDL-cholesterol (mg/dL)		
LDL-cholesterol (mg/dL)		
Uric acid (mg/dL)		
Glycated hemoglobin (%)		
Protein C reactive (mg/L)		
Serum COMP		
Serum HA		
Serum CPII		
IL-1β		
TNF-α		

IL-6	
SCALES:	
WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index (%)	
KOOS: Knee injury and Osteoarthritis Outcome Score (%)	
FACHS: Functional Ambulation Classification of the Hospital at Sagunto	
0=Non-ambulation	
1=Non-functional or dependent ambulation	
2=Household ambulation	
3=Surroundings of the house ambulation (neighborhood)	
4=Community ambulation	
5= Normal ambulation	
HAD: Hospital Anxiety and Depression Scale	
0-7 points, Normal	
8-10 points, Borderline abnormal (borderline case)	
11-21 points, Abnormal (case)	
GADS: Goldberg Anxiety and Depression Inventory	
No anxiety or depression	
Anxiety, scores of five or more	
Depression, scores of two or more	

ANEXO 2. ESCALAS

Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)

Name:_____ Date:_____

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):

Knee Injury and Osteoarthritis Outcome Score (KOOS)

Today's date: _____/_____/_____ Date of birth: _____/_____/_____
Name: _____

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 ___

Thank you very much for completing all the questions in this questionnaire.

Hospital Anxiety and Depression Scale (HAD)

Tick the box beside the reply that is closest to how you have been feeling in the past week. Don't take too long over you replies: your immediate is best.

D	A		D	A	
		I feel tense or 'wound up':			**I feel as if I am slowed down:**
	3	Most of the time	3		Nearly all the time
	2	A lot of the time	2		Very often
	1	From time to time, occasionally	1		Sometimes
	0	Not at all	0		Not at all
		I still enjoy the things I used to enjoy:			**I get a sort of frightened feeling like 'butterflies' in the stomach:**
0		Definitely as much		0	Not at all
1		Not quite so much		1	Occasionally
2		Only a little		2	Quite Often
3		Hardly at all		3	Very Often
		I get a sort of frightened feeling as if something awful is about to happen:			**I have lost interest in my appearance:**
	3	Very definitely and quite badly	3		Definitely
	2	Yes, but not too badly	2		I don't take as much care as I should
	1	A little, but it doesn't worry me	1		I may not take quite as much care
	0	Not at all	0		I take just as much care as ever
		I can laugh and see the funny			**I feel restless as I have to be**

		side of things:			**on the move:**
0		As much as I always could		3	Very much indeed
1		Not quite so much now		2	Quite a lot
2		Definitely not so much now		1	Not very much
3		Not at all		0	Not at all
		Worrying thoughts go through my mind:			**I look forward with enjoyment to things:**
	3	A great deal of the time	0		As much as I ever did
	2	A lot of the time	1		Rather less than I used to
	1	From time to time, but not too often	2		Definitely less than I used to
	0	Only occasionally	3		Hardly at all
		I feel cheerful:			**I get sudden feelings of panic:**
3		Not at all		3	Very often indeed
2		Not often		2	Quite often
1		Sometimes		1	Not very often
0		Most of the time		0	Not at all
		I can sit at ease and feel relaxed:			**I can enjoy a good book or radio or TV program:**
	0	Definitely	0		Often
	1	Usually	1		Sometimes
	2	Not Often	2		Not often
	3	Not at all	3		Very seldom

Please check you have answered all the questions

Scoring:

Total score: Depression (D) _____ Anxiety (A) _____

0-7 = Normal

8-10 = Borderline abnormal (borderline case)
11-21 = Abnormal (case)

Goldberg Anxiety and Depression Inventory (GADS)

The following is an adaptation of Dr. Goldberg's Depression Screening Questionnaire developed in 1993. You may self score this test with the instructions at the bottom of the screening questions. **A simple screening test such as this will not provide a diagnosis or treatment for symptoms of depression or other mood disorders. It is best if you use the results to identify possible symptoms and for seeking professional assistance.**

When answering the questions think back over the last ten to fourteen days and reflect on the relevance of each statement for your personal experience.

0 = Not at all 1 = Just a little 2 = Somewhat 3 = Moderately 4 = Quite a lot 5 = Very much

1. I do things slowly.	0 1 2 3 4 5
2. My future seems hopeless.	0 1 2 3 4 5
3. It is hard for me to concentrate on reading or other tasks.	0 1 2 3 4 5
4. The pleasure and joy has gone out of my life.	0 1 2 3 4 5
5. I have difficulty making decisions.	0 1 2 3 4 5
6. I have lost interest in aspects of life that used to be important to me.	0 1 2 3 4 5
7. I feel sad, blue, and unhappy most of the time.	0 1 2 3 4 5
8. I am agitated and restless much of the time.	0 1 2 3 4 5
9. I feel fatigued.	0 1 2 3 4 5
10. It takes great effort for me to do simple things.	0 1 2 3 4 5
11. I feel that I am a guilty person who deserves to be punished.	0 1 2 3 4 5
12. I feel like a failure.	0 1 2 3 4 5
13. I feel lifeless - - - more dead than alive.	0 1 2 3 4 5
14. My sleep has been disturbed: too little, too much, or broken sleep.	0 1 2 3 4 5
15. I spend time thinking about how I might kill myself.	0 1 2 3 4 5
16. I feel trapped or caught.	0 1 2 3 4 5
17. I feel depressed even when good things happen to me.	0 1 2 3 4 5
18. Without trying to diet, I have lost, or gained, weight.	0 1 2 3 4 5

Screening test scoring ranges:
0 – 9 No depression likely.
10 – 21 Possible symptoms that may be due to depression or other medical issues.
22 – 35 Mild to Moderate Depression.
36 – 53 Moderate to Severe Depression.
54 and up Severely Depressed.

The higher the number, the more severe your depression is likely to be. **Please seek professional assistance for symptoms of depression and if your symptoms are severe or life threatening please stay safe and call 911 or go to your nearest emergency room.**
Dr. Ivan Goldberg was a well-known and respected psychiatrist in New York City for over fifty years. He was best known for innovative treatments of medication resistant depression and bipolar disorder. He served on the staff of the National Institute of Mental Health, in the Departments of Psychiatry at the Columbia-Presbyterian Medical

Center and Columbia University's College of Physicians and Surgeons. He also founded PsyCom.net in 1997, an online resource site for clinicians and consumers.
Adapted by Lora Eiswerth-Cox, PhD (08/2017) 6500 West 44th Ave, Wheat Ridge, CO 80033

5 Sit-to-stand test

Description: Assesses functional lower extremity strength, transitional movements, balance, and fall risk.

Equipment: Stopwatch; standard height chair with straight back (16 inches high).

Therapist Instructions: Have the patient sit with their back against the back of the chair. Count each stand aloud so that the patient remains oriented. Stop the test when the patient achieves the standing position on the 5th repetition.

Patient Instructions: "Please stand up straight as quickly as you can 5 times, without stopping in between. Keep your arms folded across your chest. I'll be timing you with a stopwatch. Ready, begin."

Interpretation:
- Lower times = better scores
- MDC: 3.6-4.2 sec [1, 2]
- MCID: 2.3 sec [3]

Age-Matched Norms[4]:

Age Bracket	Time (sec)
60-69 yo	11.4
70-79 yo	12.6
80-89 yo	14.8

Fall Risk:
- Geriatrics
  - -need for further assessment of fall risk: ≥ 12 sec[5]
  - -recurrent falls: > 15 sec[6]
- Vestibular Disorders
  - -fall risk: > 15 sec[7]
- Parkinson's Disease
  - -fall risk: > 16 sec[8]

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10 Meter walk test

General Information:

- individual walks without assistance 10 meters (32.8 feet) and the time is measured for the intermediate 6 meters (19.7 feet) to allow for acceleration and deceleration
    - start timing when the toes of the leading foot crosses the 2-meter mark
    - stop timing when the toes of the leading foot crosses the 8-meter mark
    - assistive devices can be used but should be kept consistent and documented from test to test
    - if physical assistance is required to walk, this should not be performed
- can be performed at preferred walking speed or fastest speed possible
    - documentation should include the speed tested (preferred vs. fast)
- collect three trials and calculate the average of the three trials

Set-up (derived from the reference articles):

- measure and mark a 10-meter walkway
- add a mark at 2-meters
- add a mark at 8-meters

Patient Instructions (derived from the reference articles):

- Normal comfortable speed: “I will say ready, set, go. When I say go, walk at your normal comfortable speed until I say stop”
- Maximum speed trials: “I will say ready, set, go. When I say go, walk as fast as you safely can until I say stop”

10 Meter Walk Testing Form

Name:_____
Assistive Device and/or Bracing
Used:_____ Date:_____

Seconds to ambulate 10 meters (only the middle 6 meters are timed)
Self-Selected Velocity: Trial 1_____sec.___ Fast Velocity: Trial 1_____sec.___
Self-Selected Velocity: Trial 2_____sec.___ Fast Velocity: Trial 2_____sec.___
Self-Selected Velocity: Trial 3 _____sec.___ Fast Velocity: Trial 3_____sec.___
Self-Selected Velocity: Average time___sec.__ Fast Velocity: Average time___sec.__

Actual velocity: Divide 6 by the average seconds
Average Self-Selected Velocity:_____m/s

Average Fast-Velocity:_____m/s

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ANEXO 3. ARTÍCULOS PUBLICADOS

Alabajos-Cea A, Herrero-Manley L, Suso-Martí L, Sempere-Rubio N, Cuenca-Martínez F, Muñoz-Alarcos V, Pérez-Barquero JA, Viosca-Herrero E, Vázquez-Arce I. **Screening Clinical Changes for the Diagnosis of Early Knee Osteoarthritis: A Cross-Sectional Observational Study**. Diagnostics (Basel). 2022 Oct 30;12(11):2631. DOI: 10.3390/diagnostics12112631. PMID: 36359475; PMCID: PMC9689265.

diagnostics

MDPI

Article

Screening Clinical Changes for the Diagnosis of Early Knee Osteoarthritis: A Cross-Sectional Observational Study

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Abstract: Background: The main objective was to evaluate differences in the clinical, motor, or functional variables in patients with Early Osteoarthritis (EOA) and individuals at risk of developing osteoarthritis (OA). **Methods:** A cross-sectional study was performed. All the participants were divided into two groups: EOA patients and healthy subjects (HS) at risk of developing OA. The main outcomes were clinical tests, such as those of knee morphology, instability, or proprioception; motor and functional variables, such as knee strength, range of motion, walking speed, and the sit-to-stand test; pain and disability, assessed through the Western Ontario McMaster Universities Osteoarthritis Index (WOMAC) and Knee injury and Osteoarthritis Outcome Score (KOOS) scales; and knee alignment and leg length inequality, assessed via X-ray images. **Results:** A total of 97 participants were included (54 EOA and 43 HS). Patients with EOA showed a greater presence of knee pain ($p < 0.01$). In addition, more EOA patients showed instability both in the left ($p < 0.01$) and right legs ($p < 0.05$). Regarding the knee alignment variable, significant differences were found ($p < 0.04$), with more patients with EOA diagnosed as possessing a varus alignment. In addition, EOA patients showed lower knee strength, since statistically significant differences were found regarding flexion and extension strength in the left leg (Mean Difference (MD): 12.92; $p = 0.03$; $d = -0.46$ and MD:7.81; $p = 0.04$; $d = -0.39$). Differences were found for the sit-to-stand test scores, showing lower results for the EOA group (MD: −1.91; $p < 0.01$; $d = 0.54$). **Conclusions:** The results of this research show statistically significant differences between patients with EOA and HS at risk of developing OA with respect to pain, disability, instability, knee strength, and the sit-to-stand test. Our results suggest that the evaluation of clinical, motor, and functional features could contribute to an early management of knee OA.

Keywords: osteoarthritis; knee osteoarthritis; early osteoarthritis; musculoskeletal disorders; risk factors

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1. Introduction

Osteoarthritis (OA) is a common joint disease that causes disability and a reduction in patients' quality of life. It is a leading cause of chronic pain and health-care utilization [1]. OA is characterized by cartilage loss, subchondral bone changes, synovial inflammation, and meniscus degeneration [2]. Basic research approaches have allowed for the identification of pathophysiological factors that determine the existence of OA. However, the main part of this research is performed in the late stage of OA, and the pathological processes involved in the early stages of joint disease are not well understood [3].

Previous studies suggest that many of the structural findings grounded in X-ray evidence in persons with knee OA are late phenomena, which occur after a considerable progression of the pathology [4,5]. In this regard, it has been suggested that the limited

efficacy of non-surgical treatments for OA may be due partly to their use at a late point in the evolution of the disease, when structural deterioration is often advanced [4]. For these reasons, there is great scientific and social interest in 'early osteoarthritis' (EOA), as it is believed that identifying patients affected by EOA in order to initiate early interventions and therapeutic approaches could prevent disease progression and severe structural changes in the joint associated with later stages of OA [6].

However, this has not been studied in depth, and there is no consensus concerning what changes may be associated with EOA, which prevents the identification of these patients at an early stage. Since it has been shown that imaging studies may not be the best alternative in this regard, it has been suggested that some modifiable factors such as physical features and motor or functional variables could aid the identification of patients with EOA [7,8]. Our hypothesis is that we will find clear clinical, motor, and functional alterations in patients with EOA compared to healthy subjects. Therefore, the main objective of this study was to evaluate which clinical, motor, or functional variables could be related to the appearance of EOA.

2. Materials and Methods

2.1. Study Design

A cross-sectional study with a non-probabilistic sample was performed. The design followed the international recommendations for Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) [9]. 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.

2.2. 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 the recruitment and follow-up of participants started in July 2018 and lasted until February 2021. All participants were divided into two groups: EOA and healthy subjects (HS) at risk of developing OA.

The subjects recruited were evaluated by a group of three experienced physical medicine and rehabilitation clinicians, always performing the same roles in the evaluation. The inclusion criteria for EOA patients were based on Luyten's proposal for EOA classification, as the criteria used found a specificity of 76.5% for detection of clinical progression, making them valid criteria for research use [10]. The criteria were as follows: (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) are needed 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 for standing and weight-bearing (at least 2 projections—PA fixed flexion and skyline for patellofemoral OA) [11]. For matched controls, criteria were (a) patient age greater than or equal to 40 years; (b) body mass index greater than or equal to 25; (c) Kellgren and Lawrence score of 0–1. Exclusion criteria were the same for both groups: (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.

2.3. Outcome Measures

2.3.1. Descriptive, Demographic Data and Control Variables

In this section, we included general demographic information included in other large databases, and well-established conventional predictors, such as gender, age, educational level, and marital status [8,12]. Personal history of hand or hip OA, as well as familial history of OA, were registered. Familial history was defined as parents, siblings, or

grandparents having a diagnosis of OA, having undergone arthroplasty of the knee or hip, or if they were reported to have Heberden's nodes. Occupational risk, which was considered as occupational kneeling and lifting, and lifestyle habits such as smoking and drinking alcohol were registered. We also registered hormonal status in women; sport activities, defined as regular leisure activities; and the presence of previous knee injuries. Finally, we collected weight, height, and calculated BMI.

2.3.2. Clinical Tests

Knee Morphology

Changes such as swelling, joint effusion, Baker's cyst, or any others were documented.

Flexion Deformity

The patient was viewed from the side, and the long axis of the thigh and the leg were determined, and the angle between them was measured with the goniometer [13].

Leg Circumference

For leg circumference measurement, a manual circumference measurement at 10 cm from the upper side of the patella was used. A standard, non–elastic, bendable tape with a sensitivity level of 0.1 cm, using one-centimeter width for the measurements, was used. The tape was enclosed around the limb while the observer held the zero end of the tape with one hand and the other end of the tape with the other hand. Measurement results were observed from the point where the tape intersects with number zero and were recorded in centimeters to achieve standardization [14].

Knee Instability

To assess knee instability, the traditional passive tests were used. These tests included the Lachman test, the anterior/posterior drawer test, the pivot shift test, the quadriceps active test, and the varus/valgus stress test [15]. The primary structures that were tested were the anterior cruciate ligament, posterior cruciate ligament, and medial and lateral collateral ligaments [15].

Joint Proprioception

To measure knee joint proprioception, patient was in bedside-sitting position with legs out on the plinth and thighs fully supported. Subject was blindfolded to avoid any visual cues. Examiner passively extended knee joint from flexed position to the target angle of 30 degrees at very slow speed (about 10 degree/second). Subject attempted to identify test position whilst holding it actively for four seconds and then passively returned to the starting position. Then, subject was asked to reproduce target position actively using the same limb [16].

2.3.3. Motor and Functional Variables

Knee Strength

For the specific evaluation of muscle strength, the isometric thigh muscle strength was used [17]. The evaluation was performed by a handheld dynamometer (HHD) as described by other authors [18]. The dynamometer used was the NedDFM/IBV employing the software NedDiscapacidad/IBV. Participants were asked to take a second or two to exert maximal effort and then continue trying to straighten their knee as vigorously as possible until the tester asked them to stop (about 4 s later). A total of 3 measures were performed and the average was used to quantify muscle strength [18].

To test the knee extension strength, subjects were seated, with their knees at about 90 degrees of flexion. HHD was placed against the anterior distal third of the leg of participants. To test the knee flexion strength, subjects were lying in prone position, with the knee under examination flexed about 90 degrees. HHD was placed against the posterior distal third of the leg of participants. Figure 1 represents the measurement protocol.

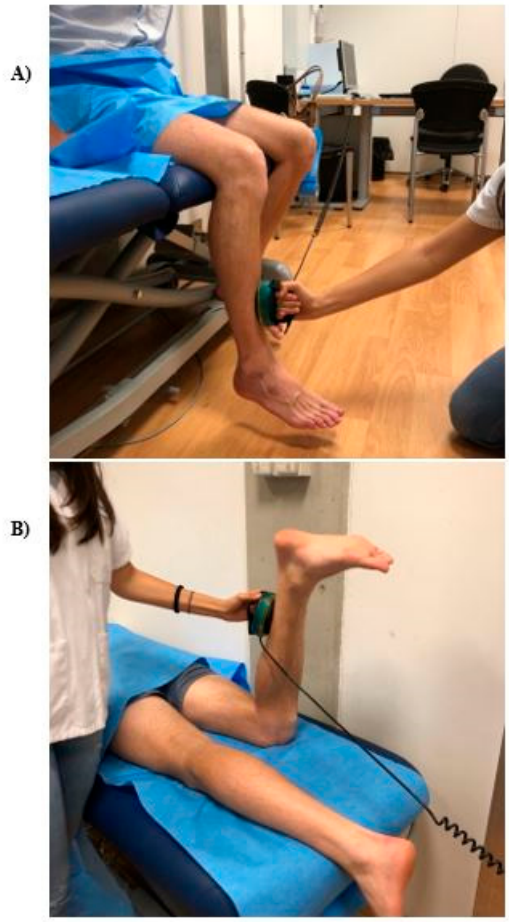

Figure 1. Knee strength measurement: (**A**) extension movement; (**B**) flexion movement.

Knee Range of Motion

To obtain knees' range of motion (ROM) measurements, particular care was taken to align the goniometer to the femur by palpating the greater trochanter and then aligning the proximal arm of the goniometer close to the femur. The distal arm of the goniometer was parallel to the tibia [19].

Sit-to-Stand

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 standing movement aloud so that the patient remained oriented. The clinician stopped the test when the patient achieved the standing position on the 5th repetition [20].

Walking Speed

Subject walked without assistance 10 m (32.8 feet) 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. Test was performed at the fastest speed possible. There were three trials collected and the average of the three trials was calculated for the measurement [21,22].

2.3.4. 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" and "the maximal pain

imaginable". It has been shown to have good re-test reliability (r = 0.94, $p < 0.001$) and a minimal detectable change of 15.0 mm [23,24]. Pain intensity was measured both at rest and while walking.

Pain Type

Pain was also assessed with National Health and Nutrition Examination Survey (NHANES)-type pain questions, wherein duration of pain is indicated as 'most days in a month' (NHANES A and NHANES C), following published recommendations [25].

Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)

This instrument is the most extensively used for the functional and symptomatic assessment of patients with osteoarthritis. The WOMAC questionnaire is self-administered and is used to assess patients who progress with hip and/or knee osteoarthritis. The questionnaire is a multidimensional scale composed of 24 items divided into 3 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 [26].

Knee Injury and Osteoarthritis Outcome Score (KOOS)

The KOOS is a knee-specific instrument, developed to assess a patient's opinion about their knee and associated problems. The KOOS evaluates both short-term and long-term consequences of knee injury. It holds 42 items in 5 separately scored subscales: 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 [27].

2.3.5. Image Variables

Knee Alignment

Knee alignment was measured based on bilateral standard anterior–posterior weight-bearing radiographs as the angle formed by the intersection of the mechanical axes of the femur (the line from femoral head center to femoral intercondylar notch center) and the tibia (the line from ankle talus center to the center of the tibial spine tips). A knee was defined as varus when alignment was more than 0° in the varus direction, valgus when it was more than 0° in the valgus direction, and neutral when alignment was 0° (the angle made by the femur and tibia on a knee X-ray does not consider the proximal femur, femoral or tibial shafts, or ankle, so it is highly variable as opposed to full-limb measurements) [15].

Leg-Length Inequality (LLI)

We measured LLI in a bilateral standard anterior–posterior weight-bearing radiograph. We drew a line from the top of the femoral head that was lower than the other one. In addition, we then measured the distance between that line and the highest point of the other femoral head.

2.4. Procedures

An information sheet with an explanation of the procedure and an informed consent form were given to all the participants. Once the subjects had read the information from the study, they were allowed to ask any questions about its nature. The subjects that agreed to participate proceeded to fill in the sociodemographic questionnaire. Self-reported measures of disability, pain, and disability variables were then assessed. Finally, the physical examination was performed, including physical tests and motor and functional tests. The study protocol lasted approximately one hour. In order to avoid the influence

of fatigue on the physical tests, an interval of 3 min between tests was maintained. This procedure was identical for both groups.

2.5. 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 the Social Sciences (SPSS 24, IBM Inc., Chicago, IL, USA). The categorical variables are shown as frequencies and percentages. The quantitative results are represented by descriptive statistics (confidence interval, mean, and standard deviation). For all variables, the z-score was assumed to follow a normal distribution based on the central limit theorem because all the groups had more than 30 participants [28,29]. Student's *t*-test was used for 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 pain and disability measures and between physical measurements 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 [30].

3. Results

A total of 97 participants were included in the study, with a mean age of 51.51 ± 5.89 (36 men and 61 women). A total of 54 of the participants met the criteria to be classified as EOA while 43 were classified as HS. All the physical tests established in the protocol were performed on all the participants included in the study; no abandonment of any study participant was recorded. No adverse effects were reported during the assessments. There were no statistically significant differences between the groups in terms of the descriptive, demographic, and control variables (Table 1).

Table 1. Descriptive, demographic data and control variables.

	EOA (*n* = 54)	**HS (*n* = 43)**	***p* Value**
Age (years)	51.81 ± 5.65	51.05 ± 6.21	0.44
BMI (kg/m^2)	27.28 ± 4.08	28.01 ± 2.96	0.59
KL Grade			
0	19 (35)	23 (54)	0.67
1	35 (65)	20 (46)	
Gender			
Men	22 (40.8)	14 (32.5)	0.78
Women	32 (59.2)	21 (67.5)	
Hormonal status			
Pre-menopausal	12 (37.5)	14 (66.6)	0.19
Post-menopausal	20 (62.5)	7 (33.3)	
Smoking			
Yes	9 (16.6)	4 (9.3)	0.55
No	21 (38.9)	19 (44.2)	
Ex	24 (44.5)	20 (46.5)	

Table 1. *Cont.*

	EOA (*n* = 54)	**HS (*n* = 43)**	***p* Value**
Alcohol			0.66
Never	6 (11.1)	4 (9.3)	
Seldom	14 (25.9)	12 (27.9)	
1–2 times/month	13 (24.1)	11 (25.6)	
1–2 times/week	17 (31.5)	13 (30.3)	
1 time per day	3 (5.5)	2 (4.6)	
More than 1 a day	1 (1.9)	1 (2.3)	
Previous Injuries Left			0.35
No	42 (77.3)	27 (62.8)	
Yes	12 (22.2)	16 (37.2)	
Meniscus	8	3	
Ligament	0	4	
Bone	0	2	
Cartilage	1	2	
Unspecific	3	5	
Previous Injuries Right			0.47
No	40 (74.1)	25 (58.2)	
Yes	14 (25.9)	18 (41.8)	
Meniscus	4	7	
Ligament	5	2	
Bone	1	1	
Cartilage	1	2	
Unspecific	3	6	
Knee morphology			0.89
Normal	52 (96.3)	43 (100)	
Altered	2 (3.7)	0 (0)	
Occupational risk			0.68
Never	16 (29.6)	10 (23.3)	
Seldom	12 (22.2)	11 (25.6)	
1–2 times/month	3 (5.6)	5 (11.6)	
1–2 times/week	6 (11.1)	1 (2.3)	
1 a day	9 (16.7)	9 (20.9)	
Always	8 (14.8)	7 (16.3)	
Family history			0.56
Yes	38 (70.4)	32 (74.4)	
No	16 (29.6)	11 (25.6)	
OA Hand history			0.25
Yes	11 (20.4)	6 (14.0)	
No	43 (79.6)	37 (86.0)	

Table 1. *Cont.*

	EOA (*n* = 54)	**HS (*n* = 43)**	***p* Value**
OA Hip history			0.66
Yes	8 (14.8)	7 (16.3)	
No	46 (85.2)	36 (83.7)	
Sport			0.54
Yes	24 (45.5)	27 (62.8)	
No	30 (55.5)	16 (37.2)	
Education level			
Primary	9 (16.6)	6 (13.9)	0.92
Secondary	19 (35.2)	15 (34.9)	
College	26 (48.2)	22 (51.2)	
Marital status			
Single	6 (11.1)	7 (16.2)	
Married	36 (66.7)	32 (74.4)	0.22
Divorced	10 (18.5)	2 (4.7)	
Widow	2 (3.7)	2 (4.7)	

The categorical variables are shown as frequencies and percentages. The quantitative results are represented by descriptive statistics (confidence interval, mean, and standard deviation). BMI: Body Mass index; EOA: Early Osteoarthritis; HS: Healthy subjects; KL: Kellgren-Laurence.

3.1. Clinical and Image Variables

Regarding differences in the clinical and image variables, the patients with EOA presented more knee pain ($p < 0.01$). In addition, more EOA patients showed instability both in the left ($p < 0.01$) and the right leg ($p < 0.05$). Significant differences were found with respect to the knee alignment variable ($p < 0.04$), wherein more patients with EOA diagnosed as possessing varus alignment. Detailed results are presented in Table 2.

Table 2. Clinical and image variable results.

	EOA (*n* = 54)	**HS (*n* = 43)**	***p* Value**
Pain			
Yes	**45 (83.3)**	**16 (37.2)**	**<0.01**
No	**9 (16.6)**	**27 (62.8)**	
Pain side			
Left	7 (15.6)	3 (18.8)	0.55
Right	14 (31.1)	4 (25)	
Both	24 (53.3)	9 (56.2)	
NHANES Pain Left			0.67
No pain	34 (63.0)	29 (67.5)	
A	10 (18.5)	9 (20.9)	
C	10 (18.5)	5 (11.6)	
NHANES Pain Right			0.2
No pain	30 (55.6)	29 (67.4)	
A	14 (25.9)	5 (11.6)	
C	10 (18.5)	9 (20.9)	
Crepitus Left			0.65
Yes	39 (72.2)	33 (76.7)	
No	15 (27.8)	10 (23.3)	

Table 2. *Cont.*

	EOA (n = 54)	HS (n = 43)	p Value
Crepitus Right			0.66
Yes	34 (62.9)	29 (67.4)	
No	20 (37.1)	14 (32.6)	
Instability Left			
Yes	18 (33.3)	5 (11.6)	0.01
No	36 (66.6)	38 (88.4)	
Instability Right			
Yes	26 (48.1)	12 (27.9)	0.05
No	28 (51.9)	31 (72.1)	
Deformity Left			0.69
Yes	16 (29.6)	13 (30.2)	
No	38 (70.4)	30 (69.8)	
Deformity Right			0.86
Yes	16 (29.6)	12 (27.9)	
No	38 (70.4)	31 (72.1)	
Knee alignment Left			0.04
Neutral	6 (11.1)	11 (25.6)	
Varus	32 (59.3)	16 (37.2)	
Valgus	16 (29.6)	16 (37.2)	
Knee alignment Right			0.47
Neutral	7 (12.9)	5 (11.6)	
Varus	32 (57.4)	21 (48.8)	
Valgus	15 (27.8)	17 (39.6)	
Leg length inequality			0.13
Yes	18 (33.3)	8 (18.6)	
No	36 (66.7)	35 (81.4)	
Leg circumference			0.32
Yes	42 (77.7)	34 (79.1)	
No	12 (22.3)	9 (20.9)	
Proprioception Left			0.88
Altered	44 (81.5)	32 (74.4)	
Normal	10 (18.5)	11 (25.6)	
Proprioception Right			0.33
Altered	35 (64.8)	31 (72.1)	
Normal	19 (35.2)	12 (27.9)	

The categorical variables are shown as frequencies and percentages. The quantitative results are represented by descriptive statistics (confidence interval, mean, and standard deviation). EOA: Early Osteoarthritis; HS: Healthy subjects.

3.2. Motor and Functional Variables

Regarding the differences between the groups, the patients with EOA showed higher levels of pain intensity at rest with a medium effect size (Mean Difference (MD): −2.35;

$p = 0.01$; d = 0.5) and walking with a large effect size (MD: −2.21; $p < 0.01$; d = 0.88) (Figure 2).

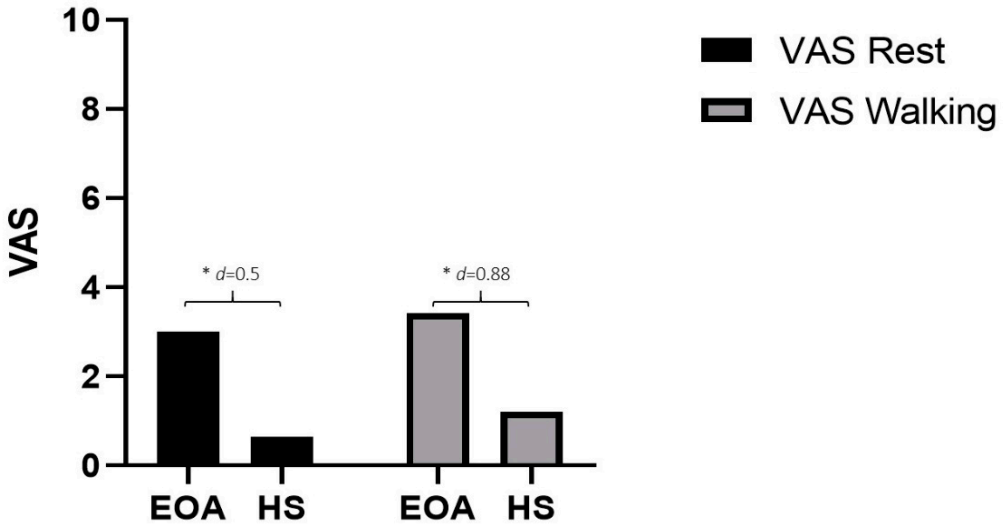

Figure 2. Differences in pain variable. * $p < 0.05$; *d*: Effect size; VAS: Visual Analogue Scale.

In addition, the EOA patients showed lower knee strength, since statistically significant differences were found for flexion and extension strength in the left leg with a small effect size (MD: 12.92; $p = 0.03$; $d = -0.46$ and MD:7.81; $p = 0.04$; $d = -0.39$). In the right leg, similar significant differences were found between groups, but only regarding flexion movement, with a medium effect size (MD: 13.06; $p = 0.01$; $d = 0.55$) (Figure 3). No differences were found for the knee ROM values between groups.

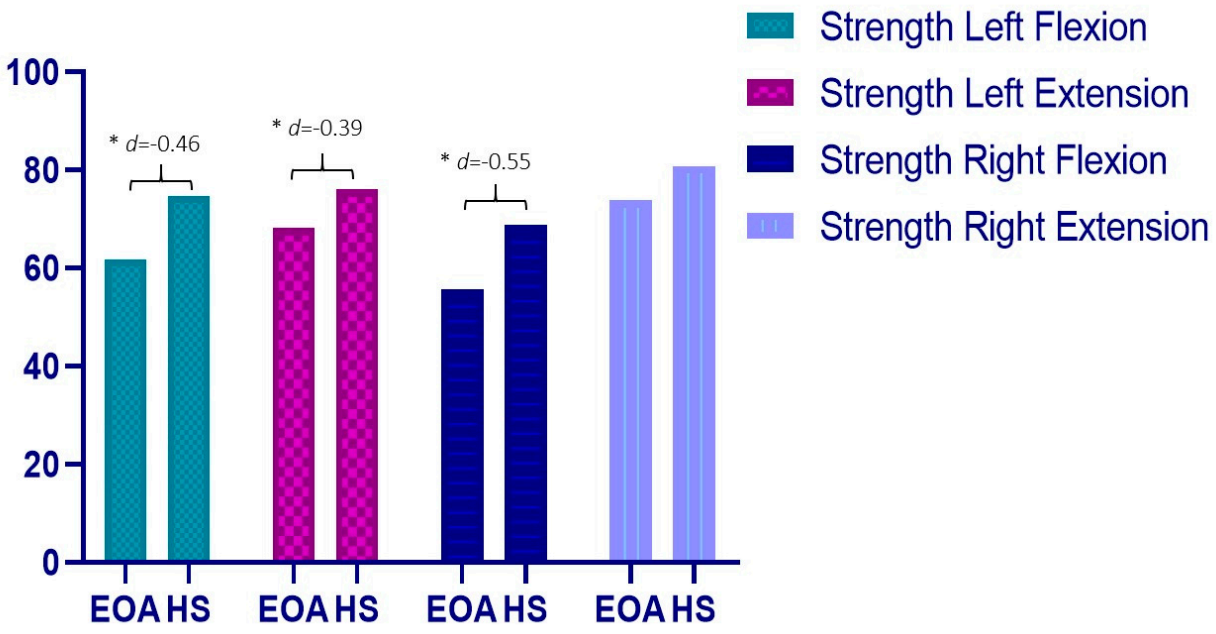

Figure 3. Differences in strength variable. * $p < 0.05$; *d*: Effect size.

Regarding the functional variables, statistically significant differences were found for the sit-to-stand test, showing more time expended for the EOA group, with a medium effect size (MD: −1.91; $p < 0.01$; $d = 0.54$) (Table 3).

Table 3. Between-group comparisons regarding pain, disability, motor, and functional variables.

Measures	EOA (n = 54)	HS (n = 43)	Mean Difference (95% CI)	Effect Size (d)
VAS Rest	3.0 ± 6.44	0.65 ± 1.53	−2.35 * (−4.35 to −0.35)	0.5
VAS Walking	3.42 ± 2.75	1.21 ± 2.23	−2.21 * (−3.24 to −1.18)	0.88
WOMAC	0.25 ± 0.13	0.12 ± 0.13	−0.13 ** (−0.19 to −0.7)	1.01
KOOS				
Pain	73.5 ± 13.79	89.29 ± 14.56	15.79 ** (10.01 to 21.56)	−1.11
Symptoms	77.87 ± 12.66	90.79 ± 12.76	12.91 ** (7.73 to 18.1)	−1.01
ADL	77.7 ± 15.94	90.83 ± 10.56	13.13 ** (7.47 to 18.79)	−0.97
QQL	52.63 ± 24.86	76.17 ± 23.96	23.54 ** (13.58 to 33.49)	−0.96
Strength Left (Kg)				
Flexion	61.91 ± 21.57	74.83 ± 33.00	12.92 * (0.45 to 25.39)	−0.46
Extension	68.24 ± 21.47	76.05 ± 17.81	7.81 * (1.26 to 16.88)	−0.39
Strength Right (Kg)				
Flexion	55.71 ± 16.52	68.77 ± 28.85	13.06 * (2.59 to 23.52)	−0.55
Extension	73.89 ± 22.98	80.86 ± 22.21	6.97 (−3.34 to 17.29)	−0.31
ROM Left Leg (°)	132.39 ± 9.61	132.43 ± 12.75	0.04 (−4.91 to 5.00)	−0.01
ROM Right Leg (°)	132.61 ± 8.11	131.84 ± 12.19	−0.78 (−5.29 to 3.74)	0.07
Sit to stand (sec)	13.18 ± 4.27	11.26 ± 2.61	−1.91 * (−3.52 to −0.31)	0.54
Walking speed (sec)	3.54 ± 0.89	3.36 ± 0.63	−0.17 (−0.53 to 0.18)	0.23

Note: ** $p < 0.01$; * $p < 0.05$; CI: confidence interval; EOA: Early osteoarthritis; HS: Healthy subjects.

3.3. Correlation Analysis

The strongest correlations were found in the EOA group between the left leg flexion strength, left knee ROM, and walking speed with walking VAS. These correlations were low (r = −0.33, r = −0.41 and r = 0.44; $p < 0.05$), and we also found the same trend for the right side, although it was not statistically significant. Correlations were also found between pain intensity at rest and ROM in both groups. Finally, correlations were found between the BMI and the ROM for left and right sides in the EOA patients (r = −0.66 and −0.55; $p < 0.01$) (Table 4).

Table 4. Correlation analysis.

Variable	Group	VAS Rest	VAS Walking	Strength Left F	Strength Left E	Strength Right F	Strength Right E	ROM Left	ROM Right	Sit-to-Stand	Walking Speed
VAS Rest	EOA	1	0.28 *	−0.01	0.15	−0.1	−0.05	−0.14	−0.32 *	0.02	0.04
	HS	1	0.69 **	−0.09	0.05	−0.16	−0.09	−0.62 **	−0.62 *	0.35*	0.4 *
VAS Walking	EOA	0.28 *	1	−0.33 *	−0.20	−0.13	−0.24	−0.41 **	−0.24	0.31 *	0.44 **
	HS	0.69 **	1	−0.13	−0.22	−0.22	−0.13	−0.28	−0.24	0.14	0.32
BMI	EOA	0.09	0.24	0.14	0.13	0.09	0.01	−0.66 **	−0.55 **	0.11	0.32 *
	HS	0.01	−0.03	0.27	0.28	0.25	−0.18	−0.31	−0.34	0.26	0.05
WOMAC	EOA	0.15	0.56 **	−0.12	−0.05	0.11	−0.15	−0.17	−0.27	0.27	0.19
	HS	0.52 **	0.63 **	−0.24	−0.17	−0.27	0.06	−0.08	−0.09	0.25	0.59 **

Note: ** $p < 0.01$; * $p < 0.05$; EOA: Early osteoarthritis; HS: Healthy subject.

4. Discussion

The main objective of this study was to evaluate which clinical, motor, or functional variables could be related to the appearance of EOA. Our study highlights some relevant data in relation to the early diagnosis of OA. In recent years, many efforts have been made to diagnose and classify these patients. However, this remains a challenge in such a heterogeneous disease, and our data provide new information about the risk factors and mechanisms involved in EOA [31]. Firstly, some of the risk factors (gender, personal history, or daily habits) previously identified in the scientific literature have not been found in our population with OAE. However, some other related physical or functional features have been associated with OA in this population, suggesting the importance of these factors in the diagnosis and prevention of OA.

First, it is believed that non-modifiable factors such as age, gender, familial OA, and hormonal status could have an important role in the development of OA. Women have consistently been shown to be at higher risk of hip, knee, and hand OA, and whether this increase in risk is constant with age and changes in relation to endogenous estrogen production and menopause has been studied [32]. However, we found no differences in these variables. In addition, personal OA histories have been studied, with controversial results. Some studies have found the hand and/or hip OA history as one of the main factors that is consistently associated with knee OA [32], while other authors found it to be insignificant [8]. Our results follow the line of the latter authors, as we found no differences in the personal history of OA between subjects with EOA and HS.

On the other hand, some modifiable factors such as overweight and obesity (usually quantified using BMI), occupational risk, knee extensor muscle weakness, leg-length inequalities, or lifestyle habits could also significantly contribute to the onset of the pathology. A higher BMI was associated with greater knee pain accounting for OA severity in persons with or at a high risk for knee OA in the Osteoarthritis Initiative [33]. However, in our population, correlations were found between BMI and ROM in the subjects with EOA, but not with respect to pain intensity. Regarding lifestyle habits, drinking alcohol and smoking have been found to be statistically insignificant as either risk or protective factors [8,32]. Our data are in accordance with this statement, since no significant differences were found between the groups. The association of occupational activities with the development of knee OA has also been studied, finding an increased risk in floor-layers or in frequent occupational kneeling and lifting [34]. These differences were not found in our data, but it should be considered that our sample represented a small number of people with an occupational risk. Perhaps a larger sample of people with a high occupational risk would be necessary to detect differences in this aspect.

Regarding physical activity, a Cochrane Library's review concluded that people are confused about the cause of their pain, and without adequate information from healthcare professionals, they avoid activity for fear of causing harm [35]. In addition, sport activities, defined as regular leisure activities, have been found to predict the progression of knee OA [34]. Being less sedentary was associated with better function in the Osteoarthritis Initiative, independent of moderate–vigorous physical activity minutes [36,37]. A greater degree of walking was associated with a lower risk of incident function limitation in persons with or at higher risk for knee OA in the Multicenter Osteoarthritis Study [38]. In our population, there seems to be a trend toward a greater sedentary lifestyle in the EOA group, but the differences were not significant.

The association of risk factors with the onset of knee pain has also been studied, establishing knee pain not as a predictor, but part of outcome measures for knee OA [8,25,32]. In our population, we combined radiographic and clinical criteria to classify patients into HS or EOA, as suggested by Luyten [11], and we found that the subjects with EOA showed higher levels of disability in terms of WOMAC and pain through VAS both at rest and during walking. In addition, our results show that higher levels of pain may be related to lower levels of ROM in both EOA and HS.

A systematic review and meta-analysis showed that knee extensor muscle weakness was associated with an increased risk of developing symptomatic knee OA [7]. Ruhdorfer et al., analyzing data from the Osteoarthritis Initiative, found that the reduction in thigh muscle strength in knee OA is related to pain but not to the structural (radiographic) disease status [39]. In this regard, our results showed that motor variables such as strength, or functional variables such as functional capacity, are significantly altered in patients with EOA compared to HS at risk of developing OA. In this regard, we also found differences between the right and left leg with respect to variables such as strength or ROM. The reasons for this may be varied, given that more subjects in both groups had pain or instability in the right leg due to a greater dominance of this leg with respect to the left.

Knee alignment, both static and dynamic, has important implications for load distribution within the knee. There is insufficient evidence to draw a conclusion regarding the effects of alignment on incident OA. It is possible that malalignment may be a reflection of the severity of the disease, with joint space loss due to cartilage and meniscal abnormalities, and bone contour alterations occurring as part of the OA disease process contributing to malalignment. In middle-aged, overweight women without knee OA in the Prevention of Knee Osteoarthritis in Overweight Females study, varus alignment was associated with incident radiographic OA; the association for valgus was borderline [40]. Similarly, LLI is an easily modifiable abnormality that can also affect lower extremity biomechanics. An LLI of at least 2 cm has been shown to be almost twice as likely to correspond to prevalent radiographic knee OA, but no such association was noted for incident knee OA [34]. Our data showed a predominance of varus alignment in the EOA group, suggesting its relevance in the development of EOA, but no significant differences were found with respect to LLI in our sample.

Previous studies suggest a relationship between instability and the onset and development of OA [41]. Our results are in line with these findings, as we found higher rates of subjects with ligamentous instability in the group of patients with EOA compared to healthy subjects. In this regard, it has also been suggested that previous knee injuries may contribute to the development of OA [8,34]. Although our results do not show significant differences between the groups, a higher percentage of injuries in the EOA group has been observed.

In addition, previous studies have shown that patients with higher levels of knee strength have higher levels of functional stability [42]. Our results show lower levels of strength in patients with EOA, suggesting that stability may also be dependent on this factor, and not just on ligamentous status. We hypothesize that these lower strength levels may lead to greater joint instability, which may play a role in the development of EOA, although future studies are needed to establish a cause–effect relationship.

Limitations

This research study has several limitations that should be considered when interpreting the results. First, the cross-sectional nature of this study makes it impossible to establish causality. In this sense, we did not find significant differences in many of the variables that have previously been identified as risk factors. This may be due to the fact that these variables (i.e., knee morphology, sports practice, or knee deformity) are not risk factors for the development of OA but rather consequences of the establishment of this pathology. This could entail that our sample would not present these alterations because we are dealing with an 'early' OA. Secondly, the lack of consensus and clear definition of EOA makes it difficult to draw clear conclusions about the differences between these groups of individuals. In this regard, several classifications have been proposed for EOA, and further research into the validity of these classifications is needed [43,44]. Third, in our sample, we have found a low percentage of patients presenting occupational risk, previous injuries, or toxic life habits, which have been previously related to the onset of OA. Studies with a larger sample size or in another type of population may be necessary to obtain relevant

data in this regard. Finally, it would have been interesting to collect more information on physical activity in order to explore the implication of its intensity on the onset of EOA.

5. Conclusions

The results of this research show statistically significant differences between patients with EOA and HS at risk of developing OA with respect to pain, disability, instability, knee strength, sit-to-stand test scores, and walking speed. Our results suggest that the evaluation of clinical, motor, and functional features could contribute to an early management of knee OA. However, further longitudinal research is needed to clarify the role of these variables in the onset and development of OA.

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Article

Are Psychosocial Factors Determinant in the Pain and Social Participation of Patients with Early Knee Osteoarthritis? A Cross-Sectional Study

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Abstract: The main objective of this research is to determine the psychosocial differences between patients with knee pain or early osteoarthritis (EOA) and healthy subjects at risk of developing osteoarthritis. The secondary objective is to determine how psychosocial factors might influence pain and social participation in patients with EOA. A cross-sectional study was performed. Participants were divided according to the presence of pain or EOA. Pain intensity both at rest and walking, psychological variables such as anxiety and depression, and social participation were evaluated. A total of 105 participants were included (64 with knee pain and 41 without pain), with a mean age of 51.42 ± 5.92 (35 men and 70 women). Patients with knee pain had higher levels of anxiety (MD = −2.35; $p < 0.01$; $d = 0.66$) and depression (MD = −2.45; $p < 0.01$; $d = 0.87$), regardless of the presence of EOA. In addition, patients with higher depression levels had lower levels of social participation. The results revealed a relationship between the psychological variables, anxiety and depression, with knee pain and the onset of symptomatic OA, as well as an influence of depression levels on social participation. Improving these psychological characteristics may be useful in delaying the onset of symptomatic OA and enhancing social participation.

Keywords: osteoarthritis; early osteoarthritis; psychological factors; anxiety; depression; social participation

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1. Introduction

Osteoarthritis (OA) is a joint disorder characterized by progressive degenerative changes [1,2] that may occur due to a wide variety of factors (e.g., post-traumatic, genetic, metabolic, biomechanical). Knee OA was typically associated with degenerative changes as a result of the progressive loss of articular cartilage, as well as subchondral bone changes, synovial inflammation, and meniscus degeneration [3,4]. However, knee OA presents with multifaceted symptoms and disruptions to daily life. Individuals with symptomatic knee OA report significantly worse function and overall health-related quality of life compared to age-matched healthy adults [5].

In this regard, multiple mechanisms can contribute to the perception of pain, such as nociception, neuropathic symptoms, psychological and personality factors, genetic influences, past painful experiences, comorbid conditions, and expectations related to future pain [6,7]. Among these factors, psychosocial factors such as depressive symptoms or higher levels of anxiety have been related to higher levels of pain and disability [8,9]. OA pain and function have been associated with greater depressive symptoms, and depressive

symptoms are a robust predictor of knee pain worsening [10]. In people with knee OA, it has been described as the association with depressive symptoms, low self-efficacy in managing their OA symptoms, increased pain, catastrophizing, and increased fear of movement [11,12]. Additionally, the health benefits of a physically active lifestyle are well established in older adults with OA, where engaging in social activities might promote physical activity [13].

This relationship with psychological factors and social participation has been poorly studied for 'early OA' (EOA), before obvious structural or degenerative changes have been established in the joint [1,2,5]. A better understanding of this entity would lead to earlier diagnoses that could help stop the progression of the disease and develop better treatments [14].

Therefore, we believe that the identification of psychosocial factors related to the onset of symptomatology in patients with EOA could be an important way to detect and prevent the development of pain and symptomatology in patients with knee OA. The main objective of this research is to determine the psychosocial differences between patients with knee pain, EOA, and healthy subjects at risk of developing OA. The secondary objective is to identify the relationship between pain, psychosocial factors, and social participation in patients with EOA.

2. Materials and Methods

2.1. Study Design

A cross-sectional study with a non-probabilistic sample was performed. The design followed the international recommendations for strengthening the reporting of observational studies in epidemiology [15]. All the 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.

2.2. 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 the recruitment and follow-up of participants started in July 2018 and lasted until February 2021.

The inclusion criteria for the pain group (PG) were (a) patient age greater than or equal to 40 years who experienced pain; (b) Kellgren and Lawrence (KL) 0–1. For the no pain group (NPG), the inclusion criteria were (a) patient age greater than or equal to 40 years, without pain or any knee symptoms; (b) Kellgren and Lawrence (KL) 0–1. The exclusion criteria were the same for both groups: (a) any cognitive disability that hindered the viewing of the audio-visual material; (b) illiteracy; (c) vomprehension or communication difficulties, (d) insufficient Spanish language comprehension to follow measurement instructions; (e) the presence of any rheumatic, autoimmune, or infectious pathology.

After the clinical evaluation, we reviewed the initial classification of every subject and refined it according to Luyten's proposal for EOA classification:

(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" ($\leq$85%).

(b) Patients should present joint line tenderness or crepitus during 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) [16].

2.3. Outcome Measures

2.3.1. Descriptive, Demographic Data and Control Variables

We include in this section general demographic information such as gender, age, educational level, birth country, ethnicity, residency, marital status, and economic status [17,18]. Unhealthy behaviors such as smoking and drinking alcohol were registered. We also registered hormonal status in women and sports activities, defined as regular leisure activities. Finally, we collected weight and height data and calculated the participants' BMI.

2.3.2. Pain and Disability Variables

- Pain Intensity

The Visual Analogue Scale (VAS) was used to measure pain intensity before and after each treatment. The VAS is a 100 mm line with two endpoints representing the extreme states "no pain" and "the maximal pain imaginable". It has been shown to have a good retest reliability (r = 0.94, p <.001) and a minimal detectable change of 15.0 mm [19,20]. Pain intensity was measured both at rest and while walking.

- Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)

This instrument is the most extensively used for the functional and symptomatic assessment of patients with osteoarthritis. The WOMAC questionnaire is self-administered and is used to assess patients who progress with hip and/or knee osteoarthritis. The questionnaire is a multidimensional scale composed of 24 items divided into 3 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 [21].

2.3.3. Psychological Variables

- Anxiety and Depression Symptoms

The Spanish version of the Hospital Anxiety and Depression Scale was used to assess the presence of depression and anxiety symptoms in the participants [22]. 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 is 0.90 for the full scale, 0.84 for the depression subscale, and 0.85 for the anxiety subscale [22].

- Social Participation

The Maastricht Social Participation Profile included nine questions to determine the frequency and diversity of social involvement for older people with chronic diseases (Mars et al., 2009). The following nine items comprised social participation: 'How often in the past four weeks have you (taken part in/been to): (1) a club, interest group or activity group, church, or other similar activity; (2) a cultural or educational event such as the cinema, theatre, museum, talk, or course; (3) eaten out; (4) gone out to a pub, café, or tearoom; (5) a public event; (6) an organized games afternoon or evening; (7) a day trip organized by a club or society; (8) committee work for a club, society, or another group; (9) any organized voluntary work? The response categories ranged from zero ('not at all') to three ('more than twice a week'). We calculated the total scores for descriptive purposes, ranging from 0 to 27 (Cronbach's αbaseline = 0.64; αfollow-up = 0.64), where higher scores equated to higher social participation [23].

2.4. 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 from the study, they were allowed to ask any questions about its nature. The subjects that agreed to participate proceeded to fill in the sociodemographic questionnaire. Self-reported

measures of disability, pain, and disability self-reported variables were then assessed. Finally, a physical examination was performed, including physical tests and motor and functional tests. The study protocol lasted for approximately one hour. In order to avoid fatigue affecting the physical tests, an interval of 3 min between tests was maintained. This procedure was identical for both groups.

2.5. 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., Armonk, NY, USA). The categorical variables are shown as frequencies and percentages. The quantitative results are represented by descriptive statistics (confidence interval, mean difference (MD), and standard deviation). For all variables, the z-score was assumed to follow a normal distribution based on the central limit theorem because all the groups had more than 30 participants [24,25]. 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 pain and disability measures, as well as between physical measurements, 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 [26].

3. Results

A total of 105 participants were included in the study, with a mean age of 51.42 ± 5.92 (35 men and 70 women). All the participants were finally enrolled and analyzed (Figure 1).

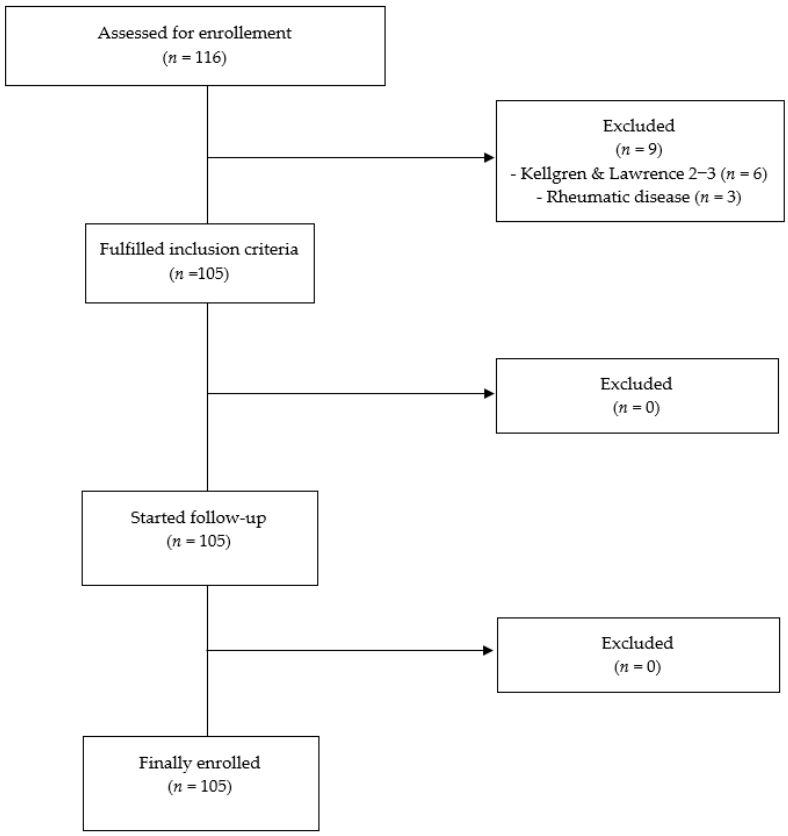

Figure 1. Study flow chart.

3.1. Pain Analysis

Participants were divided based on pain presence into two groups: PG (n = 64) and NPG (n = 41). The mean age for the PG was 51.77 ± 5.67 and 50.29 ± 6.38 for the NPG. There were no statistically significant differences between the groups in terms of age, gender, marital status, educational level, toxic habits, or hormonal status (Table 1).

Table 1. Descriptive and demographic data and control variables.

Variable	Pain Group (n = 64)	No-Pain Group (n = 41)	p Value
Age (years)	51.77 ± 5.67	50.29 ± 6.38	0.44
BMI (kg/m^2)	26.94 ± 4.08	27.38 ± 3.75	0.59
Gender			0.12
Women	39 (60.9)	31 (75.6)	
Men	25 (39.1)	10 (24.4)	
Marital status			0.36
Single	13 (20.3)	5 (12.2)	
Married	39 (60.9)	29 (70.7)	
Divorced	9 (14.1)	5 (12.2)	
Widow	3 (4.7)	2 (4.9)	
Education level			0.55
Primary	10 (15.6)	7 (17.1)	
Secondary	25 (39.1)	13 (31.7)	
College	29 (44.3)	21 (51.2)	
Birth Country			0.67
Spain	59 (92.2)	64 (100)	
Other EU countries	2 (3.1)	0 (0)	
Other non-EU countries	3 (4.7)	0 (0)	
Ethnicity			0.89
White	62 (96.9)	40 (97.6)	
Black	0 (0)	1 (2.4)	
Hispanic American	2 (3.1)	0 (0)	
Economic status			0.34
Easy	17 (26.6)	10 (24.4)	
Fairly easy	35 (54.7)	25 (60.9)	
With some difficulties	9 (14.0)	6 (14.7)	
With great difficulties	3 (4.7)	0 (0)	
Residency			0.77
With family	52 (85.3)	32 (78.1)	
Independently	12 (18.7)	9 (21.9)	
Hormonal status			0.56
Postmenopausal	19 (48.7)	15	
Premenopausal	20 (51.3)	12	
Alcohol			0.89
Never	7 (10.9)	5 (12.2)	
Seldom	23 (35.9)	11 (26.8)	
1–2 times/month	13 (20.3)	9 (21.9)	
1–2 times/week	18 (28.2)	14 (34.2)	
1 time day	2 (3.1)	2 (4.9)	
More than 1 a day	1 (1.6)	0 (0)	
Smoking			0.52
Yes	11 (17.2)	4 (9.8)	
No	27 (42.2)	18 (43.9)	
Ex	26 (40.6)	19 (46.3)	

Regarding the between-group comparisons, the t-test did not show statistically significant differences for WOMAC (0.18 ± 0.15 for PG and 0.21 ± 0.19 for NPG) and social participation (5.89 ± 3.44 for PG and 5.68 ± 2.73 for NPG). However, statistically significant differences were found for anxiety (MD = −2.35; $p < 0.01$; d = 0.66) and depression symptoms (MD = −2.45; $p < 0.01$; d = 0.87), with both showing higher values in the PG (Table 2).

Table 2. Between-group comparisons.

Measures	Pain Group (n = 64)	No-Pain Group (n = 41)	Mean Difference (95% CI)	Effect Size (d)
WOMAC	0.18 ± 0.15	0.21 ± 0.19	0.03 (−0.05 to 0.11)	-
HAD Anxiety	5.62 ± 3.54	3.27 ± 3.55	−2.35 ** (−3.76 to −0.94)	0.66
HAD Depression	3.98 ± 3.12	1.54 ± 2.43	−2.45 ** (−3.59 to −1.31)	0.87
Social Participation	5.89 ± 3.44	5.68 ± 2.73	−0.21 (−1.47 to 1.05)	-

Note: ** $p < 0.01$.

3.2. OA Analysis

Participants were divided into two groups based on the EOA criteria: EOA (n = 54) and healthy subjects (HS) (n = 41). The mean age for EOA was 51.85 ± 5.72 and 50.49 ± 6.21 for HS. There were no statistically significant differences between the groups in terms of age, gender, marital status, educational level, toxic habits, or hormonal status.

Regarding the between-group comparisons, the t-test did not show statistically significant differences for WOMAC (0.21 ± 0.16 for EOA and 0.18 ± 0.17 for HS) and social participation (5.89 ± 3.23 for EOA and 5.73 ± 3.14 for HS). However, statistically significant differences were found for anxiety (MD = −2.29; $p < 0.01$; d = 0.65) and depression symptoms, with both showing higher values in patients with EOA (MD = −2.15; $p < 0.01$; d = 0.74). Additionally, VAS showed higher values for the EOA group, and statistically significant differences were also found for VAS rest (MD = −1.38; p = 0.03; d = 0.66) and VAS walking (MD = −2.42; $p < 0.01$; d = 0.99) (Table 3).

Table 3. Between-group comparisons.

Measures	EOA (n = 54)	HS (n = 51)	Mean Difference (95% CI)	Effect Size (d)
WOMAC	0.21 ± 0.16	0.18 ± 0.17	−0.03 (−0.09 to 0.05)	-
VAS Rest	2.17 ± 2.53	0.78 ± 1.87	−1.38 * (−2.25 to −0.52)	0.62
VAS Walking	3.17 ± 2.86	0.75 ± 1.91	−2.42 ** (−3.37 to −1.48)	0.99
HAD Anxiety	5.80 ± 3.69	3.50 ± 3.39	−2.29** (−3.67 to −0.92)	0.65
HAD Depression	4.06 ± 3.19	1.90 ± 2.59	−2.15 ** (−3.29 to −1.02)	0.74
Social Participation	5.89 ± 3.23	5.73 ± 3.14	−0.16 (−1.39 to 1.07)	-

EOA: early osteoarthritis; healthy subjects. Note: ** $p < 0.01$; * $p < 0.05$.

3.3. Psychosocial Variables Analysis

Differences between participants were analyzed according to their level of HAD depression. For this purpose, the median (median = 2) was calculated, and the participants were divided into a group with higher levels of depression (n = 64) and another with lower levels of depression (n = 51). There were no statistically significant differences between the groups in terms of age, gender, marital status, educational level, toxic habits, or hormonal status.

A statistically significant higher number (Chi-squared = 8.525; p = 0.004) of patients with EOA was found in the higher depression group (n = 37) compared to the HS group (n = 20). Similarly, the number of participants with lower levels of depression was lower in the EOA group (n = 17) compared to the HS group (n = 30).

Regarding between-group comparisons, the t-test did not show statistically significant differences for WOMAC (0.19 ± 0.17 for the lower depression level group and 0.19 ± 0.15 for the higher depression level group). However, statistically significant differences were found for VAS rest, showing higher values in patients with higher depression values (MD = −1.39; $p < 0.01$; d = 0.65), VAS walking (MD = −1.87; $p < 0.01$; d = 0.68), and social participation, showing that patients with higher depression levels had lower levels of social participation (MD = 1.68; p = 0.04; d = 0.54) (Figure 2).

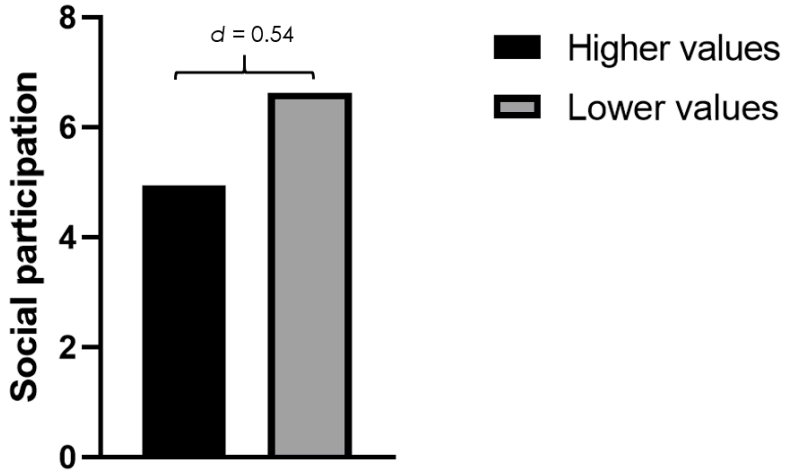

Figure 2. Social participation in participants with higher and lower levels of depression symptoms.

3.4. Correlation Analysis

Correlation analysis showed that higher levels of depression were correlated with higher levels of VAS at rest and walking, higher WOMAC, and less social participation, with a moderate correlation strength (r = 0.21 to 0.41; $p < 0.05$). In addition, higher anxiety levels were correlated with higher VAS at rest (r = 0.18; $p < 0.05$) and walking (r = 0.26; $p < 0.01$), but were not correlated with WOMAC levels and social participation (Table 4).

Table 4. Correlation analysis.

Variable	*HAD Anxiety*	*HAD Depression*
VAS Rest	0.18 *	0.32 *
VAS Walking	0.26 **	0.41 **
WOMAC	0.06	0.23 *
Social Participation	−0.14	−0.21 *

Note: ** $p < 0.01$; * $p < 0.05$.

4. Discussion

The main objective of this research was to determine the psychosocial differences between patients with symptomatic EOA, asymptomatic EOA, and HS at risk of developing OA. Firstly, the results showed that patients with knee pain had higher levels of anxiety and depression, regardless of the presence of EOA. No differences were found in the WOMAC values, suggesting that psychological variables could have a stronger relationship with the occurrence of pain.

Knee pain is the primary complaint of those with knee OA and is associated with worse physical function, quality of life, and periarticular knee muscle function [27,28]. In this regard, numerous studies have shown discordance between the findings of imaging tests and the presence of painful symptomatology in patients with knee OA [29–31]. The main factor that could explain the discrepancy between degenerative signs and pain is that pain is a complicated condition with a multitude of components and pitfalls in measurement. The experience of pain is generated or modified by sensorial, emotional, and cognitive factors and, in turn, may induce higher levels of anxiety or depression in patients experiencing it [30].

Among these factors, the presence of anxiety or depression has been linked to a greater perception of pain and a lower quality of life [32]. This is a key aspect because pain is the main symptom of patients with OA and one of the main reasons for health care utilization [33]. In addition, it has been found that patients with OA who also present anxiety or depression have a worse perception of pain and lower functional capacity [34]. Our results show that anxiety and depression levels could be linked to the presence of knee

pain and EOA, which could suggest a relationship between psychological factors and the onset of symptomatic OA. Furthermore, the correlation between depression and WOMAC suggests that using strategies to control these factors could improve the functional capacity of these patients, as suggested by previous studies [35].

Our secondary objective was to determine how psychosocial factors might influence pain and social participation in patients with EOA. In this regard, our results showed that social participation was not significantly influenced by pain or EOA. However, statistically significant differences were found among participants with higher levels of depression. Social participation is a frequently overlooked variable, yet it has previously been associated with higher mortality rates [36]. Previously, less social participation has been associated in patients with OA, and it has been suggested that it could be caused by poorer physical ability [37]. In this regard, it has been suggested that depression can be understood as a continuum of affective disorders developed by the influence of biopsychosocial factors. [38] According to our results, depression has also been associated with lower social participation in older adults, though it has not been previously studied in the OA population [39].

Finally, our data show that OA or pain could be less relevant factors than depression levels in relation to social participation, which underlines the need to include psychological interventions focused on reducing depressive symptoms in these patients from the beginning of the disease. Furthermore, they underline the need to rethink the clinical relevance of EOA. These results suggest that it may be more meaningful to assess pain or psychosocial factors in order to achieve better diagnostic and prognostic results. Further research on this matter is needed.

Limitations

This study has some limitations that must be considered. The cross-sectional nature of this study makes it impossible to establish causality. Longitudinal studies are needed to reveal whether psychosocial factors are a cause or a consequence of knee pain in OA. In addition, it would have been interesting to assess more psychological variables as cognitive, emotional, and emotive factors may be related to the onset of symptoms in EOA and play a role in social participation outcomes [40]. Moreover, no corrections have been made for multiple comparisons, and this should be considered in the interpretation of the results. Finally, it should be noted that this is a single-center study with a limited sample size; thus, there could be selection bias. This could prevent us from extrapolating these findings to other clinical contexts. More studies are needed to further investigate the relationship between EOA and psychosocial factors.

5. Conclusions

The results of our study revealed a relationship between psychological variables, anxiety and depression, with knee pain and the onset of symptomatic OA. In addition, our data show that depression levels could be a relevant factor in relation to social participation in patients with EOA.

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Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: Not applicable.

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

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The Role of Vitamin D in Early Knee Osteoarthritis and Its Relationship with Their Physical and Psychological Status

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Abstract: Osteoarthritis (OA) is a common joint condition and one of the greatest causes of disability worldwide. The role of vitamin D in the origin and development of the disease is not clear, although it could have important implications for diagnosis and treatment. For this proposal, a cross-sectional study with a non-probabilistic sample was performed. In total, 48 with early osteoarthritis (EOA) and 48 matched controls were selected, and serum 25(OH)D and parathyroid hormone (PTH) levels were analyzed. In addition, physical and psychological variables were measured to establish their relationship with vitamin D levels. Patients with EOA showed lower levels (22.3 ± 7.3 ng/mL) in comparison to matched controls (29.31 ± 9.2 ng/mL). A statistically significant higher number (Chi-squared = 8.525; $p = 0.004$) of patients with EOA had deficiency levels (<20 ng/mL) compared to the control group. Patients with lower vitamin D levels showed higher levels of pain intensity, disability, and anxiety, as well as poorer values for sit-to-stand, walking speed, and social participation. Correlation analysis showed a relationship between serum 25(OH)D, PTH and pain intensity, and social participation. These results highlight the relevance of vitamin D in the early diagnosis and prevention of EOA.

Keywords: osteoarthritis; early osteoarthritis; vitamin D

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1. Introduction

Osteoarthritis (OA) is defined as a common joint condition that typically causes chronic pain and is one of the greatest causes of disability worldwide, being considered a major public health challenge [1]. Knee OA has been associated with degenerative changes due to the progressive loss of articular cartilage, subchondral bone changes, synovial inflammation, and meniscus degeneration [2,3]. It is of prime importance to find predictors for knee OA progression to improve treatment options and to prevent this disabling disease [4,5].

Unfortunately, although some theories regarding the pathogenesis of OA do exist, the exact mechanism is not well charted [6]. The most frequent nutritional deficiency worldwide is vitamin D deficiency (defined as serum level of 25-hydroxyvitamin D [25-(OH)D] < 20 nmol/L) [7]. Specifically, more than 40% of the adult population over the age of 50 has this deficiency, being lower in women [8]. It is well known that vitamin D has an important influence on the state of many articular structures, such as cartilage and

subchondral bone, as well as muscle tissues, all of which play a part in the progression of knee OA [9]. Similarly, parathyroid hormone levels (PTH) could play an important role in the loss and formation of bone and these levels have been related to subchondral bone remodeling, and therefore, to the radiological and clinical progression of knee OA [10].

In relation to this, previous studies suggest that vitamin D could stimulate proteoglycan synthesis in mature chondrocytes through a metabolic transformation via vitamin D receptors [11,12]. Moreover, vitamin D deficiency could impede bone remodeling causing OA through complex pathophysiological processes, and other studies suggested that low serum vitamin D could be associated with an increased risk of knee OA progression [13]. Conversely, vitamin D supplementation could be able to prevent the progression of OA by increasing bone remodeling and also by reducing the abnormal pathophysiological process [14]. Additionally, it was suggested that supplementation may help improve disease progression in patients with vitamin D deficiency but does not have any additional benefits on those with optimal levels of vitamin D [15]. However, recent studies showed that low levels of vitamin D are not associated with the risks of developing knee OA, except perhaps with the progression of knee OA [12,16]. In addition, vitamin D supplementation may not help to control pain or to reduce structural disease progression in this condition [16,17].

It has been suggested that the structural findings in OA are a late phenomenon [18,19]. For this reason, non-surgical treatments for OA are often ineffective, which may be due in part to its use late in the course of the disease, when structural deterioration is usually advanced [18]. Therefore, there is a great scientific and social interest in 'early osteoarthritis' (EOA), as it is believed that identifying patients affected by EOA to initiate early interventions and therapeutic approaches could prevent progression and severe structural changes in the joint associated with later stages of OA [20].

Most of the studies that have reported a link between vitamin D and OA have been conducted in patients with advanced stages of the disease; however, little is understood regarding the effect that vitamin D and PTH could have on the initiation and progression of EOA. Early identification of these factors could be critical for early diagnosis, which would facilitate early treatment to prevent the dramatic development of knee OA. Therefore, the aim of this cross-sectional study was to study the association of serum concentrations of vitamin D with knee EOA. The secondary objective was to determine the association of serum concentrations of PTH with knee EOA and to determine the relationship between vitamin D deficiency, PTH level, and pain intensity, disability, psychological, and functional variables in patients with knee EOA.

2. Materials and Methods

2.1. Study Design

A cross-sectional study with a non-probabilistic sample was designed. The international recommendations for Strengthening the Reporting of Observational Studies in Epidemiology were followed [20]. The research procedures were performed according to the ethical standards of the Declaration of Helsinki and approved by an Ethics Committee (CEIm La Fe 2017/0147). All participants received an explanation and signed a written informed consent.

2.2. Participants

Subjects were recruited 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, due to the criteria used found a specificity of 76.5% for detection of clinical progression, being valid criteria for research use [21]. Criteria were as follows: (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) [22]. To match with EOA patients, controls healthy subjects with similar descriptive and sociodemographic characteristics were selected. The inclusion criteria were (a) patient age greater than or equal to 40 years; (b) KL grade 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.

2.3. Outcome Measures

2.3.1. Vitamin D and Parathyroid Hormone Levels

For the collection of blood, separation of plasma, and long storage of the samples, 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 Biobanco La Fe and kept at −50 °C until measurements of serum intact PTH and 25OHD were taken using commercial ELISA kits (IDS Co., Bolden, UK), with intraassay coefficients of variation ranging from 5% to 15%.

Serum 25(OH)D and PTH concentrations were determined by radioimmunoassay. Vitamin D levels were classified as follows: vitamin D deficiency, serum 25(OH)D concentration < 20 ng/mL; vitamin D insufficiency, serum 25(OH)D concentration 20–29 ng/mL; and vitamin D sufficiency, serum 25(OH)D concentration ≥ 30 ng/mL [23,24].

2.3.2. Pain and Disability Variables

Pain Intensity

To measure pain intensity, the Visual Analogue Scale (VAS) was used. The scale is a 100-mm line with two endpoints representing the extreme states "no pain" (0) and "the maximal pain imaginable" (10). The VAS scale has been shown to have good retest reliability (r = 0.94, $p < 0.001$) [25,26].

Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)

The WOMAC questionnaire is self-administered and is used to assess OA disability. It is composed of 24 items divided into 3 aspects: functional pain (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 an internal consistency of 0.82 for pain and 0.93 for physical function subscales [27].

2.3.3. Functional Variables

Five-Time Sit to Stand

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 oriented. The clinician stopped the test when the patient achieved the standing position on the 5th repetition [28]. The amount of time needed to realize the test was extracted in seconds.

Walking Speed

The subject walked without assistance 10 m (32.8 feet) 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 [29,30].

2.3.4. Psychological Variables

Anxiety and Depression Symptoms

To assess anxiety and depression symptoms, the Hospital Anxiety and Depression Scale (HADS) was used. HADS includes 14 items in a 4-point Likert-type scale. For the full scale, the internal consistency is 0.90. For the depression subscale, the internal consistency is 0.84, and 0.85 for the anxiety subscale [31].

Social Participation

To determine the frequency and diversity of social involvement, the Maastricht Social Participation Profile was used [32]. The scale includes 9 items: 'How often in the past four weeks have you (taken part in/been to): (1) a club, interest group or activity group, church or other similar activity; (2) a cultural or educational event such as the cinema, theatre, museum, talk or course; (3) eaten out; (4) out to a pub, cafe or tearoom; (5) a public event; (6) an organized games afternoon or evening; (7) a day trip organized by a club or society; (8) committee work for a club, society or another group; (9) any organized voluntary work?' The response categories range from zero ('not at all') to three ('more than twice a week'). The psychometric properties were appropriate (Cronbach's αbaseline = 0.64; αfollow-up = 0.64), and higher scores equated to higher social participation [32].

2.4. Procedures

The procedure and an informed consent form were explained and given to all the participants. The included subjects filled out the sociodemographic questionnaire and self-reported measures of disability, pain, and psychological variables. Finally, the serum 25(OH)D concentrations and functional tests were assessed. This procedure was identical for both groups.

2.5. Statistical Analysis

The sociodemographic data of the participants were analyzed. The data were summarized using frequency counts, descriptive statistics, and summary tables. Statistics Package for Social Sciences (SPSS 24, IBM Inc., Armonk, NY, USA) was used for data analysis. 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 vitamin D and PTH measures with psychological and physical measurements were analyzed 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 [33].

3. Results

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

Table 1. Descriptive and demographic variables.

Measures	EOA (n = 48)	Controls (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
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; EOA: Early Osteoarthritis.

3.1. Vitamin D and PTH Levels

Regarding serum 25(OH)D concentrations, patients with EOA showed lower levels (22.3 ± 7.3 ng/mL) in comparison to matched controls (29.31 ± 9.2 ng/mL), showing statistically significant differences between groups.

Student's *t*-test showed statistically significant differences (p = 0.03), with a medium effect size (MD: −7.01; d = 0.72). However, no statistically significant differences were found for PTH levels between both groups (MD: −1.42, $p > 0.05$) (Table 2).

Table 2. Vitamin D and PTH levels.

Measures	EOA	Controls	Mean Difference (95% CI)	Effect Size (d)
Vitamin D (Serum 25(OH)D concentration)	22.30 ± 7.3	29.31 ± 2.59	−7.01 ** (−10.39 to −1.23)	0.88
PTH concentration	40.78 ± 15.53	39.36 ± 14.76	−1.42 (3.15 to −7.69)	-

Data are expressed as mean ± standard deviation. EOA: Early Osteoarthritis; PTH: Parathyroid Hormone Levels. ** $p < 0.01$.

Participants in both groups were stratified according to baseline levels based on serum 25(OH)D concentration. A statistically significant higher number (Chi-squared = 8.525; p = 0.004) of patients with EOA had deficiency levels compared to the control group. For patients with EOA, 54.2% had values below 20 ng/mL (deficiency), 31.3% had values below 30 ng/mL (insufficiency), and only 14.5% had normal values (<30 mg/mL). Regarding the matched controls, the highest proportion (45.8%) presented values of insufficiency (<30 ng/mL) and normality (33.3%). Only 20.9% presented deficiency in this value (<20 ng/mL) (Figure 1).

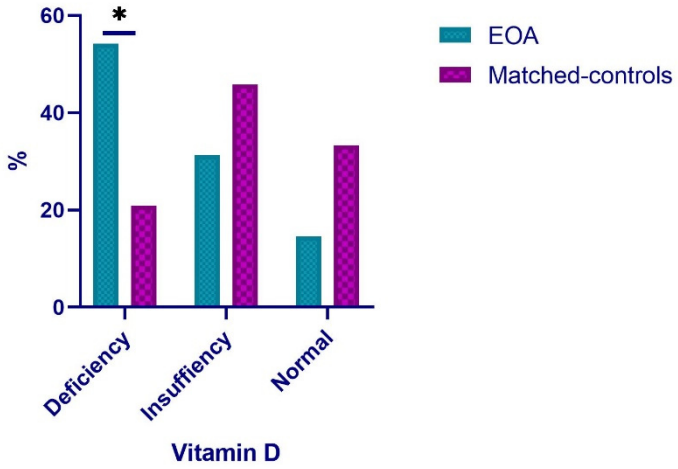

Figure 1. Distribution of EOA patients and matched controls according to vitamin D levels. * $p < 0.05$; EOA: Early Osteoarthritis.

3.2. Physical and Psychological Status

The 48 patients with EOA were divided according to their vitamin D levels. In total, 26 participants presented deficiency in their levels (<20 ng/mL) and 22 presented higher values of 20 ng/mL.

About pain intensity levels, the *t*-test showed statistically significant differences, showing higher levels of pain intensity in patients with lower vitamin D levels (MD = 2.73; $p < 0.01$; d = 0.88). Similarly, statistically significant differences were found in the WOMAC values with a higher score in the deficient group (MD = 5.51; $p = 0.032$; d = 0.41) (Table 3).

Table 3. Physical and psychological status in patients with EOA according to vitamin D levels.

Measures	EOA Deficiency (<20 ng/mL)	EOA Sufficiency (>20 ng/mL)	Mean Difference (95% CI)	Effect Size (*d*)
Pain intensity	4.95 ± 3.52	2.22 ± 2.59	2.73 ** (−3.39 to −0.76)	0.88
WOMAC Total	29.27 ± 12.45	23.76 ± 13.93	5.51 * (−14.65 to −6.64)	0.41
Sit-to-stand (s)	16.29 ± 3.44	10.53 ± 2.54	5.76 ** (−6.34 to −0.81)	1.90
Walking speed (km/h)	4.99 ± 1.38	3.07 ± 0.54	1.92 ** (−1.34 to −0.11)	1.83
Anxiety	7.36 ± 4.17	4.01 ± 3.05	4.35 * (−3.86 to −2.15)	0.88
Depression	6.21 ± 3.06	3.31 ± 3.06	2.9 * (−2.96 to −0.15)	0.94
Social participation	4.57 ± 3.61	8.73 ± 2.55	−4.16 ** (−2.82 to −1.14)	1.01

Data are expressed as mean ± standard deviation. ** $p < 0.01$; * $p < 0.05$.

Regarding functional tests, the *t*-test showed statistically significant differences for sit-to-stand and walking speed, showing poorer values for patients with vitamin D deficiency (MD = 5.76; $p < 0.01$; d = 1.90 and MD = 1.92; $p < 0.01$; d = 1.83, respectively) (Table 3).

Finally, regarding psychological variables, patients with vitamin D deficiency showed statistically significant differences for anxiety and depression in comparison to patients with higher vitamin D levels (MD = 3.35; p =0.028; d = 0.88 and MD = 2.9; $p = 0.038$; d = 0.94, respectively). In relation to social participation, statistically significant differences were also found, with lower levels for patients with vitamin D deficiency (MD = −4.16; $p < 0.01$; d = 1.01) (Table 3).

The physical and psychological status according to vitamin D levels is summarized in Figure 2.

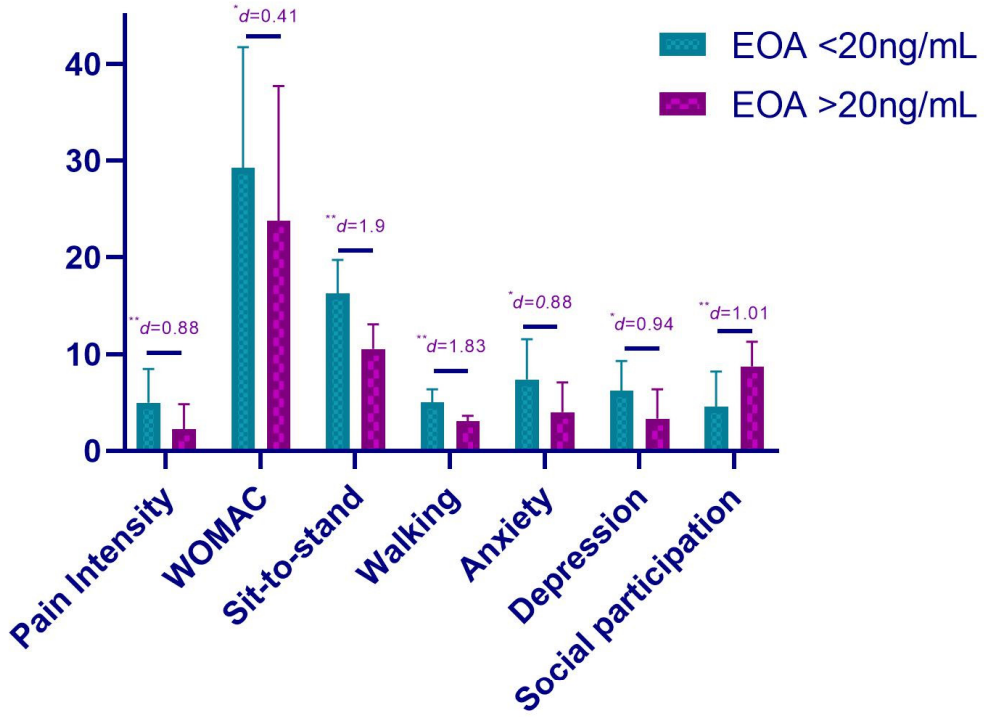

Figure 2. Physical and psychological status according to vitamin D levels. ** $p < 0.01$; * $p < 0.05$.

3.3. Correlation Analysis

The correlation analysis was performed in patients with EOA, showing strong correlations between vitamin D levels and pain intensity (r = −0.651; $p < 0.01$) and between vitamin D levels and anxiety (r = −0.623; $p < 0.01$). In addition, moderate correlations were found between vitamin D levels and disability (r = −0.443; $p < 0.05$), depression (r = −0.351; $p < 0.05$), and social participation (r = 0.355; $p < 0.05$). Regarding PTH levels, the strongest correlation was found with pain intensity (r = −0.686; $p < 0.01$). Additionally, a moderate correlation between PTH and social participation was found (r = 0.331; $p < 0.05$) (Table 4).

Table 4. Correlation analysis.

	Vitamin D (Serum 25(OH)D Concentration)	PTH
Pain intensity	−0.651 **	−0.686 **
WOMAC Total	−0.443 *	−0.234
Anxiety	−0.623 **	−0.153
Depression	−0.351 *	−0.041
Social participation	0.355 *	0.331 *

** $p < 0.01$; * $p < 0.05$. PTH: Parathyroid Hormone Levels.

4. Discussion

The primary aim of this cross-sectional study was to compare the level of vitamin D of patients with EOA with matched controls. The secondary objectives were to compare the level of PTH of patients with EOA with matched controls and to determine the relationship between vitamin D deficiency, PTH level, and pain intensity, disability, psychological, and functional variables in patients with knee EOA. Results showed that EOA patients showed statistically significant lower levels of vitamin D than matched controls, but not PTH levels. It was also found that vitamin D deficiency had a statistically significant relationship with a higher level of pain intensity, disability, anxiety, and depressive symptoms, and lower social participation and physical performance. A lower PTH level is associated with higher pain intensity and lower social participation.

Patients with EOA had vitamin D insufficiency with a mean of 22.3 ng/mL, with a majority of patients having deficiency (54.2%). Similar to these results, Wu et al. found in

their meta-analysis that patients with chronic pain, including OA, had a lower average vitamin D concentration than controls [21]. They found that patients with OA had a 20% difference in concentration [21]. Patients with a deficiency of vitamin D showed a statistically significant negative strong relationship between vitamin D concentration and pain intensity. The relationship between pain intensity and vitamin D is controversial [22–24]. For example, Cakar et al. found no relationship between vitamin D concentration and pain intensity. However, they included patients with KL grade 2 or more [22]. Contrary to them, our study included patients with EOA, so, a deficiency in vitamin D might have greater implication in the early stage of knee OA.

Vitamin D has been shown to influence the nociceptive pathway. Tague et al. found that vitamin D deficiency leads to hyperinnervation by nociceptors and hypersensitivity of mice skeletal muscles [34]. Lower levels of vitamin D are associated with higher mechanical sensitivity in patients with chronic pain [26]. Roesel hypothesized that a vitamin-D deficiency state might alter the functioning of descending inhibitory control pathways [35]. It also seems to have anti-inflammatory properties [36]. Amer and Quayyum found an inverse relationship between vitamin D and C-reactive protein in participants with a low level of vitamin D [37]. Similarly, Sun et al., 2021 showed that PTH attenuates OA pain by inhibiting subchondral sensory innervation, suggesting a critical role of PTH in OA pain [38]. Nevertheless, it is necessary to highlight that pain perception is a multifactorial experience involving the biological body state, cognitive and motivational-affective state, and the context of the individual [31]. Future studies should therefore interpret our results on vitamin D deficiency and PTH only as possible factors involved in the complexity of chronic pain.

In those patients with deficiency, we also found a statistically significant negative moderate relationship between the level of vitamin D and the level of disability. Vitamin D is essential for muscle health, as it plays a role in the maintenance of an adequate calcium plasma concentration and the differentiation of myoblast cells [35,36]. A deficiency might have altered physical performance during physical tests. Actually, Javadian et al. found a positive relationship between vitamin D concentration and quadriceps femoris muscle strength in patients with OA [23]. Future studies should evaluate the specific influence of vitamin D deficiency on the skeletal muscle properties of patients with EOA.

Finally, we also found a statistically significant positive moderate relationship between vitamin D concentration, PTH level, and social participation and a statistically significant negative strong to moderate relationship between vitamin D concentration and the presence of anxiety and depressive symptoms in that subgroup of patients. Sun exposure is the major source of vitamin D. Holick et al. warn that without sufficient sun exposure, it is not possible to produce the right amount of vitamin D [39]. Patients with higher anxiety levels, depressive symptoms, and level of pain intensity may therefore diminish their social participation and interaction, and consequently their sun exposure. Actually, Knippenberg et al. reported that there is a relationship between higher depressive symptoms and lower reports of sun exposure [40]. Future studies should assess the influence of psychological and social variables on vitamin D levels in patients with OA.

Our results on the relationship with social participation bring another factor into play, the level of physical activity [41]. It has been shown that most patients with early OA do not follow the recommendations from the Centers for Disease Control and Prevention and the American College of Sports Medicine for physical activity [42]. Higher increases of the self-reported or objective level of physical activity are associated with a higher increase of vitamin D, and participation in physical activity may increase the opportunity for sun exposure [34,43] Similarly, the practice of physical training has been shown to increase the concentration of PTH [35–38]. Future studies should focus on the interaction between the vitamin D concentration, PTH level, and the level of physical activity in patients with EOA.

Limitations

Due to the nature of the study, it is not possible to assess any cause-and-effect relationship nor the temporal relationship between the deficiency of vitamin D, PTH level, and the different variables. It is not possible to determine the direction of the relationship (e.g., if the deficiency of vitamin D is the result of the presence of OA or a responsible for its incidence). We included only Caucasian participants from the Spanish population. Because skin color hugely influences the production of vitamin D, it is not possible to extrapolate results to the worldwide population [39].

5. Conclusions

Patients with knee EOA show a lower level of vitamin D than matched controls. The presence of vitamin D deficiency among patients with knee EOA is significantly related to a higher level of pain intensity, disability, anxiety and depressive symptoms, lower social participation, and physical performance. Lower PTH level is associated with higher pain intensity and lower social participation. These results highlight the relevance of vitamin D in the early diagnosis and prevention of EOA.

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ANEXO 4. Otras publicaciones relacionadas con los datos obtenidos en la elaboración de la tesis en los que la doctoranda no es primera autora.

- Papaneophytou C, Alabajos-Cea A, Viosca-Herrero E, Calvis C, Costa M, Christodoulides AE, Kroushovski A, Lapithis A, Lapithi VM, Papayiannis I, Christou A, Messeguer R, Giannaki C, Felekkis K. **Associations between serum biomarkers of cartilage metabolism and serum hyaluronic acid, with risk factors, pain categories, and disease severity in knee osteoarthritis: a pilot study**. BMC Musculoskelet Disord. 2022 Mar 2;23(1):195. DOI: 10.1186/s12891-022-05133-y. PMID: 35236298; PMCID: PMC8889762.

- 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, Blanco-Díaz M. **Serum lipid biomarkers and inflammatory cytokines associated with onset and clinical status of patients with early knee osteoarthritis.** Front Nutr. 2023 Mar 15;10:1126796; DOI: 10.3389/fnut.2023.1126796; PMID: 37006936; PMCID: PMC10050464

- 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 Jun 9;11(6):1670; DOI: 10.3390/biomedicines11061670; PMID: 37371765; PMCID: PMC10295890

ANEXO 5. Otros resultados obtenidos del estudio de nuestra población, que se encuentran actualmente aceptados, en proceso de publicación.

- Herrero-Manley L, Alabajos-Cea A, Suso-Martí L, Viosca-Herrero E., Vázque-Arce I. **Classification criteria for early knee osteoarthritis: a review article**. Aceptado en Aktuelle Rheumatologie, ISSN 0341-051X. Manuscript ID: AktRheum-2023-03-0907-OA.R3