A GROUP OF RESEARCH ANALYSING THE FEET OF PEOPLE WITH RHEUMATOID ARTHRITIS

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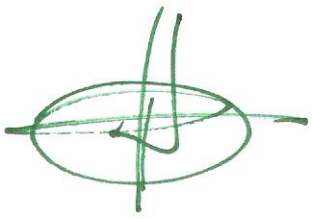

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I certify that the work submitted as a thesis by Miss Laura Ramos Petersen. “A GROUP OF RESEARCH ANALYSING THE FEET OF PEOPLE WITH RHEUMATOID ARTHRITIS”, has been conducted under my supervision and I consider that it satisfies the conditions in terms of content and scientific rigor to be presented.

To be stated, I sign this document in Manchester November 19th, 2020.

Sign. Professor Christopher Nester

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Abbreviations

- AOS = Ankle Ostearthritis Scale
- ARA = American Rheumatism Association
- BMI = Body Mass Index
- CBT = Cognitive– Behavioural Therapy
- CCP = Cyclic Citrullinated Peptide
- CMC = Carpometacarpal
- CR = Conventional Radiography
- CRP = C Reactive Protein
- DAS-28 = Disease Activity Score-28
- DI = Disability Index
- DIP = Distal Interphalangeal
- DMARDs = Disease-Modifying Anti-Rheumatic Drugs
- ESR = Erythrocyte Sedimentation Rate
- EULAR = European League Against Rheumatism
- FAAM = Foot and Ankle Ability Measure
- FADI = Foot and Ankle Disability Index
- FFI = Foot Function Index
- FHSQ = Foot Heal Status Questionnaire
- FO = Foot Orthoses
- HAQ = Health Assessment Questionnaire
- HCQ = Hydroxychloroquine
- HLA = Human Leukocyte Antigen
- HRQoL = Health-Related Quality of Life
- ICC = Intraclass Correlation
- JAFI = Juvenile Arthritis Foot Disability Index
- JIA = Juvenile Idiopathic Arthritis
- LEF = Leflunomide
- LFIS = Leeds Foot Impact Scale
- MCP = Metacarpophalangeal
- MFPDI = Manchester Foot Pain Disability Index
- MTP = Metatarsophalangeal
- MTX = Methotrexate
- MRI = Magnetic Resonance Imaging
- NICE = National Institute for Health and Care Excellence
- NSAID = Non-Steroidal Anti-Inflammatory Drugs
- OAFQ = Oxford Ankle and Foot Questionnaire
- OT = Occupational Therapy
- PA = Physical Activity
- PIP = Proximal Interphalangeal
- PROMs = Patient-Reported Outcome Measures
- PT = Posterior Tibial
- RA = Rheumatoid Arthritis
- RF = Rheumatoid Factor

- SAFE = Salford Rheumatoid Arthritis Foot Evaluation
- SDAI = Simple Disease Activity Index
- SEFAS = Self-Reported Foot and Ankle Score
- SJC = Swollen Joint Count
- SSZ = Sulfasalazine
- TENS = Transcutaneous Electrical Nerve Stimulation
- TJC = Tender Joint Count
- TNF = Tumour Necrosis Factor
- ULN = Upper Limit of Normal
- US = Ultrasound
- VAS = Visual Analog Scales

Abstract

Introduction

Rheumatoid arthritis (RA) shows high prevalence and morbidity worldwide and its biggest impact can be observed in the small joints of the hands and feet. Foot symptoms are almost ubiquitous among patients with RA and are frequently severe. Pharmacological and other non-pharmacological interventions such as foot orthoses can play an important role in managing foot pathologies in patients whose systemic disease is controlled. However, the current situation is that there is a lack of qualitative and quantitative research to provide enough information about this topic. Furthermore, reliable and valid tools to assess the disease and interventions effect are vital. Therefore, it is required to identify the most suitable instrument to assess the effect that RA has on the feet of patients with RA, also including juvenile idiopathic arthritis.

Methods

This thesis comprises six separate studies: first, four quantitative studies were performed to help to understand the potential role of RA and RA treatments on patients' feet. Next, a protocol was developed to compare physical activity, general and foot health and foot health experiences in patients with RA when wearing three different types of foot orthoses. Finally, a qualitative study aimed at understanding the RA patients' experiences before and after wearing foot orthoses for 6 months.

The qualitative studies included in this thesis are systematic reviews and meta-analysis focusing on patients with RA to determine the effectiveness of foot orthoses, to examine the impact of biologics on their feet and to identify self-reported outcome measures specific to the foot and ankle.

Results

The findings of the quantitative and qualitative studies focused on foot orthoses suggest that the use of foot orthoses alleviate foot pain, reduce disability and improve physical activity. The systematic review which evaluates biologics on RA patients' feet shows that postoperative surgical site infection or delayed wound healing were not associated with biologics use. Furthermore, the Self-Reported Foot and Ankle Score questionnaire presents acceptable methodological quality to assess the foot and ankle in patients with RA.

Conclusion

Taken together, the results of this work show that foot orthoses are effective in the management of foot pain in patients with RA, reducing disability and improving physical activity. Some valid questionnaires are available to assess the disease and interventions effect in terms of foot and ankle, especially in clinical practice.

Resumen

Introducción

La participación del pie es casi universal en la artritis reumatoide (AR): la prevalencia del dolor de pies aumenta con la duración de la enfermedad y afecta al 90% de los pacientes durante el curso de su enfermedad. La patología del pie no es el límite de la enfermedad establecida, de hecho, es vista como el principal signo de una temprana AR. La afectación del pie ocupa un segundo lugar tras la presentación en las manos, que es el primer lugar de la presentación de la AR. Es importante mencionar que encontramos erosiones en las radiografías primero en el pie que en las manos. Además, la patología articular del pie se piensa que es predictiva del daño radiológico a largo plazo en la AR.

La alta prevalencia de los síntomas en el pie no muestra signos de descenso a pesar del rápido avance en las terapias farmacológicas, con datos recientes que sugieren que el 99% de los pacientes que toman anti-TNF continúan con síntomas en el pie. Incluso en pacientes con la enfermedad en remisión (DAS 28 score < 2.6) con frecuencia tienen actividad residual de la enfermedad en el pie. De hecho, una gran cohorte europea de 848 pacientes con AR de 8 años de seguimiento informó que el 29% de los pacientes en remisión tienen problemas con la sensibilidad en los pies y el 31% una articulación del pie hinchada.

Al igual que en otras partes del cuerpo, los síntomas de la AR en el pie no están únicamente limitados al sistema musculoesquelético. Hay con frecuencia manifestaciones extraarticulares. Recientemente, estudios también han destacado la prevalencia de la neuropatía y el 59% de los pacientes con AR se piensa que han reducido la sensibilidad en sus pies. Además, cerca del 10% de los pacientes informa del desarrollo de una úlcera en el pie durante el curso de su enfermedad, la mitad de los cuales va a tener múltiples episodios de ulceración.

El amplio impacto psicosocial de la AR y, específicamente, de la enfermedad en los pies, está reconocido en la literatura. Los estudios han identificado el impacto de la AR en los pacientes con respecto a su propia imagen, su sexualidad y sus relaciones personales, y junto a la preocupación sobre que la deformidad, forman un conjunto de factores importantes para buscar la opción de la cirugía. Además de la deformidad visible, la ganancia de peso y los cambios en la marcha, los efectos emocionales también pueden ocurrir y el impacto derivado del incremento de la fatiga es reconocido.

A parte del impacto psicosocial del proceso de la enfermedad en sí, también es claro el efecto psicosocial secundario de los muchos tratamientos usados. Esto es particularmente importante en el miembro inferior, donde accesorios y algunos calzados pueden afectar negativamente al ser un impacto perjudicial en algunas facetas de muchos de los pacientes. A diferencia de otras intervenciones, el calzado específico reemplaza a algo que normalmente llevamos. El calzado está intrínsecamente relacionado con la moda, la imagen del cuerpo y la sexualidad, lo que la pérdida de la elección del calzado tiene un impacto psicosocial negativo en los pacientes. Mientras que en los hombres el reemplazo del calzado a veces no es significante, porque este calzado se parece al que llevan normalmente, no ocurre lo mismo en el caso de las mujeres, donde la pérdida de elección y la feminidad impactan en varios aspectos de sus vidas.

Aproximadamente el 90% de los pacientes informa de quejas relacionadas con los pies en los primero 10 años con la AR. La mayoría de los problemas sobre los que informan los pacientes están relacionados con el deporte y el ocio, así como la calidad de vida relacionada con el pie. La deformidad del pie más común en la AR es el Hallux Valgus (HV) (62.5%), seguido por el metatarsus primus varus (MPV) (41.3%), la disfunción del tendón del tibial posterior, aplanamiento del arco longitudinal medial y deformidad en valgo del calcáneo. La deformidad del antepié tiene una correlación significante con los picos de presión y la duración de la carga en la AR. Secundariamente, los pacientes con AR registran consecuentemente alta presión sobre las cabezas metatarsianas y los picos de presión están acompañados de una alta prevalencia de callosidades y dolor.

A pesar de la introducción de terapias más agresivas, como inhibidores del factor de necrosis tumoral para el tratamiento de la enfermedad sistémica, la prevalencia de la participación del pie no parece estar disminuyendo. La evidencia muestra que cuando el proceso de la enfermedad llega a afectar al pie, estos impactos negativos se agravan significativamente afectando la movilidad y la capacidad funcional. Las intervenciones conservadoras están centradas en el tratamiento eficaz de la patología del pie, las cuales incluyen ortesis, calzado terapéutico, y auto cuidados, que han mostrado los beneficios en el manejo del dolor en los pacientes y sus problemas derivados.

Las intervenciones no farmacológicas, como las ortesis plantares, pueden desempeñar un papel importante en el tratamiento de las patologías del pie en pacientes cuya enfermedad sistémica está controlada. Sin embargo, las intervenciones no farmacológicas no están definidas en guías de práctica clínica, teniendo el potencial para causar confusión a los profesionales de la salud cuando toman decisiones clínicas. Por ejemplo, hay una considerable

heterogeneidad en el diseño de las plantillas y las medidas de resultado utilizadas en los diferentes ensayos clínicos publicados, causando dificultad para los profesionales de la salud a la hora de evaluar cuál de las pruebas publicadas son más eficaces en la evaluación del manejo del dolor en el pie de pacientes con AR. La situación actual es que existe una falta de investigación cualitativa y cuantitativa que brinde suficiente información sobre este tema. Además, es de vital importancia el uso de herramientas fiables y válidas para evaluar la enfermedad y el efecto de las intervenciones. Por lo tanto, se requiere identificar el instrumento más adecuado para evaluar el efecto que tiene la AR en los pies de los pacientes con AR, incluyendo también la artritis idiopática juvenil.

El propósito principal de este trabajo es analizar los pies de las personas con AR. A la misma vez, este trabajo también consta de una serie de objetivos secundarios:

1. Determinar la efectividad de las ortesis plantares en pacientes con AR, en comparación con otros tratamientos (otros tipos de tratamiento del pie, es decir, tratamiento simulado, vendaje…) para disminuir la discapacidad y reducir del dolor.
2. Identificar herramientas de medida que brinden información proporcionada directamente por el paciente (PROMs) específicos de los efectos de la AR en el pie y el tobillo.
3. Evaluar la calidad metodológica y las propiedades psicométricas de los PROMs específicos de los efectos de la AR en pie y tobillo.
4. Identificar PROM específicos para niños y adolescentes con artritis idiopática juvenil (AIJ) en pie y tobillo.
5. Evaluar la calidad metodológica y las propiedades psicométricas de los PROM para niños y adolescentes con AIJ en pie y tobillo.
6. Comparar la actividad física, la salud general y de los pies y las experiencias de salud de los pies en personas con AR cuando usan tres tipos diferentes de ortesis plantares.

Material y métodos

Esta tesis comprende seis estudios separados: primero, se realizaron cuatro estudios cuantitativos para ayudar a comprender el papel potencial de los tratamientos de AR y el efecto de la AR en los pies de los pacientes. A continuación, se desarrolló un protocolo para comparar la actividad física, la salud general y de los pies y las experiencias de salud en relación con los pies en pacientes con AR cuando usan tres tipos diferentes de ortesis plantares. Finalmente, un estudio cualitativo tuvo como objetivo comprender las experiencias de los pacientes con AR antes y después de usar ortesis plantares durante 6 meses.

Los estudios cualitativos incluidos en esta tesis son revisiones sistemáticas (RS) y metanálisis centrados en pacientes con AR para determinar la efectividad de las ortesis plantares, examinar el impacto de los productos biológicos en sus pies e identificar PROMs específicas para el pie y el tobillo.

El primer estudio que compone esta tesis es una RS y metaanálisis que identifica la efectividad de las ortesis plantares en pacientes con AR, en relación con la discapacidad y el dolor. Los estudios incluidos fueron todos ensayos clínicos aleatorizados (ECA) o estudios cuasiexperimentales, que llevaron a cabo un análisis de los resultados obtenidos, incluyendo al menos dos observaciones (antes y después de la intervención). Se realizó una búsqueda en las bases de datos SCOPUS, Cuiden Plus, EMBASE, CINAHL, Cochrane y Medline, siendo la última búsqueda en junio de 2017. Todos los estudios fueron realizados de acuerdo con la siguiente estructura PICO:

- Participantes: hombres o mujeres con AR, mayores de 18 años y que presentan dolor en el pie. Estudios centrados en AR juvenil y en el análisis de la marcha fueron excluidos.
- Intervención: comparación de ortesis plantares (ortesis plantares personalizadas: prescrito de acuerdo con las necesidades de cada paciente; ortesis plantares funcionales: eficacia de las ortesis plantares para mejorar una habilidad; plantilla simple o placebo: diseñados para adaptarse a los pies de los pacientes pero no dar soporte al pie o controlar su movimiento de cualquier manera; ortesis fabricadas a medida: diseñadas y fabricadas a medida para un protocolo estandarizado de moldes de impresión tomados de los pie.
- Comparación: otro tipo de tratamientos, como otros tipos de ortesis plantares.
- Elementos de medida: evaluación del dolor o la discapacidad, utilizando un instrumento adecuado para medir estos resultados.

Todos los estudios incluidos en el metaanálisis final de este estudio compararon dos grupos de pacientes: los que usaron ortesis plantares durante un mínimo de 4 semanas y los que no lo hicieron, y midió la discapacidad y la funcionalidad de los pacientes, a través del cuestionario Foot Function Index (FFI) o utilizando una escala de dolor analógica (EVA).

En la primera etapa de la revisión, fue llevada a cabo una evaluación doble ciego de los títulos y resúmenes. Fue realizada por dos revisores independientes para determinar si cada elemento cumplía los requisitos predeterminados para la inclusión. Si este paso no estaba claro, se evaluaba el texto completo del artículo.

El segundo y tercer estudio de esta tesis son RS que tratan de identificar PROMs específicos de los efectos de la AR en el pie y el tobillo y evaluar la calidad metodológica y las propiedades psicométricas de estos PROMs específicos de los efectos de la AR en pie y tobillo. El segundo estudio se centra en la población mayor de 18 años con AR, mientras que el tercer estudio se centra en la artritis idiopática juvenil o AIJ.

Ambas RS incluyeron una búsqueda de los estudios en las bases de datos PubMed, SCOPUS, CINAHL, PEDro y Google Scholar, siendo la última búsqueda en febrero de 2018 para el segundo estudio y en diciembre de 2018 para el tercero. Ambas RS incluyeron estudios en los que se validaban diferentes PROMs especializados en pie y tobillo, tanto el cuestionario original como las adaptaciones a los distintos idiomas, con la diferencia de que el segundo artículo se centraba en pacientes con AR mayores de 18 años y el tercero en pacientes con AIJ. El tipo de PROMs que eran evaluados en los estudios dentro de la RS eran las propiedades psicométricas o clinimétricas basadas en criterios de Terwee (validez de contenido; consistencia; validez de criterio; validez de constructo; reproducibilidad: acuerdo, fiabilidad; sensibilidad; efecto suelo/techo; interpretabilidad) o criterios COSMIN (validez estructural; consistencia interna; confiabilidad; error de medición; prueba de hipótesis para la validez de constructo; invariancia de validez / medición cultural; validez de criterio y capacidad de respuesta).

En ambas RS, dos revisores evaluaron independientemente la calidad de los estudios utilizando la lista de verificación de COSMIN actualizada, que permite valorar la calidad metodológica de los estudios con respecto a tres dominios (fiabilidad, validez y capacidad de respuesta). También fueron valoradas las propiedades psicométricas propuestas por Terwee et al., siendo cada tema calificado como positivo "+" (descripción o valor o medida o argumento relacionado con la propiedad psicométrica adecuados), "-" negativo (inadecuado o valores inferiores a los estándares aceptados para la propiedad psicométrica), indeterminado "?" (métodos o medidas o diseño dudosos) o ausente "0" (sin información disponible sobre la propiedad psicométrica), excepto para la capacidad de respuesta, que se calificó solo como presente / ausente. En ninguno de los casos se pudo desarrollar un metaanálisis debido a la falta de homogeneidad en las dimensiones y los elementos de medida de los estudios incluidos.

El cuarto estudio que compone esta tesis es un protocolo sobre un ECA con tres tipos de ortesis plantares. Los pacientes incluidos serán mayores de 18 años, con AR y con una historia de dolor en la articulación subastragalina bilateral y / o tobillo y / o talonavicular, con una

puntuación de al menos 3,5 en una escala EVA. Las diferentes intervenciones son las siguientes:

- Grupo 1: ortesis personalizadas creadas a partir de la técnica en directo. Las ortesis serán de resina con una combinación de 1,2 mm de podiaflex para el retropié y el medio pie y de 0,8 mm para el antepie.
- Grupo 2: ortesis personalizadas creadas a partir de un proceso digital derivado del uso de un escáner. Las ortesis serán de 2 mm de polipropileno.
- Grupo 3: ortesis prefabricadas de base posterior de 5 mm de etilvinilacetato (EVA) debajo del talón y arcos, y 2,5 mm y 4 mm de capas de EVA debajo de las áreas del talón / arco y el antepié respectivamente.

Los tres tipos de ortesis tendrán la misma cubierta de EVA (Shore A 30) de 1,5 mm y poliuretano (Shore A 22), lo que facilitará que los pacientes no identifiquen qué tipo de ortesis les fue asignada.

La parte cuantitativa del protocolo incluye la medición de la actividad física y cuestionarios sobre el nivel de dolor, la funcionalidad y discapacidad en relación con el pie, antes de usar las ortesis y después de 6 y 12 meses de uso. La parte cualitativa incluye entrevistas antes y después de usar las ortesis durante 6 meses, para conocer las expectativas y experiencias de los pacientes. En cada uno de los grupos, serán incluidos 15 participantes.

El quinto estudio incluido en esta tesis en una RS sobre el uso de tratamientos biológicos en pacientes con AR. Para ello, fue llevada a cabo una búsqueda en las bases de datos de MEDLINE Ovid, Pubmed, CINAHL, Cochrane Library, Evidence Search and Web of Science. La última búsqueda fue llevada a cabo en abril de 2020. Los estudios incluidos debían ser ECA o estudios observacionales que siguiesen la siguiente estructura PICO:

- Participantes: pacientes con AR mayores de 18 años.
- Intervención: eficacia de los tratamientos biológicos con relación a los pies.
- Comparación: otro tipo de tratamiento farmacológico o conservador.
- Elementos de medida: evaluación de los efectos de los biológicos en los pies de los pacientes con AR, utilizando un instrumento apropiado para medir estos resultados como la puntuación modificada de Sharp-van der Heijde (SvdH) o el uso de la guía para la prevención infección en el lugar donde se ha llevado a cabo la cirugía.

La evaluación de la elegibilidad de los estudios se realizó de forma independiente de una manera estandarizada no cegada por dos revisores. Extrajeron los datos de los estudios

incluidos y los desacuerdos entre ellos se resolvieron por consenso. El riesgo de sesgo de los estudios fue evaluado con la guía Cochrane y la versión adaptada de la escala Newcastle Ottawa.

El sexto estudio incluido en la presente tesis es una investigación cualitativa. Dicho estudio explora las experiencias y percepciones de las personas con AR antes y después de usar ortesis plantares durante 6 meses. Estos participantes forman parte de un estudio mayor, el cual ha sido descrito en el protocolo que forma el cuarto estudio de esta tesis. Las entrevistas no seguían una estructura determinada, pero sí que se centraban en contestar a la pregunta ¿cuáles son las experiencias antes y después de utilizar ortesis plantares durante 6 meses en un paciente con AR?

Las entrevistas se realizaron en dos fases. La primera entrevista se llevó a cabo antes de que al participante se le entregaran las ortesis y se realizó una segunda entrevista después de 6 meses. La recogida de datos se realizó entre 2019 y 2020. Las entrevistas se realizaron cara a cara y se grabaron con una grabadora de voz digital. Las notas de campo complementaron los datos. Las entrevistas fueron realizadas por un investigador que tenía experiencia en ortesis plantares y pacientes con AR, tanto en el contexto clínico como de investigación. Las entrevistas y el análisis de datos fueron realizados por el mismo investigador, y se les informó a los participantes que el investigador también era podólogo.

Se realizó un análisis temático (TA) de las transcripciones para analizar los datos e identificar códigos y temas. Se utilizó un enfoque inductivo para comprender las experiencias de las personas con AR antes y después de usar ortesis plantares durante 6 meses. TA es un enfoque sistemático que detalla de manera transparente el proceso de desarrollo de códigos y temas. Un investigador realizó un análisis (línea por línea) de las experiencias transcritas de cada participante. A partir de ese trabajo, se leyeron todas las transcripciones y se desarrollaron los códigos. Se utilizó el software de análisis de datos cualitativos NVivo para facilitar la codificación y el análisis. Una vez que se generaron los códigos, los temas y los grupos se desarrollaron de manera iterativa, examinando un coautor los hallazgos.

Primero se generaron los códigos de las entrevistas realizadas antes del uso de las ortesis plantares, seguidos de los códigos de las entrevistas realizadas 6 meses después. Finalmente, se compararon todos los códigos y se desarrollaron temas a partir de todo el conjunto de datos. Se prestó especial atención tanto a la frecuencia de códigos emergentes como a su importancia para múltiples participantes.

Resultados

Los hallazgos de los estudios cuantitativos y cualitativos centrados en las ortesis plantares sugieren que el uso de ortesis plantares alivia el dolor de pie, reduce la discapacidad y mejora la actividad física.

La RS que evalúa los productos biológicos en los pies de los pacientes con AR muestra que la infección posoperatoria del sitio quirúrgico o la cicatrización tardía de la herida no se asociaron con el uso de productos biológicos. Además, el cuestionario Self-Reported Foot and Ankle Score presenta una calidad metodológica aceptable para evaluar el pie y el tobillo en pacientes con AR.

Centrándonos en el primer estudio incluido en esta tesis, un total de 118 artículos científicos fueron identificados. Finalmente, tras excluir duplicados, los artículos que no cumplían los criterios de inclusión y los artículos que presentaban alto nivel de sesgo, 5 artículos fueron incluidos en la RS y posterior metaanálisis. Todos los estudios incluidos fueron ECA, publicados entre 1996 y 2016. El seguimiento varió de 4 meses a 3 años. Los estudios se llevaron a cabo en Nueva Zelanda, Corea, Estados Unidos, Eslovenia y Reino Unido. Los elementos de medidas evaluados fueron principalmente dolor de pie y discapacidad, aunque en algunos casos también fueron analizadas la rentabilidad, análisis de sangre, presión plantar y se realizaron análisis de capacidad para caminar. El dolor de pie se midió en todos los estudios incluidos y la discapacidad fue medida por 3 de los 5 estudios incluidos.

Para medir con precisión el impacto de las ortesis plantares en términos del dolor y la discapacidad, se establecieron dos tipos de resultados: los obtenidos en el seguimiento a largo y a corto plazo, definidos como estudios con un seguimiento> 6 meses o ≤ 6 meses, respectivamente. Los metaanálisis se basaron en un cálculo de la diferencia estandarizada de las medias, con modelos de efectos aleatorizados, porque algunos estudios informaron resultados primarios obtenido por diferentes métodos de evaluación o cálculo.

En cuanto al dolor, los estudios presentaron que hay una mejora a corto y largo plazo con el uso de ortesis plantares, aunque las diferencias no sean significativas. En relación con la discapacidad, se observó una disminución de la discapacidad en el pie a corto plazo sin diferencias significativas y a largo plazo, nuestro metaanálisis si mostró diferencias significativas en la disminución de la discapacidad.

En el segundo estudio que forma parte de esta tesis, 431 artículos fueron seleccionados inicialmente para formar parte de la RS. Finalmente, tras excluir duplicados y artículos que no

cumplían los criterios de inclusión, 14 fueron incluidos, lo que representa 7.793 pacientes (61,4% mujeres con una media de 56,8 años). Las dimensiones de los PROMs incluidos en los diferentes instrumentos se agruparon en tres áreas: dolor (en el pie o el tobillo); estado de salud percibido y calidad de vida (en general, relacionado con las extremidades inferiores o relacionado con el pie); y discapacidad (en relación con las actividades de la vida diaria,

limitación de la función general, limitación de función deportiva / recreativa). El tiempo para completar cualquiera de los PROM varía alrededor de 15 minutos.

Las propiedades psicométricas analizadas con los criterios Terwee mostraron que el cuestionario Self-Reported Foot and Ankle Score, incluido en la dimensión del dolor, representada el cuestionario con mayor calidad en general. En la dimensión de estado de salud percibido y calidad de vida, el cuestionario Foot Health Status Questionnaire era el mejor. En la dimensión de discapacidad, el cuestionario Rheumatoid and Arthritis Outcome Score era el que presentaba mejores resultados.

La calidad metodológica fue evaluada con COSMIN, siendo los criterios con peores puntuaciones validez de criterio, medición error, consistencia interna y capacidad de respuesta.

En el tercer estudio presentado en esta tesis, después de realizar la búsqueda descrita anteriormente, se obtuvieron un total de 67 estudios inicialmente, de los cuales 46 se duplicaron en las distintas bases de datos. Después de aplicar los criterios de inclusión / exclusión y de realizar la lectura de los títulos y resúmenes se eliminaron 16 artículos, quedando cinco estudios para el análisis final. Los artículos seleccionados vienen derivados de dos cuestionarios originales: Oxford Ankle and Foot Questionnaire for children (OAFQ) y el Juvenile Arthritis Foot Disability Index (JAFI). Ambos cuestionarios presentan una estructura similar en términos de dominios, pero no en relación con el número de ítems que contiene. Básicamente, ambos se centran en tres dominios: físico, escolar y lúdico y emocional en el caso del cuestionario OAFQ (15 ítems y cada uno de los ítems incluidos se responden usando una escala Liker de 5 puntos); y deterioro, limitación de actividad y restricción de participación en el caso del cuestionario JAFI (27 ítems, también usando una escala Likert).

En el desarrollo y validación de los cuestionarios originales, el cuestionario OAFQ incluyó a 158 participantes, todos niños y adolescentes con AIJ. El cuestionario JAFI incluyó una muestra más pequeña de participantes, con solo 73 niños y adolescentes, de los cuales 29 estaban sanos.

Las adaptaciones transculturales del cuestionario OAFQ (al italiano, holandés y danés) se obtuvieron con respecto a una muestra total de 207 niños y adolescentes (48,79% niñas), de 5 a 16 años.

Las propiedades psicométricas de los estudios valoradas de acuerdo con los criterios de Terwee muestran que todos los PROMs presentan una puntuación positiva en validez del contenido. La calidad metodológica de los estudios examinados fue evaluada según los criterios COSMIN, mostrando que entre todos los PROMs analizados, la adaptación transcultural al italiano del cuestionario OAFQ obtuvo una puntuación "+" en más criterios que cualquier otra versión.

En el quinto estudio que forma parte de esta tesis, un total de 180 artículos fueron seleccionados inicialmente, que tras eliminar duplicados y eliminar artículos que nos cumplían los criterios de inclusión, dejaron un total de 8 estudios finalmente. Todos los 8 estudios incluidos estaban publicados en inglés, desde el año 2004 al 2016. La duración de la intervención fue de entre 12 meses y más de 5 años. El número total de participantes involucrados fue de 1.856. Cinco de los ocho estudios incluyen información sobre el sexo y muestran que 965 participantes eran mujeres. Solamente uno de los ECA presenta ciego de los participantes.

Todos los estudios incluyeron resultados relacionados con el pie, como progresión de la enfermedad valorada mediante radiografías, infección del sitio quirúrgico, desarrollo de infecciones o cicatrización de heridas. El estado de salud general o la evaluación de la AR también se midieron.

En cuanto a la infección del sitio quirúrgico, 62,5% de los estudios incluidos la valoraron, mostrando que el uso de biológicos no es un factor de riesgo. En relación con el retraso de la cicatrización, 3 de los 8 artículos incluidos lo valoraron, concluyendo que el uso de biológicos no es un factor de riesgo. Por último, en relación con la progresión de la enfermedad valorada mediante radiografías, los resultados mostraron que el uso de biológicos puede influir positivamente retrasando la progresión o no mostrando diferencias entre los grupos.

En el estudio cualitativito, un total de 12 entrevistas fueron analizadas. Todos los participantes eran mujeres y tenían entre 32 y 75 años, con una media de 64 años. El rango de duración de la enfermedad de AR (en la primera entrevista) fue de 1,5 a 45 años, con una media de 17,8 años. Tras analizar las entrevistas, tres temas fueron resultantes, los cuales fueron acordados

por el investigador y el coautor para mejorar la validez de los datos. Los tres temas que se identificaron a partir de los datos fueron los siguientes:

1) Mejora de la actividad física;

Antes de usar ortesis plantares, los participantes hicieron comentarios sobre el positivo impacto mental de practicar deporte, pero también sobre el cansancio que esto les producía en sus pies y piernas. Algunos informaron cambios en la movilidad como resultado de su enfermedad, por ejemplo, conducir en lugar de caminar para reducir la cantidad de actividad.

Después de usar las ortesis plantares durante 6 meses, todos los participantes declararon que sus niveles de actividad física habían mejorado. Sintieron que podían caminar de forma más segura y, en consecuencia, un mayor nivel de actividad física. Algunos informaron una mejora en su vida social como resultado de una reducción de los síntomas de AR en sus pies, conectando la comodidad física con sus niveles de actividad y asociando la mejora percibida en su actividad física y bienestar general con una mejor calidad de vida. Los participantes declararon una mayor interacción social, lo que mejoró su bienestar físico y mental. Todos los pacientes expresaron beneficios asociados en su actividad física debido al uso de ortesis plantares.

2) Calzado ... una situación delicada;

Los participantes expresaron un dilema en relación con el calzado cuando quieren usar ortesis, y esto formó el segundo tema. Algunos participantes expresaron problemas con su calzado antes y durante el uso de las ortesis, incluida la limitación y adaptación de sus opciones. Por otro lado, algunos pacientes revelaron que se habían adaptado al uso de las ortesis dentro de sus zapatos.

Durante la intervención, algunas personas siguieron experimentando problemas con su calzado. Incluso después de usar las ortesis plantares, el calzado sigue siendo un problema para algunos participantes. Algunos comentaron sobre las dificultades para encontrar zapatos apropiados para usar con ortesis. El costo, la calidad y la estética del calzado significaban que las opciones eran limitadas y que comprar zapatos para satisfacer todas sus necesidades era difícil.

3) Implicaciones sociales de los pies con AR.

Antes de utilizar las ortesis, los pacientes explicaron que los síntomas en sus pies limitan su vida social, por lo que era necesario adaptar su actividad social a su condición. Esa adaptación

fue única para cada participante. Algunos modificaron su vida social, basándola en sus propios hogares, y otros pacientes optaron por tener menos vida social, lo que puede resultar en aislamiento.

Más allá de eso, los pacientes describieron el impacto en sus vidas al interactuar con otros, sintiéndose negativos sobre cómo sus pies influyeron en su decisión de interactuar con los demás, y la carga y el impacto que esto tuvo en ellos mismos y en los demás. Algunos pacientes se sentían avergonzados por sus pies y se sentían ansiosos cuando alguien les miraba los pies, especialmente en verano. Afirmaron sentirse tristes cada vez que tenían que justificar la morfología de sus pies y la elección de calzado. Esto fue más evidente en las mujeres jóvenes.

Conclusiones

En conjunto, los resultados de este trabajo muestran que las ortesis plantares son eficaces en el manejo del dolor de pie en pacientes con AR, reduciendo la discapacidad y mejorando la actividad física. Se encuentran disponibles algunos cuestionarios válidos para evaluar el efecto de la enfermedad y las intervenciones en términos de pie y tobillo, especialmente en la práctica clínica.

Con respecto al primer estudio incluido en esta tesis, a pesar de la mala calidad metodológica de la mayoría de los estudios considerado en este metaanálisis, se puede concluir que las ortesis plantares alivian el dolor y la discapacidad en pacientes con AR. La ausencia de diferencias significativas entre el grupo intervención y el grupo control pueden deberse a los pequeños tamaños de muestra incluidos en estos estudios. Otro factor explicativo podría ser la sensibilidad insuficiente del FFI para detectar el dolor y la discapacidad. Se necesitan más estudios, con un seguimiento a largo plazo, para determinar qué tipo de ortesis plantares se debe proporcionar, o si el tratamiento conservador es más eficaz para mejorar la discapacidad y reducir el dolor.

Valorando la afectación de la AR en los pacientes mediante el uso de PROMs, podemos establecer unas conclusiones dependiendo de si el paciente es mayor de 18 con AR o de si presenta AIJ. En el primero de los casos, el cuestionario Self-Reported Foot and Ankle Score es el que alcanzó el mayor número de criterios positivos (según Terwee y COSMIN) en la RS, y actualmente se puede decir que es el cuestionario más adecuado para pacientes AR. Por otro lado, con pacientes con AIJ, se puede concluir que, a pesar de la muy baja calidad de la evidencia disponible, la adaptación al italiano del cuestionario Oxford Ankle Foot

Questionnaire presenta una calidad metodológica aceptable. Sin embargo, se requieren más estudios, con mayor rigor metodológico.

Con respecto a la RS que estudia el efecto de los tratamientos biológicos en el pie de los pacientes con AR, la evidencia sugiere que el uso de biológicos no es un factor de riesgo para la infección posoperatoria del sitio quirúrgico o la cicatrización tardía de la herida. No hay diferencias entre tratamientos biológicos y no biológicos en términos de progresión radiográfica.

Con respecto al estudio cualitativo incluido en esta tesis, se puede concluir que este estudio es el primer estudio de investigación cualitativa que se enfoca en esclarecer tanto el impacto como las actitudes hacia el uso de ortesis plantares en personas con AR en relación con sus pies. También en cómo ese uso ha impactado en su actividad física, en su bienestar y calidad de vida.

Los participantes informaron que el uso de ortesis plantares tiene un impacto positivo en la comodidad, el dolor y la actividad física y lo asocian con una mejora del bienestar general y la calidad de vida. Sin embargo, las barreras para el uso y los aspectos negativos de las experiencias se relacionan con las opciones de calzado, que pueden ser ya limitadas y un problema para las personas cuyos pies se ven afectados por la AR y que podrían beneficiarse de las ortesis plantares.

1. INTRODUCTION

1.1. Rheumatoid Arthritis.

1.1.1. Rheumatoid Arthritis History.

Rheumatoid arthritis (RA) is derived from the Greek word *rheuma* which means "flow, current" and its suffix -*oid* which alludes to "resembling". The word *arthron* means “joint” and its suffix -*itis* means “inflammation” (1).

RA is not a recent disease. Arthritis and diseases of the joints have been negatively impacting the population since ancient times (2). The history of RA started around 1500 BC when Ebers Papyrus described in his papyrus manuscript a condition which is similar to RA (3).

Archaeological studies suggest that mommies had deformities which are exclusive from arthritis. Those archaeological studies indicate that skeletal remains in Europe and North Africa have not presented rheumatic lesions (marginal erosions at the bone-cartilage join), but in excavations in North America, there was a high incidence of this type of bone lesions (4). However, was not until 1859 when the British rheumatologist Sir Alfred Barring Garrod named the disease as rheumatoid arthritis (5). To him goes the credit of clearly separating rheumatoid arthritis from terms such us arthritis deformans and rheumatic gout. Sir Garrod recognised the chronic and incapacitating condition of the disease (6).

In 1880 William Ord expanded the Garrod's concept adding typical symptomatology of the disease, such us joint inflammation, joint effusion, bone and cartilage atrophy and synovial hypertrophy. Later, Thomas Sydenham and afterward, Beauvais identify that in RA tendon sheaths and bursae can be affected. It was recognised that the disease begins as synovitis and cartilage damage may follow (7).

In 1945, a therapeutic criteria committee was established in New York, directed by Otto Steinbrocker. As a result, two scales were created. One of the scales was called "classification of rheumatoid progression", and this scale was divided into 4 levels, which were the following: complete remission, significant improvement, slight improvement and disease progression. The other scale was called “classification of functional capacity”, and it was created to assess disability into 4 levels: complete functionality, adequate functional capacity, limited functional capacity and partial or total disability. Those scales were implemented to assess the therapeutic interventions, whether they were efficient or not (8).

The rheumatoid factor (RF) was initially described by Waaler in 1939 and in 1948 it was rediscovered by Rose in his studies. Finally, in 1957, Kunkel concluded that there were an association between the RF and one type of protein, 19 S ɣ-globulin, which contains certain antibodies. This fact is of particular interest because it was able to consider RA as an autoimmune disease (9). About 80% of patients are "seropositive" for RF, which predicts a more aggressive and destructive course.

In 1973 Zvaifler described what was formulated some previous years. It was that the primary pathogenic potential in RA as initiator of the disease was the RF (10). Therefore, inflammatory cells are recruited to the rheumatoid joint which contribute to local destruction (4).

The immune-complex theory explains many of the acute inflammatory aspects of RA, but in 1976 Stastny outlined the prominent T-cell infiltrate, suggesting that these cells are key participants. It was demonstrated in his studies that RA lymphocytes proliferate differently depending on the patient. They proliferate normally in allogeneic mixed-leukocyte reactions when stimulated by normal lymphocyte but with deficient responses when stimulated by cells from other RA patients (11). Consequently, the same or similar genetic responses within RA patients were demonstrated, which helped to identify the most specific genes in the human leukocyte antigen (HLA) region (4,12).

The role of T-cell could be confirmed with the new molecular techniques available in the late 1980s. Those techniques measure levels of cytokine profile of RA in synovial fluid or synovial tissues. In 1990, Firestein et al. concluded that the highest concentration of cells were macrophage and fibroblast products, while T-cell was not abundant (13). An example of macrophage and fibroblast cytokines which are abundant in RA is tumour-necrosis factor (TNF)-a. Hence biological agents such as anti-TNF-α antibody, started to be important as RA treatment (14).

In 1987, the American Rheumatism Association (ARA) revised the classification of RA criteria which was originally proposed in 1956 by a committee of the ARA (15). The 7 new criteria allowed health care professionals to differentiate RA from other similar pathologies. Its main objective was to avoid mistakes in RA diagnoses. The importance of predictive markers such as autoantibodies was not yet known, and only the RF was included, as well as the radiographic changes (joint erosion, loss of periarticular bone density). RA was defined by the presence of 4 or more criteria, and symptoms should be for longer than 6 weeks (Table 1) (16). This work has been criticized for its lack of sensitivity in early disease.

Table 1. RA classification criteria by American Rheumatism Association in 1987 (16).

1) Morning stiffness in and around joints lasting at least 1 hour before maximum improvement.
2) Soft tissue swelling (arthritis) of 3 or more joint areas observed by a physician.
3) Swelling (arthritis) of the proximal inter phalangeal, metacarpophalangeal, or wrist joints.
4) Symmetric swelling (arthritis).
5) Rheumatoid nodules.
6) The presence of the RF.
7) Radiographic erosions and/or periarticular osteopenia in hand and/or wrist joints.

Later, those criteria were modified by American College of Rheumatology (formerly, the ARA) and the European League Against Rheumatism (EULAR) in 2010. Therefore, new classification criteria for RA acuter for early disease were developed. This new classification system focuses on features at early stages of RA identifying persistent and/or erosive process, rather than defining the disease by its late-stage features, which helps to prevent individuals from reaching the chronic and erosive state. As a result, it is possible to identify patients with early or established RA from those with a combination of other rheumatologic diagnoses (17).

In 1947, EULAR was formed, constituting the European non-governmental organization which represents the people with arthritis/rheumatism, health professional and scientific societies of rheumatology of all the European nations. Its aims are to reduce the burden of rheumatic diseases on the individual society, improving treatments, prevention and rehabilitation.

1.1.2. Epidemiology.

RA shows high prevalence and morbidity worldwide (18). Epidemiological studies demonstrate that RA is the most common chronic autoimmune disease of the joints, affecting approximately 0.5–1% of the general population. There is variability in terms of prevalence and incidence depending on regionally variable (19). There are no reports of areas or ethnic groups in which this disease is not found. Previous data shows some higher incidence rates of RA, such as American-Indian populations (5.3%) (20) and Chippewa Indians (6.8%) (21). In contrast, the incidence is lowest amongst the Chinese and Japanese (0.2–0.3%) (22,23) (Figure 1).

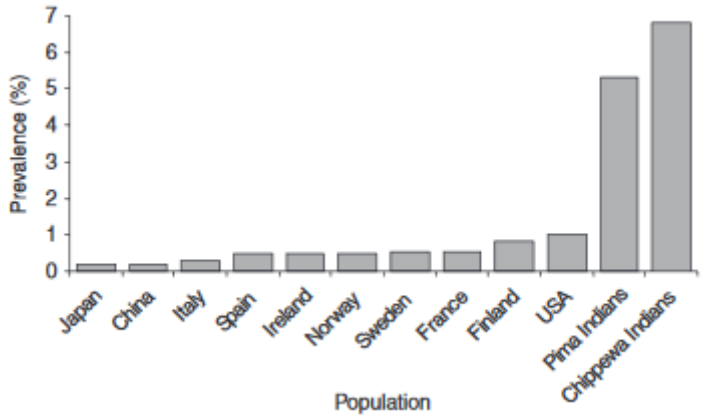

Figure 1. Prevalence of RA in various populations (19).

Therapeutic changes and new strategies have achieved a decrease in disease activity. As a result, there is an increase in patient's quality of life, but a burden for the health care system. This is because of the increased number of visits to healthcare professionals for improved treatment monitoring and newer, more expensive drugs. The RA case-load constitutes 0,5% of the total in Europe and 0,2% in the rest of the world. This growing case-load has an cost impact (24,25).

In respect of life expectancy, there are differences between patients with and without RA. It has been demonstrated that 50% of patients with RA have a decreased life expectancy (3 – 10 years) compared to the general population (26). Diseases related with a decreased life expectancy are cardiovascular and respiratory diseases, malignant tumours, gastrointestinal system disorders and severe infections (27).

1.1.3. Causes.

Regarding the RA etiopathogenesis, the following factors are considered most recently (3,28):

- Genetics: different genes have been described.
- Environmental pathogens: microorganisms that, as a response of the immune system, generate markers like those of RA.
- Non-infectious environmental: sex, age, hormones, lifestyle (smoking, diet).

RA is considered a multifactorial disease. In most cases RA presents an insidious onset, however, the autoimmune reaction can be generated by adding of environmental factors, such as life-style, genetics and infectious factors (29).

Genetics are a major influence on the development of RA. There is a higher prevalence of RA within families, showing a heritability of RA of 40-50%, which is higher for seropositive than for seronegative RA (24). It has been estimated that heritability of RA is 60% in seropositive RA and 20% in seronegative (25). Heritability is not modified by sex, but evidence suggests that seropositive RA is more familial than seronegative RA (26).

Women are at a greater risk of RA development than men, in a 2:1 to 3:1 ratio (27). It has been suggested that the higher incidence of RA in women is due to the influence of hormones. It is suggested that this higher incidence is in part due to the stimulatory effects of estrogen on the immune system (29). In general, male sex hormones, particularly testosterone, are lower in men who have RA (19).

RA can take place in patients at any age. Even though, it has been demonstrated that incidence rises with age, to >2% among women age 65 years or older. RA peaks in patients between 30 and 50 years of age (30,31).

It has been described that epidemiology of RA is suggestive of a genetic effect, but epidemiology of RA can also be influenced by environmental factors (19,31). The term environmental includes those factors external to the individual, such as diet, hormone therapy, smoking or infection (32–35).

Diet has gained attention as a risk factor for the development of RA. It has been identified that Mediterranean diet has beneficial effects in reducing pain and increasing physical function in people with RA, but there is no evidence to support that this diet prevents RA (36). Diets which include caffeine, low in antioxidants and high in red meat may contribute to an increased risk

(31,37). Despite RA and celiac being separate entities, they share multiple inflammatory aspects and a trend towards responsiveness to a gluten free diet has been observed. Therefore, a gluten-free diet may be recommended (38).

Cigarette smoking or passive inhalation of cigarette smoke are direct RA risk factors. Males are almost three times more likely to develop RA if they are smokers. Within the RA population, there is a higher percentage of smokers than within the general population (39,40).

RA may be evoked by upper urinary tract infections by Proteus bacteria (35). Urinary tract infections are one of the most common infections in women however uncommon in males, which agrees with the fact that RA is more common in women (27,37).

1.1.4. Signs, symptoms and clinical manifestation.

RA is the most common autoimmune rheumatic disease with joint involvement, characterized by progressive damage of synovial-lined joints and variable extra-articular manifestations (28). There is a chronic inflammation, which causes short-term pain, joint swelling and long-term progressive joint destruction. The progressive and irreversible damage of the synovial-lined joints causes a loss of joint space and deformity. This anatomical deformation as well as the disease evolution, leads to functional deterioration of the locomotor system (30,41).

Synovitis is one of the typical clinical manifestations of RA. It can be assessed with a simple visual and physical assessment, which provides important information about the state of the disease. For a correct assessment, the following signs must be taken into account: localised heat and erythema, pain on palpation and decreased joint range of motion (31).

Although clinical presentations of RA may vary, symmetric swelling of the small joints is ubiquitous. RA most frequently affects the metacarpophalangeal, metatarsophalangeal, proximal interphalangeal and wrist joints (32). Bone damage in the small joints from hands and feet occurs in the early years of disease and it can be shown in patients' x-rays. However, bone damage of the large joints (knees, hips, shoulders, ankles and elbows) usually occurs later in the disease progression (33,34). Despite large joints not being routinely monitored for damage progression in RA, there is an association between large joint damage and small joint damage. Therefore, monitoring small joint damage is enough to guide treatment decisions to prevent disability and large joint damage (35).

Bone erosion is a process that is identified in 80% of patients in the first year of disease development (36). Bone erosion is not exclusive to RA, as it is also present in other arthritis types, but there are some typical characteristics of erosion in RA that provide us clinical information on the severity of the process, treatment effects and prognosis. Those characteristics are joint distribution, symmetry, type of joints, location and absence of bone regeneration (37).

Extra-articular manifestations can involve pulmonary, ocular, cardiovascular and nervous systems, among others (Table 2). They can occur at any time in the disease process, regardless of age and time of evolution. A higher incidence is observed in patients with severe involvement and is directly proportional to higher mortality (41).

Inflammation in RA may affect the brain (fatigue and reduced cognitive function), liver, lungs, exocrine glands and muscles, but this fact is not unique from RA (36).

Table 2. Extra-articular manifestations in Rheumatoid Arthritis (41).

Constitutional symptoms • Fever • Asthenia • Weight loss • Malaise • Anorexia	Cardiovascular • Vasculitis (coronary arteritis) • Pericardial inflammation and effusion • Myocarditis • Mitral valve disease • Conduction defects
Neurologic • Compression neuropathy (such as carpal tunnel syndrome) • Mononeuritis multiplex • Cervical myelopathy • Central nervous system disease (stroke, seizure, haemorrhage, encephalopathy, meningitis)	Hematologic • Anaemia • Thrombocytosis • Granulocytopenia • Eosinophilia • Cryoglobulinemia • Hyperviscosi
Skin • Distal leg ulcers • Palmar erythema • Cutaneous vasculitis	Renal • Glomerulonephritis • Vasculitis • Secondary amyloidosis
Ocular • Keratoconjunctivitis sicca • Episcleritis • Scleritis • Conjunctivitis	Pulmonary • Pleural effusions • Pulmonary nodules • Interstitial fibrosis • Pneumonitis • Arteritis
Rheumatoid nodules • Subcutaneous • Lung parenchymal	Hepatic • Elevated liver enzymes

Pain is one of the most challenging and debilitating symptoms for patients with RA. Patients identify pain as one of their most dominant symptoms, being the primary reason to seek medical care, and the reduction of pain being there priority (38). RA pain may be due to joint inflammation and augmented by sensitization and structural join damage. It can be chronic

and endure as the years go by, although it can vary, localized or widespread, the progress can be constant or intermittent and is often associated with psychological distress and fatigue. Pain includes different dimensions, such as somatic, emotional and psychological functioning impairment (39,40).

The fact that patients with RA present chronic pain, functional disabilities and decreased health-related quality of life, can be considered the reason of the high prevalence of depression in these patients. Anxiety and depression are common among patients with RA, compared to the general population (42,43).

Furthermore, patients with RA can experienced fatigue, which differs from “normal” tiredness. Fatigue is intrusive, overwhelming, not restored by sleep, and patients struggle to manage it alone (44). Fatigue has a significant negative impact on patients’ ability to perform daily self-care and therefore, socially relevant tasks, with a physical and mental detriment (45). Because of fatigue, patients can experience higher levels of interpersonal stress, including with family members and friends (46).

Morning stiffness is a characteristic of RA and prevalent in 40-50% of patients, being a key symptom of RA disease activity (47). However, it is no longer a criteria of 2010 ACR/EULAR Classification Criteria for RA (17). Morning stiffness is one of the clinical features of synovitis, which is particularly apparent in the morning. It is mainly shown around the joints, lasting at least 1 hour before maximum improvement, although duration is related to disease activity. Patients need to be informed to differentiate stiffness from pain, which are both subjective signs (41).

1.1.5. Diagnosis.

The diagnosis of RA is determined by patient history which leaves a high index of suspicion and physical examination (48).

A certain and prompt diagnosis of RA is crucial to detect RA in early states. Rapid disease treatment has been shown to reduce inflammation, which limits structural damage. There is a window of opportunity for highly successful treatment of RA in the first year, hence why an early diagnosis is so important (49).

The classification criteria of RA proposed by the ACR in 1987, and later modified in 2010 by ACR/EULAR, is the criteria currently in use. It allows us to classify RA in earlier stages helping us to identify RA sooner and preventing bone destruction (3,17). It does not include any other methods of diagnosing synovitis besides clinical examination, but insists on a presence of at least 1 joint with definitive synovitis. It is important to rule out other potential diagnoses that could also explain the synovitis before diagnosing RA as the potential cause. The patient must have a total score of ≥ 6 (of a possible 10) from 4 domains to present criteria of RA (Table 3) (17).

Table 3. RA classification criteria by ACR/EULAR in 2010 (17). *RF – rheumatoid factor; anti-CCP – anti cyclic citrullinated peptide; ULN – upper limit of normal; CRP – C reactive protein; ESR – erythrocyte sedimentation rate.*

Joint involvement (clinical synovitis, that could be confirmed by imaging)	
1 large joint	0
2-10 large joints	1
1-3 small joints	2
4-10 small joints	3
>10 joints (at least 1 small)	5
Serology	
RF and anti-CCP normal	0
RF or anti-CCP normal ≤ 3 ULN	2
RF or anti-CCP normal > 3 ULN	3
Acute-phase reactants	
CRP and ESR normal	0
CRP or ESR abnormal	1
Duration of symptoms	
< 6 weeks	0
≥ 6 weeks	1
"Definite" RA diagnoses with a total score ≥ 6	

Certain signs and symptoms must be assessed to facilitate the diagnosis such as: morning stiffness, pain, inflammation, symptomatology duration greater than 6 weeks, family history, symmetry in symptoms, symptoms which started in small joints, smoking, serology and biochemistry with high values of RF, and certain antibodies, like anti-CCP antibodies (ACPA) (31,50). To not find high values of RF or ACPA markers in laboratory tests, does not exclude the possible diagnosis of the disease. It must be considered that these markers are not exclusive to RA and do not appear in 100% of patients. Furthermore, they can also appear in healthy individuals, and have been observed in other inflammatory diseases (51).

The diagnosis of RA will be considered valid in patients diagnosed with nonspecific arthritis and a long-standing disease. A lack of swollen joints can be presented, but other clinical signs typical of RA collected in their clinical history or finding radiological tests show the typical joint erosion are necessary (17).

At the physical assessment, typically patients with RA suffer from symmetric polyarticular joint pain and swelling. Those symptoms are more pronounced in the small joints, including metacarpophalangeal (MCP), proximal interphalangeal (PIP) of the hands and metatarsophalangeal (MTP) joints, excluding the thumb and hallux. Other commonly affected small joints in early RA include the wrist. Also, RA can be present in medium/large joints, including the shoulder, elbow, hip, knee and ankle joints, however this is associated with more severe disease (Figure 2) (3).

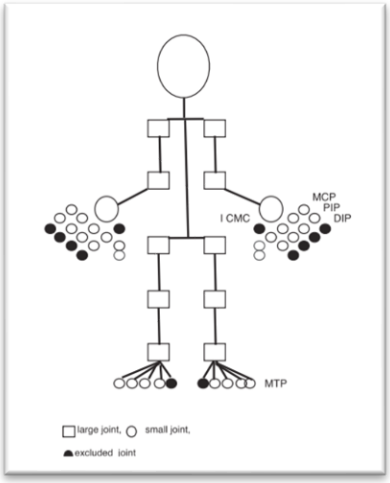

Figure 2. Joint type of classification criteria of RA on earlier stages (3). CMC – carpometacarpal; MCP – metacarpophalangeal; PIP – proximal interphalangeal; DIP – distal interphalangeal; MTP - metatarsophalangeal.

A common symptom of RA is joint pain and swelling, accompanied by morning stiffness (52). Morning stiffness lasting more than one hour suggests an inflammatory aetiology. Patients with RA may also suffer from systemic symptoms of fatigue, weight loss, and anaemia (53,54).

Some diagnostic tests are available. Laboratory measures include C-reactive protein, erythrocyte sedimentation rate, or both. The RF is presented in most patients with RA, but it is not considered specific for RA as it can also be present in patients with other diseases (29,53).

To measure disease activity, the Disease Activity Score-28 (DAS28) is used. The DAS28 is composed of scores in the 28 joints that are examined in this assessment. It includes tender joint count (TJC), swollen joint count (SJC), patient global assessment (0 to 10 scale), physician global assessment (0 to 10 scale) and C-reactive protein level or erythrocyte sedimentation rate (55).

RA must be differentiated by physicians from another aetiology. The differential diagnosis includes disease such as systemic lupus erythematosus, systemic sclerosis, psoriatic arthritis, sarcoidosis, crystal arthropathy, and spondyloarthropathy. This differentiation may be done through physical assessment, imaging or blood analysis (54).

EULAR recommends the use of imaging in RA diagnosis when there is diagnostic doubt. Conventional radiography (CR), ultrasound (US) or magnetic resonance imaging (MRI) can be used to help in the acute diagnosis of RA. The use of imaging predicts the progression from undifferentiated inflammatory to clinical RA. These techniques are considered for more accurate assessment of inflammation due to their ability in the detection of joint inflammation (56).

CR has been considered the traditional gold standard for imaging in RA. However. it lacks sensitivity in assessing disease activity. With the use of CR, joint damage and erosion can be seen, assessing the progression of the disease and whether the implemented therapeutic treatments are being effective. CR is not able to detect early disease manifestations such as inflammatory changes in soft tissues or the earliest stages of bone erosion (57). In contrast, US and MRI, allow direct visualization of destructive and early inflammatory joint changes in RA (58).

1.1.6. Treatments

After RA diagnosis and an initial evaluation is completed, treatment should begin. A rapid RA treatment is important to reduce inflammation, hence limiting structural damage. Goals of therapy are maintaining quality of life and minimizing joint pain, preventing deformity, extra-articular manifestations and radiographic damage (59).

There is a period when the disease is more likely to respond to treatment. It is the pre-clinical period, when there is a relationship between a rapid diagnosis and an early initiation of disease treatment. EULAR and ACR have stablished that this period is within the first 12 weeks, after the first signs and symptoms (17,60). Multiple studies have shown that during this period, complex interactions between the environmental and genetic causes occur. Starting treatment in this period is associated with less joint damage and a greater chance of reaching remission in the shortest time possible (60).

- Pharmacological management

The strategy available in current RA guidelines is a treat-to-target strategy. To treat active RA with the aim of achieving a target of remission or low disease activity if remission cannot be achieve, but always considering people's rights to be involved in discussions and make informed decisions about their care (61).

Nowadays the treatment tends to be for life and modifiable. Periodically, doses must be checked, just in case it is necessary to change or adapt it to the level of activity of the disease (62). The Rheumatoid Spanish Association established that the check-up should be at least every 3 months when there is a lack of achieving a target of remission, and every 6 months when a target of remission is achieved. This assessment must include DAS28 and/or Simple Disease Activity Index (SDAI) evaluations (63).

  - Disease-modifying anti-rheumatic drugs (DMARDs)

For RA treatment, initial pharmacological management and further pharmacological management are available. The National Institute for Health and Care Excellence (NICE) guideline recommends that the first course of action is to administer conventional disease-modifying anti-rheumatic drugs (cDMARD) monotherapy using oral methotrexate (MTX), leflunomide (LEF) or sulfasalazine (SSZ) as soon as possible and ideally within 3 months of

onset of persistent symptoms. Hydroxychloroquine (HCQ) is also a first-line treatment for patients with mild or palindromic RA (61).

Management of RA has changed over the time. EULAR and ACR updated their RA management guidelines to provide similar strategies, both recommending MTX monotherapy as the first option for early RA (50,64). Even MTX is considered a cornerstone drug for RA treatment, it presents toxicity challenges, such as pulmonary effects (65).

Further pharmacological management includes biological and targeted synthetic DMARDs (bDMARD). When RA is not well controlled with a cDMARD, the next treatment step is to continue with a bDMARD (66). The difference between cDMARDs and bDMARDs is that the bDMARDs includes biological agents that contain monoclonal antibodies and recombinant receptors to block the inflammatory response responsible for RA symptoms (67). Also, there are cost differences between both DMRDs, although effective, bDMARDs are significantly expensive (Table 4) (54). When biological therapy is effective, a considerable decrease in the RF is observed, and this reduction is closely linked to a reduction of disease activity (68). TNF inhibitors are the first options between bDMARDs treatment.

Table 4. Most common Biologics and Conventional Disease-Modifying Antirheumatic Drugs (54).

** Estimated retail price based on COFARES (accessed October 2020).*

cDMARD			
Drug	**Typical dosage**	**Administration**	**Cost***
Methotrexate	25 mg per week	Orally	1.90€
Leflunomide	10 mg per week 20 mg per week	Orally	29.96€ 53.92€
Sulfasalazine	500 mg twice per day	Orally	5.06€
Hydroxychloroquine	200 mg per day	Orally	12.16€
bDMARD			
TNF inhibitors • Adalimumab	40 mg every two weeks	Subcutaneously	-
• Certolizumab	400 mg every four weeks	Subcutaneously	1044.07€
• Etanercept	50 mg every week	Subcutaneously	-
• Golimumab	100 mg every four weeks	Subcutaneously	2381.51€
• Infliximab	3 to 5 mg per kg every six to eight weeks	Intravenously	554.90€
Abatacept	125 mg every week for 4 weeks	Subcutaneously	932.50€
Rituximab	100mg every six months	Intravenously	456.49€
Tocilizumab	162 mg every week or every two weeks	Subcutaneously	1074.73€

- Non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids

NSAIDs and corticosteroids can be combined with DMARDs. Clinicians often prescribe corticosteroids to relieve acute symptoms, in combination with DMARDs and NSAIDs if necessary. The target of NSAIDs is to reduce inflammation and pain, and therefore decreasing stiffness and increasing clinical improvement. NSAIDs do not modify joint destruction as they do not modify the disease process (29).

In the same way, corticosteroids are required in acute forms of the disease to reduce inflammation and pain, slowing down joint damage. Administration of corticosteroids in addition to standard therapy reduces the rate of bone erosion progression in RA. However, clinicians are always cautious because of the adverse effects of this therapy, such us osteoporosis, metabolic and endocrine or cardiovascular side effects (69).

A lower dose of DMARDs and reducing NSAIDs and corticosteroids can be considered when a target of remission or low disease activity have been achieved thanks to the main treatment chosen. This reduction must not be abrupt to avoid a flare (70).

- Non-pharmacological management

RA may be managed due to pharmacological treatments. However, some patients still report significant levels of disease impact, which has been assessed by patient-reported outcome measures (PROMs) (71). This disease impact is divided and evaluated mainly in seven domains: pain, functional disability, fatigue, sleep, physical wellbeing, emotional wellbeing and coping (72,73). Additional non-pharmacological therapy is required to target uncontrolled domains. Many therapeutic options are available, such as physiotherapy, occupational therapy, psychological interventions, diet or podiatry.

- Physiotherapy

Physiotherapy improves general fitness and encouraging regular exercise. Physiotherapy interventions includes electrical stimulation, acupuncture, low-level laser therapy, therapeutic ultrasound, thermotherapy, transcutaneous electrical nerve stimulation (TENS) and exercises. Those exercises may help enhance joint flexibility, muscle strength and improve balance (74).

- Occupational therapy

Occupational therapy (OT) may be required to learn how patients can deal with their difficulties with everyday activities. OT facilitates task performance and decreases the consequences of RA for daily life activities. Interventions can be classified as comprehensive therapy, training of motor function, training of skills, instruction on joint protection and energy conservation, counselling, instruction about assistive devices and provision of splints (75,76).

A Cochrane systematic review concluded that there is evidence that OT has a positive effect on functional ability in patients with rheumatoid arthritis (77).

- Psychological interventions

Numerous psychosocial and behavioural treatments have been developed to address these symptoms, such as stress management training, cognitive– behavioural therapy (CBT) and/or education. With these methods, patients with RA learn how to cope with their functional problems and make decisions about how to best self-manage their condition (78,79). Those techniques play a role in reducing depressive symptoms and anxiety among patients with RA (80).

- Diet

Diet performs an important role. A healthy lifestyle and nutrition including some dietary patterns and supplements, such as an anti-inflammatory diet, vitamin D and probiotics, have showed to have protective effects on RA (81,82). Besides, obesity complicates remission in RA and negatively impacts in PROMs during therapy (83).

There is research on the relationship between fasting mimicking diets and inflammation. A literature review concluded that commitment to an eating pattern including a fasting component could suppress the inflammatory process (84).

Herbal plants have been utilized since the ancient era. The efficacy of turmeric/curcumin extract (about 1000 mg/day of curcumin) provides evidence in the treatment of arthritis (85). Herbal therapies such as turmeric/curcumin extract, present anti-inflammatory properties and minimum side effects (86).

- Podiatry

Podiatry to treat patients foot problems and to improve patients foot health. Hence, it is necessary to assess the necessity of therapeutic footwear and/or functional insoles if

indicated. This is discussed in deep in the section 1.4 Insoles in people with Rheumatoid Arthritis of this thesis.

In summary, RA interventions are focused on an early diagnosis and to treat the disease with new therapeutic strategies to control symptoms and prevent joint damage and deformation. ACR and EULAR have written up the following recommendations in 2016 to meet those objectives (50,64):

- Treatment of early arthritis is aimed at better possible care and the decision must involve a discussion between patient and rheumatologist.
- The rheumatologist is in charge for the care of patients with early arthritis, with the aim of a more personalized follow-up to obtain better results.
- The diagnosis of early arthritis requires a complete medical history, complementary laboratory and radiology tests.
- Patients with symptoms of joint inflammation, pain and stiffness must be seen by the rheumatologist within 6 weeks of the onset of symptoms.
- Clinical assessment is necessary to confirm arthritis.
- If the definitive diagnosis of RA cannot be confirmed, follow-up and short-term reassessment is needed.
- At risk patients with persistent arthritis must start treatment, even if they do not meet the criteria classification, in less than 3 months.
- MTX is the drug of choice when there is no contraindication.
- NSAIDs are effective in controlling the symptoms, but its use should be with a minimum effective dose and a short period of time.
- Systemic glucocorticoids are effective, reducing pain, inflammation, and structural progression. Due to their side effects, they are recommended as adjuvant treatment and for less than 6 months.
- The main treatment goal is to achieve clinical remission, adverse events will guide the changes in therapeutic strategy.
- Assessments of disease activity and treatment adjustment must be carried out for 1 to 3 months until the treatment objective is achieved.
- Physical and occupational therapy are recommended as a contributory treatment.
- Quitting smoking, dental check-ups and weight control are recommended.
- Education of the disease process, pain, and disability should be offered as contributory treatment and interventions.

1.2. Rheumatoid Arthritis foot and ankle

Foot symptoms are almost ubiquitous among patients with RA and are frequently severe, despite the exceptional progress in RA treatments. The first manifestations are usually in the forefoot, followed by the hindfoot and midfoot, although not always in that order. The clinical evolution tends to be fast, describing significant structural changes from 6 months (87,88).

Most patients experience moderate or severe daily foot pain and radiological changes, which remain a common and disabling symptom (89,90). Foot pain, joint stiffness, deformity and loss of foot function are the major factors that indicate detriment in foot-health-related quality of life. Pain is due to structural and functional alterations associated with inflammation and impacts on physical activity of patients with RA (91)

Inflammation of the small joints of the hands and feet is part of the signs and symptoms that characterise RA and it can be used to make a diagnosis, typically occurring early in the course of the disease (3,17). Besides joint impairment, patients with RA present soft tissues symptoms. Longer disease duration and higher Body Mass Index (BMI) are main predictive factors for reporting foot symptoms, and specifically, foot pain, stiffness, swelling and numbness, being very closely correlated with each other (89).

As a result of foot deformity, pain and stiffness, reduced mobility is highly associated with a loss of independence, with considerable consequences for social integration (92). The consequences of foot damage include reduced sensitivity, ulcers, deformities, increase of fatigue, weight gain and psychosocial impact of impaired self-image, sexuality and personal relationships (89,92–94).

Foot impairment causes walking disability in 75% of the patients with RA, with impaired gait as a result (92).

Foot deformities can be analysed depending of the affected foot region. Those deformities are identified in the forefoot in 90% of patients, 40-60% in the midfoot and between 30-60% in hindfoot and ankle (95):

- Forefoot

  RA has a propensity for the small joints of the hands and feet, which results in a common occurrence of forefoot deformity. In the first three years of the disease evolution, 65% of patients have an alteration in at least one of the MTP joints, and the presence of synovitis

in these joints is considered an early sign of RA. First symptoms frequently appear at this foot region and remain persistent during the disease (96).

Forefoot deformities cause trouble more often than ankle and the rest of the foot. The average rheumatoid forefoot deformity presents hallux valgus and subluxation or dislocation of the lesser toes (hammer and claw toe deformities) at the MTP joints (Figure 3) (97). The development of HAV in patients with RA occurs in less time than in general patients due to the following structural alterations of the foot (95,98):

- Hindfoot in valgus deviation, due to subtalar joint eversion position during all phases of gait.
- Increased medial pressure on the forefoot.
- Synovitis in the first MTP joint, which causes the joint capsule laxity and instability.
- Joint erosion which helps deviation in the transverse plane of the first MTP joint.
- Increased laxity of the Lisfranc ligament increasing the intermetatarsal angle.
- Elongation, partial or total rupture of the posterior tibial tendon.

Although by far the most common hallux deformity in RA is hallux valgus, patients can present other deformities such as metatarsus primus varus, hallux tortus, hallux rigidus, hallux flexus, hallux elevates, hallux varus, and combined deformities (97).

RA manifestation are frequently found in the MTP joints. The greatest level of swelling within the small joints is present in the MTP joints where there is a destructive impact of the quality and structure of the joints and surrounding soft tissues. This joint swelling accompanied by synovitis of the MTP joints may be the main cause of foot pain in early RA (99,100).

Forefoot deformities are often accompanied by ulcers, which can infect the foot and result in major septic complications (92,101).

Also, callosities are often found on the plantar surface due to the abnormal load distribution. Patients with RA present higher peak pressures than normal values, with an atypical pressure and force distribution. With these raised pressures, skin callosities and bursae try to protect the foot joints, but due to this protective response, an increase of local pressures at the MTP joints is developed, which exacerbates the symptoms (102).

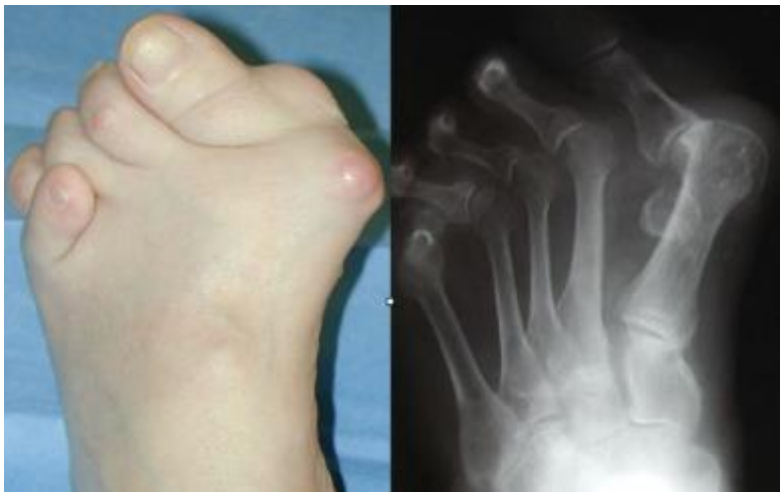

Figure 3. Clinical image and Rx of typical rheumatoid forefoot deformities (97).

- Midfoot

Midfoot includes naviculo-cuneiform and tarsometatarsal joints, constituting the longitudinal arch of the foot and allowing the weight to be transferred from the hindfoot to the forefoot during gait. Generally, midfoot is not affected in isolation in patients with RA, however, it is affected in the holistic aspect (103). It has been observed that in the first years of the disease, the midfoot joints are not usually affected. But in the period of 5 to 10 years of evolution, midfoot deformity increases with joint erosion, causing synovitis, distension of the joint capsule and associated ligaments. All these factors alterations help the increased stiffness (104).

Midfoot deformity can progress into a flattening of the longitudinal arch, instability and midfoot width increase (87,105,106).

- Hindfoot

Hindfoot deformities often start insidiously and progresses with a slowly developing valgus deformation, making it difficult to diagnoses them and to differentiate them from ankle involvement (92).

The role of the hindfoot is to transfer load forward to the midfoot and forefoot during the stance phase of gait, and the hindfoot is frequently found in a valgus position in patients with RA. This valgus alteration in the central distribution of pressures, exacerbated by destruction of soft-tissue, may have detrimental effects on patients gait (102). In a high percentage of patients, even in the remission period, a hindfoot joint destruction it has been observed. This fact leads to an alteration in joint alignment, a reduction in mobility

and a change in pressure distribution to the medial aspect of foot. These changes develop a valgus deformation (95,98).

Due to the progressive deformity, the talar head drops into plantar flexion without the support of the calcaneus, and the navicular presents a lateral subluxation. As a result, patients with RA may present a pes planovalgus deformity with forefoot abduction. Furthermore, plantar fasciitis can originate from this pathological clinical presentation (103).

- Ankle

The ankle joint is less commonly involved than other joints of the foot in patients with RA. Extra-articular abnormalities in this region may include rheumatoid nodules occurring on the Achilles tendon below the dermis (103).

Additional extra-articular foot manifestations in RA include neurological manifestations. Neurological signs may be tarsal tunnel syndrome and interdigital neuroma. They manifest after compression caused by rheumatoid nodules, rheumatoid pannus, valgus deformity and/or other reasons. The severity of the neuropathy depends on the level where the affected nerve is damaged. The range of severity can be from a loss of local sensitivity to disabling pain or even paralysis (30).

Tendinopathy is a relatively frequent pathology associated with foot deformation in RA. The most studied tendon is the posterior tibial (PT) tendon. The rest of the tendons have an inferior rate of dysfunction, being the reason why the PT tendon is the most commonly affected tendon (105). PT tendon dysfunction has been implicated by some investigators as a cause of hindfoot deformity in RA. Patients with this pathology show a loss of the longitudinal arch, inability to perform a heel-rise, lack of a palpable posterior tibial tendon and planovalgus deformity (107).

Proliferative synovitis may have consequences on tenosynovium or bursal synovium, in addition it can occur earlier than articular synovitis. It can be detected as subcalcaneal burtisis with the musculoskeletal ultrasonography scanning of the plantar surface of the heel. This proliferative synovitis causes patients with RA to develop persistent plant heel pain (108). Thus, it is important that patients who complain of foot pain, have their feet scanned. In some

cases, scanning the dorsal surface of the foot is not enough, and to scan the plantar surface of the foot is needed to detect proliferative synovitis in tenosynovium or bursa (109).

From a general and most common point of view, foot symptoms in RA cause some biomechanics alterations, some of these are listed below (88,97,106):

- Decreased walking speed.
- Reduction of swing phase.
- Walking and running with difficulty.
- Increased instability.
- Greater support base (distance between the two feet).
- Lack of joint proprioception (associated with neuropathy).
- Painful MTP joints.
- Lack of bone and joint alignment.
- Limited ranges of motion.
- Step length reduction.

Although foot and ankle assessment is an important part in the clinical evaluation, because most patients with RA experience foot symptoms, the foot and ankle are excluded from the joint count at DAS-28 (55). However, it has been demonstrated that reduced joint counts are an appropriate and valid tool for disease activity assessment (110). On the other hand, foot involvement is considered in the RA classification criteria by ACR/EULAR in 2010 (17).

1.3. Measurement instruments for patients with Rheumatoid Arthritis.

RA is a disease with heterogeneous signs and symptoms. In health care science, disease outcomes are interpreted with objective data, but not everything is measurable. There is subjective information such as quality of life, pain or functionality, and valid and reliable data is necessary (111). Patients suffer a loss of quality of life related to health and functional capacity alteration, increasing anxiety and depression, morbidity and mortality. For this reason, reliable measurement instruments are needed to provide valid information to the health care professional, related to how the patient feels during the different phases of the disease (112,113).

An outcome measure is a tool which is utilized to assess a patient's current status. It is a useful tool prior, during and after treatment, providing credible and reliable information about a patient's status (114). Before treatment, an outcome measure provides baseline data, and those results may help with treatment election and to determine the disease course. Once treatment has commenced, the same tool is useful to assess patients changes along the treatment (115).

Methods of measurement in RA include descriptive scales, modified visual analog scales (VAS), numeric scales, multidimensional scales, verbal rating scales and PROMs. PROMs can record patients´ perspectives of their health, illness and evaluating the effectiveness of health care intervention from the patient's perspective, both in research and as routine quality indicators (114). Their use is recommended because they collect information in a reliable, feasible and a valid way for the population with whom they are to be used. They also have the specific advantage of being meaningful to the individual patient, reflecting the issues that affect their health and lives (116).

PROMs can be characterised in terms of what they intend to measure, including health status, physical activity impairment, quality of life or health related quality of life. From a holistic perspective of RA, PROMs are mainly focused on the measures of physical function (117), fatigue (45) or, mainly, Health-related quality of life (HRQoL). HRQoL refers to a patient's subjective appraisal of the impact of a disease and its treatment on multidimensional aspects of their life. The most widely used instrument for measuring general HRQoL in rheumatology is the Health Assessment Questionnaire (HAQ) disability index (DI), which contains a subscale for

walking disability. It is the most widely used because it is a valid and reliable tool to measure functional status in RA patients (118).

Furthermore, the multidimensional consequences of foot problems can be assessed and evaluated using PROMs. Those tools are becoming increasingly popular among foot and ankle specialist. There are many instruments available for the foot and ankle (119). For example, the Foot and Ankle Ability Measure (FAAM) and the Foot and Ankle Disability Index (FADI). Those self-reported questionnaires have been validated for assessment of the foot and ankle, more specifically, for chronic ankle instability (120).

However, only a few PROMs are specific to RA, such us Leeds Foot Impact Scale (LFIS) or the Salford Rheumatoid Arthritis Foot Evaluation (SAFE) (121). Their main domains are pain, perceived health status and HRQoL and disability; all foot and ankle related. In addition, some specific PROMs for foot have been validated for patients with RA, such us the questionnaire Foot Function Index (FFI) (122).

The following questionnaires are the most commonly used to assess the foot and ankle in RA (123):

- FFI

This questionnaire was developed by Budiman and colleagues in 1991 to measure the impact of pathologies on foot and ankle function. It is divided into three subscales: pain (9 items), disability (9 items), and activity limitations (5 items) using a VAS scale. A lower score on the scale means that the patient's pain, disability or limitations are lower (124).

It has been validated for patients with RA (122).

- Ankle Ostearthritis Scale (AOS)

It is an adapted scale of FFI for inflammatory osteoarticular involvement of the ankle. It was designed by Domsic and colleagues in 1998. It consists of two subscales, pain and disability, adjusted for specific ankle problems. Its evaluation method uses a VAS scale, being the ends of the pain subscale "no pain" and "worst pain"; and the ends of the disability items “without difficulty” and “unable to perform". A lower score on the scale means that the patient's pain or disability levels are lower (125).

This questionnaire presents an intraclass correlation (ICC) of 0.95 for the pain subscale, and 0.94 for the disability subscale (126).

- Foot Heal Status Questionaire (FHSQ)

A questionnaire designed by Bennett and colleagues in 1998 to assess foot health. It consists of 13 items and it can be divided into three subscales: foot pain (4 items), foot functionality (4 items), general foot health (2 items) and footwear (3 items). The first three subscales have a good intercorrelation. It presents an ICC between 0.85 at 0.88. Total score ranges from 0, "poor foot health," to 100, "optimal foot health" (127). It is valid to analyse the foot in rheumatic patients, but a specific adaptation for the disease is recommended (128).

- Manchester Foot Pain Disability Index (MFPDI)

This questionnaire was created in 2000 by Garrow and colleagues. It consists of 19-items, each of which has three possible response categories: "none of the time", "on some days" or "on most/every day(s)". The 19 items could be formed into the following subscales: functional limitation (10 items), two pain intensity constructs (7 items) and personal appearance (2 items). This questionnaire puts emphasis on disability, pain and ambulation problems caused by foot pain. (129).

- Leeds Foot Impact Scale (LFIS)

In 2004, Helliwell and colleagues developed this foot impact scale to assess the impact of RA and to measure the effect of interventions. It is a 51-item validated impact scale to assess foot status in RA, and they are grouped in 2 subscales. Those domains are impairments/shoes and activities/participation (93).

- Self-Reported Foot and Ankle Score (SEFAS)

This ankle questionnaire was constructed by Cöster and colleagues in 2012. It can be used to evaluate pain and functional status in patients with osteoarthritis or inflammatory arthritis of the ankle, and as outcome of surgery (130). Also, SEFAS has acceptable validity, reliability, and responsiveness in patients with various forefoot, hindfoot, and ankle disorders (131).

The questionnaire contains 12 items with 5 response options. Each of the 12 multiple-choice questions scores from 0 to 4, where a sum of 0 points represents the most severe disability and 48 represents normal function. The questionnaire covers pain, function, and limitation of function (130).

- FAAM

This questionnaire was developed by Martin and colleagues in 2005 to evaluate the physical function of people with musculoskeletal disorders in the foot and ankle. It consists of 21-item activities of daily living and 8-item sports subscales, which together produced information across the spectrum ability. It presents an ICC between 0.89 and 0.87. Despite its specificity, it does not present a good correlation with scales that assess pain and quality of life. It adapts better to changes in physical function associated with the foot and ankle (132,133).

- Health assessment questionnaire disability index (HAQ-DI)

HAQ-DI is a questionnaire for RA originally created by Fries in 1978. Nowadays, it is an ordinal scale with 20 items on daily functioning during the past week. The following categories are assessed by the HAQ-DI: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and outdoor activities. It can be completed in 5 minutes. Each response is scored on a 4-point scale of ability: without any difficulty, with some difficulty, with much difficulty, and unable to do (134,135).

Furthermore, some questionnaires are available to assess the foot and ankle of patients with Juvenile idiopathic arthritis (JIA). It is the most common rheumatic disease in paediatric patients (136):

- Oxford Ankle and Foot Questionnaire for children (OAFQ)

This questionnaire was developed by Morris and colleagues in 2008 to assess the disability associated with foot and ankle problems in children aged from 5 to 16 years of age.

The effect of foot or ankle problems is measured on three domains of children's lives: physical, school and play, and emotional. It uses 15 items and each of the included statements are answered using a 5-point Likert scale: never, rarely, sometimes, very often. The questionnaire is appropriate for children with a range of conditions and can provide clinically useful information to supplement other assessment methods (137).

- Juvenile Arthritis Foot Disability Index (JAFI).

In 2004, André and colleagues developed this questionnaire for assessing foot-related disability among children/adolescents with JIA.

It uses a Likert Scale grades from never (4) to always (0) to assess the following three domains: Impairment, Activity Limitation and Participation Restriction. It has 27 items. It might be useful for the assessment of physiotherapy treatment outcomes and for other local treatments (138).

1.3.1. Quality of life.

One of the most accepted definitions of quality of life is the one from the World Health Organization, which defines it as “individuals’ perceptions of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns” (139). Quality-of-life measures levels of wellness. In a health-related environment, the purpose is to evaluate health status in individuals with medical disorders that impair everyday function or cause symptoms. The concept which is more commonly used is the more descriptive term ”health-related quality of life” or HRQoL (140).

RA is a systemic disease that not only presents extra-articular manifestations but also has psychological effects, such as mental health and functional problems. It has been demonstrated that they present a significant negative impact on their HRQoL. Patients with RA suffer from major and diverse effects on HRQoL compared to general population, spanning both physical and mental domains of well-being (141,142).

Reduced HRQoL in RA patients is associated with the following signs and symptoms (100,143,144):

- Increased levels of depression.
- Persistent pain.
- Increased levels of disease activity.
- Reduced physical function.
- Increased levels of fatigue.

A previous study claimed that patients with RA are those with the biggest disability and the worse quality of life within the rheumatic diseases (141). Because RA is associated with pain, fatigue, functional disability and deterioration of emotional state, this disease represents HRQoL and economic burden to patients and society (29).

In a chronic condition, such as RA, quality of life, anxiety/depression and mobility problems are more common than in the general population, especially in inactive people with RA (145,146). A cross-sectional study has shown that the presence of RA, a higher score on VAS pain, female gender and more advanced age are all associated with the physical impairment of HRQoL (147). Physical function is predominantly affected, and furthermore, RA has social and mental consequences (141).

Limiting the adverse effects of RA on HRQoL should be a key therapeutic goal. Patients value HRQoL even more than RA related variables, such as inflammatory biomarkers or joint counts (148).

Simultaneous loss of HRQoL and increase in disability in patients with RA generates a socioeconomic burden. It is not only due to the direct costs associated with healthcare personnel, drugs, and other health services, but also indirect consequences as functional disability, disability labour, and decreased social participation (149).

The emotional and physical impact on overall HRQoL may vary in individual patients. Despite similar levels of disease activity and severity, rheumatologists have observed individual variations in HRQoL (150). An individual's reaction and adaptation to an illness such as a chronic disease like RA depends on the individual's cognitive and emotional representation of this threat in their mind (151). It has been shown that social support has beneficial effects on RA patients, making an impact on how anxious or depressed a patient can be. Also, it may influence other factors such as level of pain and the presence of additional co-morbidities (150,152).

Symptoms of depression in RA are directly correlated with anxiety, helplessness, pain, and disability. This is also inversely correlated with HRQoL and self-efficacy (153), with comorbid depression being common in patients with RA (154). Therefore, NICE recommends that patients with RA should be offered a holistic annual review, including an assessment of mood (61).

Previous qualitative studies on patients with RA concluded that patients described discordance in terms of symptom assessment and understanding how RA affects everyday life (155). Provision of equal priority to mental and physical health problems and improved continuity of care could help disclosure of mood concerns and, consequently, to HRQoL (154).

1.3.2. Physical activity.

Physical activity (PA) is defined as any bodily movement produced by skeletal muscles that results in energy expenditure, which is positively correlated with physical fitness (156).

PA is associated with improved health outcomes in many populations, even those whom suffer disorders, such as diabetes, obesity and mental health disorders (157–159). Benefits on RA patients have been shown, due to the overall management of RA (160). There is an association between benefits on RA patients and rheumatological, cardiovascular and psychosocial outcomes. These benefits include attenuated inflammatory disease activity, decreased fatigue, reduced joint pain, improved physical function and reduced risk for cardiovascular and metabolic disease (161,162).

Evidence supports the benefit of aerobic and strengthening exercise in RA, indicating that the goal should be moderate to hard, 2 to 3 times a week, progressively incremented and with professional support (145). Recent research is focused on interventions promoting PA (163).

Regular PA improves patients' symptoms and disability in RA (164). Therefore, most patients with RA should be encouraged to undertake aerobic and/or strength training exercise (162).

Unfortunately, a systematic review shows that the level of PA may be lower among individuals with RA when compared with healthy controls or normative data (165). People living with RA engage in very little moderate-intensity PA, and they spend most of the day sedentary. A high prevalence of inactivity in adults with RA has been demonstrated (166). Most of this patient group remain insufficiently active to accrue such positive health benefits, and spend a large proportion of their day engaged in sedentary behaviour (83,167,168). Consequently, as a previous qualitative study concludes, maintaining and promoting physical activity is an integral part of foot health. Therefore, a health damage within an inactivity situation can be presented (169).

Research evidence supports that worse quality of life is observed in patients not doing physical activity(170). Specially in chronic conditions like RA, where quality of life, anxiety/depression and mobility problems are more common in inactive people with RA, than active people with RA (145,146).

PA can be measure by questionnaires or equipment. Specially, an assessments of PA with the use of a tool can offer a more objective measure (171). Assessing PA in patients with RA using accelerometery has become more usual, including being used in clinical practice (172,173). Accelerometers are

validated and reliable instruments that record and store raw acceleration data, which provides information of sedentary behaviour and physical activity (174).

1.4. Foot orthoses for people with Rheumatoid Arthritis.

Previously, it has been described that foot problems are frequently identified in patients with RA, being a prevalent and debilitating symptom of RA throughout the disease course, in both early and established stages of the disease (89,92,99). Those foot problems reside in deformities which are identified in the forefoot in 90% of patients, 40-60% in the midfoot and between 30-60% in hindfoot and ankle (95). The most common foot deformities are subluxation of the MTP joints of the lesser toes, displacement of the plantar fat pad and hindfoot deformities which develop valgus deformation (103). Their progression is related to the duration and severity of the disease and foot pain frequently persist even when clinical remission of disease activity is achieved (175).

The typical inflammation of joints in RA causes pain, deformity, decreased joint mobility, stiffness, and increased plantar pressure (28,30,41,175). Subsequently, foot and ankle problems continue to be an issue for patients with RA and treatment is required. Treatment may include non-pharmacological treatments, such as conservative or surgical treatments. Foot orthoses (FO) are an important conservative treatment option for RA-related foot problems and they are frequently prescribed in clinical practice (176).

FO are externally applied devices which provide a critical, biomechanical contact point for the human body, and they can be helpful to correct problems in the foot, knee, hip, and spine. FO are special insoles worn inside the shoe to control any abnormal movement of the foot during walking to limit foot pain and deformity. They modify the structural and functional characteristics of the neuromuscular and skeletal system (177,178). Reducing pain and disability by improving the patient's quality of life are the main objectives of FO. To achieve those objectives, FO must compensate the mechanical alterations and to reduce increased pressures (179).

Mechanical alterations play a key role in the progression of foot deformity and are increasingly thought to have a major role in the persistence of foot pathology. FO intervene as mechanical therapies offloading painful joints, reducing pain and disability and improving quality of life in patients with RA. Therefore, FO are an important adjunct therapy and the implementation of these treatments should take a more targeted and aggressive approach of foot problems in RA (94,180).

Effectiveness of FO, including both custom-made FO and standardised FO, in patients with RA has been confirmed (181,182). This effectiveness may be influenced by shorter disease duration, younger age, the use of custom-made FO and higher baseline values of pain and disability. Those factors predict greater improvements in self-reported foot pain and disability and improvements in walking time after intervention in daily activities (183). Custom-made FO are specially made for the participants rather that FO than can be purchased over the counter. Those devices are required due to the effect of RA on the foot and ankle, which may be different for each individual person (180).

Early and continuous interventions of FO in early correctable deformities in RA provide a significant reduction in foot pain in the short-term, with reduction in disability and enhance foot health outcomes in long-term. There may be a window of opportunity in early RA to beneficially target mechanical pathways to inhibit foot impairment before irreversible joint damage occurs (180,183–185). More importantly an early intervention with FO shows pain reduction within the first 3 months of use and with some small further symptomatic improvement up to 6 months. This also shows a reduction in swollen and tender joints (186). Furthermore, it has been suggested that this early management helps to avoid or delay late stage orthopaedic surgery and, through linked mechanics, protect the knee joint (102).

FO vary broadly in terms of their material, design and manufacturing method. This variation is further confounded by additions such as posting, wedges and pads (187). For example, in a previous randomized controlled trial, the following FO were used: foot orthoses with a top cover of 30 Shore polyethylene foam, a 5-mm 50 Shore ethyl vinyl acetate stabilizer element in the heel and a 30 Shore metatarsal bar made of polyethylene foam (181). A previous systematic review concludes that FO made of soft materials may reduce forefoot plantar pressure compared to foot orthoses constructed of semi-rigid materials (188), while other studies concluded that customised rigid and semi rigid FO have been shown to reduce hindfoot pain among people with RA (189).

As it has been reported in previous systematic reviews, some available studies which compare foot types do not provide specific information in terms of the type of FO, joint or joints affected, foot deformity, location of pain, evolution of the disease, drug treatment of the patient, activity level of the disease, or more outcomes that may be of interest (188). Therefore, more high quality and better designed studies with all these parameters specified are needed.

FO may be associated with some external problems, such us their combination with footwear, which has been identified as greatly influencing the women's clothing choices and how they present themselves. When patients with RA wear therapeutic footwear, an improvement in pain and mobility have been shown. However, therapeutic footwear is frequently deemed unacceptable by women with RA due to aesthetics, price or limited availability. They even alter their social behaviour and experience negative impact on body image and emotions due to their footwear (190,191). Patients that decide wearing retail footwear may seek this type footwear as an alternative to therapeutic footwear to achieve an aesthetic purpose. However, retail footwear may not be suitable and can exacerbate their foot problem. In some cases, retail footwear can create a barrier in wearing FO and can lack in comfort (191,192).

1.5. Justification

RA shows high prevalence and morbidity worldwide being the most common chronic autoimmune disease of the joints. Its biggest impact, in terms of signs and symptoms, can be mainly observed in the small joints of hands and feet. Foot symptoms are almost ubiquitous among patients with RA and are frequently severe. Those symptoms in RA may cause a disabling complication for patients. Given the consequences to patients with RA, such as impairment in physical activity or reduction in their quality of life, there is an urgent need to analyse the feet of people with RA.

A wider knowledge about the feet of people with RA allows podiatrists to help their patients with the mention disease. Research that is focused on RA within feet aims to improve the field of podiatry. Professionals like podiatrist can improve the life of their patients with conservative treatment, delivering proper devices, specially foot orthoses. However, the current situation is that there is a lack of qualitative and quantitative researchers that provide enough information about this topic. Podiatrists need to understand the disease, and which is the best device that can be provide to their patients with RA, with high quality research that supports that election. Also, podiatrist need to know what they can expect in terms of foot orthoses.

Furthermore, reliable and valid tools to assess the disease and interventions effect, especially in clinical practice are vital. Those measurement outcomes must be robust instruments with good psychometric properties. Therefore, it is required to identify the most suitable instrument to assess feet involvement in patients with RA. This research needs to cover all patients with RA, hence another analysis including patients with juvenile idiopathic arthritis is also required.

Qualitative researchers to assess the disease consequences in patients and the impact of the interventions in terms of feet are required. In a qualitative study, important findings emerge, which help professionals and patients to manage the disease.

2. OBJECTIVES

2.1. Main objective.

To analyse feet of people with rheumatoid arthritis.

2.2. Secondary objectives.

1. To determine the effectiveness of foot orthoses in patients with RA, in comparison with other treatments (other types of foot treatment, i.e., sham treatment, taping…) in terms of enhanced disability and reduced pain.
2. To identify PROMs specific to the effects of rheumatoid arthritis in the foot and ankle.
3. To evaluate the methodological quality and psychometric properties of PROMs specific to the effects of rheumatoid arthritis in the foot and ankle.
4. To identify specific PROMs for children and adolescents with juvenile idiopathic arthritis (JIA) in the foot and ankle.
5. To assess the methodological quality and psychometric properties of PROMs for children and adolescents with JIA in the foot and ankle.
6. To compare physical activity, general and foot health, and foot health experiences in people with RA when wearing three different types of foot orthoses.

3. EFFECTIVENESS OF FOOT ORTHOSES IN PATIENTS WITH RHEUMATOID ARTHRITIS RELATED TO DISABILITY AND PAIN: A SYSTEMATIC REVIEW AND META-ANALYSIS.

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REVIEW

Effectiveness of foot orthoses in patients with rheumatoid arthritis related to disability and pain: a systematic review and meta-analysis

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Abstract

Background Epidemiological studies consistently report a 90% prevalence of foot pain. Mechanical and other non-pharmacological interventions such as orthoses and footwear can play an important role in managing foot pathology in patients whose systemic disease is controlled. The effectiveness of treatment with insoles has been examined in various randomised controlled trials, which have reported immediate clinical improvements, with reduced foot pain and disability and enhanced functionality. The aim of this systematic review is to determine the effectiveness of foot orthoses in patients with rheumatoid arthritis (RA), in comparison with other treatments, in terms of enhanced disability and reduced pain.

Methods A systematic review and meta-analysis was conducted of a number of randomised controlled trials focusing on patients with RA. The search was conducted in Cochrane, CINAHL, PubMed, EMBASE, SCOPUS and Cuiden, by means of an independent peer review. The Mesh terms and fields used were foot, ankle, joint, RA, foot, orthosis, insole and foot orthosis.

Results Of the initial 118 studies considered, 5 were included in the final systematic review and meta-analysis. These five studies had enrolled a total of 301 participants, with follow-up periods ranging from 4 to 36 months. Although the use of orthoses seems to alleviate foot pain, our meta-analysis did not reveal statistically significant differences between control and intervention groups regarding long- and short-term pain relief and/or reduced disability.

Conclusions Foot orthoses can relieve pain and disability and enhance patients, but no significant differences were found between control and intervention groups.

Keywords Rheumatoid arthritis · Foot orthoses · Pain · Disability

Introduction

Foot pain and deformity is very common in patients with rheumatoid arthritis (RA). The considerable physical and psychosocial malaise that can be provoked includes neuropathy due to reduced sensitivity, ulcers (which develop in 10% of patients), the psychosocial impact of impaired self-image, sexuality and personal relationships, weight gain, increased fatigue and deformities such as *hallux valgus* and *metatarsus primus varus* [1–5]. Epidemiology studies consistently report a 90% prevalence of foot pain in these patients, despite advances in pharmacological therapy [1, 6]. Patients in disease remission [with a disease activity score (DAS28) <2.6] frequently present residual active disease in the foot [7] which is exacerbated by the complex interaction between inflammation and the mechanical loading of weight-bearing structures, resulting from accrued damage [8–10].

Review registration number: PROSPERO NCT03170947.

Gabriel Gijon-Nogueron and Laura Ramos-Petersen have contributed equally in the study/paper.

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EFFECTIVENESS OF FOOT ORTHOSES IN PATIENTS WITH RHEUMATOID ARTHRITIS RELATED TO DISABILITY AND PAIN. A SYSTEMATIC REVIEW AND META-ANALYSIS.

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Review registration number: PROSPERO (NCT03170947).

Ethical approval: Institutional review board that approved the protocol for the study: Medical Research Ethics Committee of University of Malaga (CEUMA 91- 2015H).

ABSTRACT

Background: Epidemiological studies consistently report a 90% prevalence of foot pain. Mechanical and other non-pharmacological interventions such as orthoses and footwear can play an important role in managing foot pathology in patients whose systemic disease is controlled. The effectiveness of treatment with insoles has been examined in various randomised controlled trials, which have reported immediate clinical improvements, with reduced foot pain and disability and enhanced functionality. The aim of this systematic review is to determine the effectiveness of foot orthoses in patients with rheumatoid arthritis (RA), in comparison with other treatments, in terms of enhanced disability and reduced pain.

Methods: A systematic review and meta-analysis was conducted of a number of randomised controlled trials focusing on patients with rheumatoid arthritis. The search was conducted in Cochrane, CINAHL, PubMed, EMBASE, SCOPUS and Cuiden, by means of an independent peer review. The Mesh terms and fields used were foot, ankle, joint, rheumatoid arthritis, foot, orthosis, insole and foot orthosis.

Results: Of the initial 118 studies considered, 5 were included in the final systematic review and meta- analysis. These five studies had enrolled a total of 301 participants, with follow-up periods ranging from 4 to 36 months. Although the use of orthoses seems to alleviate foot pain, our meta-analysis did not reveal statistically significant differences between control and intervention groups regarding long and short-term pain relief and/or reduced disability.

Conclusions: Foot orthoses can relieve pain and disability and enhance patients, but no significant differences were found between control and intervention groups.

Key words: Rheumatoid Arthritis, Foot Orthoses, Pain, Disability

Introduction

Foot pain and deformity is very common in patients with rheumatoid arthritis (RA). The considerable physical and psychosocial malaise that can be provoked includes neuropathy due to reduced sensitivity, ulcers (which develop in 10% of patients), the psychosocial impact of impaired self-image, sexuality and personal relationships, weight gain, increased fatigue and deformities such as hallux valgus and metatarsus primus varus (Grondal et al., 2008; Helliwell et al., 2005; S. Otter et al., 2010; Simon J. Otter et al., 2010; Turner et al., 2006). Epidemiology studies consistently report a 90% prevalence of foot pain in these patients, despite advances in pharmacological therapy (Grondal et al., 2008; S. J. Otter et al., 2011). Patients in disease remission [with a disease activity score (DAS28) <2.6] frequently present residual active disease in the foot (Van Der Leeden et al., 2010) which is exacerbated by the complex interaction between inflammation and the mechanical loading of weight-bearing structures, resulting from accrued damage (Barn et al., 2013, 2014; Woodburn et al., 2005).

Various high-quality randomised clinical trials have been conducted to evaluate the use of individual conservative therapies. Common therapies such as foot orthoses, therapeutic footwear (i.e., cushioned heel providing smooth heel strike and forefoot rocker providing rolling effect (Cho et al., 2009), self-care and injection therapies (i.e., anti-TNFalpha (S. J. Otter et al., 2011) have been shown to be effective, whereas the value of routine callus debridement has been questioned (Hennessy et al., 2012; Siddle et al., 2013; Woodburn et al., 2002). Few studies have been published on orthotic interventions in RA patients, and they have evaluated the effect of foot orthoses on plantar pressures distribution and/or on forefoot pain reduction (Novak et al., 2009), and that is why it is so important to continue studying the foot orthosis. A randomised clinical trial of the effectiveness of treatment with insoles reported an immediate clinical improvement, especially in early stages of RA, with reduced foot pain and disability and enhanced functionality (Woodburn et al., 2002). However, although some studies on the question have been published (Conceição et al., 2015; Hennessy et al., 2012), no meta-review has been conducted to summarise the conclusions drawn regarding foot orthoses and pain in studies such as Woodburn (Woodburn et al., 2002). Accordingly, the results presented by different studies may be difficult to interpret, due to inconsistencies in the experimental measures considered, such as the area under the curve in the case of Woodburn's analysis (Woodburn et al., 2002).

Therefore, based on the previous information, to respond to the hypothesis that foot orthoses are effective to reduce pain and disability in RA patients, the aim of this systematic review is to

determine the effectiveness of foot orthoses in patients with RA, in comparison with other treatments (other types of foot treatment, i.e., sham treatment, taping…) in terms of enhanced disability and reduced pain.

Method

Protocol and registration: NCT03170947.

Eligibility criteria

The studies included were all randomised controlled trials or quasi-experimental studies, which conducted a longitudinal analysis of the results obtained, including at least two observations (before and after the intervention). All studies were conducted in accordance with the following PICO structure.

- Participants

Male and female patients with RA, aged>18 years and presenting foot pain. Studies focusing on juvenile RA and/or gait analysis were excluded.

- Intervention

Comparison of foot orthoses (customised foot orthoses: prescribed in accordance with each patient's needs (de P. Magalhaes et al., 2006) functional foot orthoses: effectiveness of foot orthoses to improve an ability (Novak et al., 2009), simple insole or placebo orthoses: designed to fit the feet of patients but not hold the foot or control its motion in any way (Conrad et al., 1996), custom-made manufactured orthoses: custom designed and manufactured to a standardized protocol from impression casts taken of the feet (Woodburn et al., 2002).

- Comparison

Other type of treatments, other types of foot orthosis, sham treatment.

- Outcomes

Evaluation of pain or disability, using an appropriate instrument to measure these outcomes.

All the studies included in the final meta-analysis compared two groups of patients—those who used foot orthoses for a minimum of 4 weeks and those who did not—and measured the patients' disability and functionality, via a Foot Function Index (FFI) questionnaire or using an analogue pain scale.

Information sources

A search for published studies was carried out in the SCOPUS, Cuiden Plus, EMBASE, CINAHL, Cochrane and Medline databases, with no time limitation and using the search strategies detailed below. A secondary search was also performed, analysing the references included in the articles obtained. Unpublished studies were not included.

The last search was performed in June 2017. When the published studies failed to provide necessary data for extraction, the authors were asked for clarification or for provision of the original data if possible. The following search terms were used, together with the operators "or" and "and": foot, ankle, joint, rheumatoid arthritis, foot orthoses, foot, orthosis, support, insole, foot orthosis, plantar.

The following search strategy was applied:

("foot"[MeSH Terms] OR "foot"[All Fields]) OR ("ankle"[MeSH Terms] OR "ankle"[All Fields] OR "ankle joint"[MeSH Terms] OR ("ankle"[All Fields] AND "joint"[All Fields]) OR "ankle joint"[All Fields])) AND rheumatoid arthritis[Title] AND (("foot orthoses"[MeSH

Terms] OR ("foot"[All Fields] AND "orthoses"[All Fields]) OR "foot orthoses"[All Fields] OR ("foot"[All Fields] AND "orthosis"[All Fields]) OR "foot orthosis"[All Fields]) OR insole[All Fields] OR (support[All Fields] AND plantar[All Fields])).

Study selection

In the first stage of the review, a detailed double-blinded assessment of titles and abstracts was performed by two independent reviewers to determine whether each item met the pre-determined requirements for inclusion. If this step was not clear, the full text of the article was evaluated.

Data abstraction

The following information was extracted from each study: design, country, type of facility and participants, allocation concealment method, follow-up period, frequency of assessment, and intervention used. The following data were used to measure the clinical effectiveness of the foot orthosis: Questionnaire of Foot Function Index, the FFI is a selfadministered questionnaire. It consists of 23 items divided into 3 subscales: pain (9 items), disability (9 items), and activity limitation (5 items). For each item, there is a visual analogue scale (VAS)

divided into ten equal segments, ranging from 0 to 9. To complete the test, the patients score each item on the visual scale, with 0 being the lowest score and 9 the highest. On testing the reliability of the FFI, it demonstrated excellent internal consistency on the three subscales: pain 0.94, disability 0.92, and activity limitation 0.73 (Budiman-Mak et al., 1991) and VAS of Pain. VAS pain (Landorf & Radford, 2008) consists of a 10-cm long line divided into ten sections ranging from 0 to 10. The patient scores from 0, representing no pain, to 10, the worst pain imaginable. There was a highly significant correlation between the initial and 5 min rating both ($r=0.996$; $P<0.005$) and after ($r=0.983$; $P>0.001$) (Revill et al., 1976).

Risk assessment

An independent peer review was implemented. To resolve cases in which the two reviewers' decisions differed, a third reviewer evaluated the text and decided upon its inclusion or otherwise. The studies were evaluated with reference to the Cochrane risk of bias tool included in RevMan 5 (Maher et al., 2003). The following biases were assessed: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, attrition bias, selective reporting, and other bias. Each criterion outcome was classed as high, low or unclear risk.

Summary measures

Scores obtained for the FFI base of the VAS pain.

Synthesis of results

Data were extracted and pooled using RevMan 5.0 software (G H Guyatt et al., 2009). A random effects model was used for all comparisons, due to the heterogeneity detected among studies. Sensitivity analyses were carried out taking into account the characteristics of the intervention in each study.

The meta-analyses were carried out taking into account the standardised difference of the means, with a random effects model, because some studies reported primary outcomes using different evaluation or calculation methods. When doubts arose, the original authors were contacted to request the necessary data. With respect to the study by Woodburn et al., who reported the mean differences of the AUC, an inferential extrapolation was performed, from the difference of the means and the standard error, to adjust the results to the confidence intervals reported.

Results

Using the search strategy outlined above, we identified a total of 118 articles in the databases, as well as 11 additional records identified through other sources (secondary search: found: via the reference lists of the initial papers that were retrieved). Of these 118 items, 104 were excluded for methodological reasons and records duplicates (because they were observational studies, clinical trials or non-randomised clinical, crossover trials with a carry-over effect). The remaining 14 articles were evaluated by two independent reviewers. Of these, four were excluded due to differences in inclusion criteria (Gibson et al., 2014; Turner et al., 2007; Woodburn et al., 2003), and five were excluded due to risk of assessment bias (Bongi et al., 2014; Chalmers et al., 2000; Hodge et al., 1999; Jackson et al., 2004; Mejjad et al., 2004). Thus, only five articles fully met the inclusion criteria. Figure 4 shows the PRISMA flow diagram for the studies included in this review.

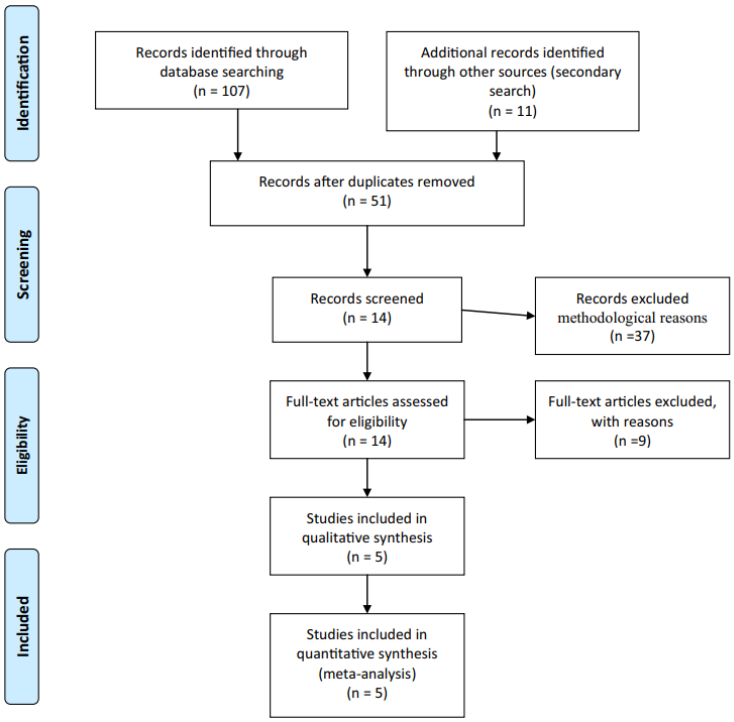

Figure 4. PRISMA flow diagram.

Articles were identified by searchingthe SCOPUS, Cuiden Plus, EMBASE, CINAHL, Cochrane and Medline databases published from 1 January 1977 to 9 June 2017; manual bibliography checks of previously published systematic reviews and Cochrane reviews supplemented these searches.

General characteristics of the studies assessed

All of the studies included were RCT, published between 1996 and 2016. Follow-up varied from 4 months to 3 years. The studies were carried out in New Zealand, Korea, USA, Slovenia and UK (Cho et al., 2009; Conrad et al., 1996; Novak et al., 2009; Rome et al., 2017; Woodburn et al., 2002). The outcome measures evaluated were mainly foot pain and disability, although in some cases cost effectiveness (Rome), blood tests (Soon Cho), plantar pressure and walking ability (Novak) analyses were also performed. Foot pain was measured in all of the studies and disability was measured by Rome, Conrad and Woodburn. The characteristics of the studies included are described in Table 5.

Table 5. Study characteristics

Study	Country	Design	Follow-up period (months)	Sample size	Subject characteristics	Intervention (by study group)	Areas of evaluation	Measurement instruments
Rome et al, 2016 [33]	New Zeland	RCT	4	41 (IG: 20 and CG: 21).	Exclusion: previous ulceration, those with a state of flare. Using foot orthoses or unwilling to change their footwear to accommodate an orthotic	IG had customised foot orthoses and CG had simple insoles.	1. Foot pain 2. Disability 3. Functional limitation 4. Cost-effectiveness	1. FFI 2. The perspective of the NHS
Conrad et al, 1996 [19]	USA	RCT	36	102 (IG: 52 and CG: 50). 88 completed the study (44 in each group)	ARA functional class I or II; radiological changes in feet; active disease; flexible functional discrepancies in their feet that could be controlled by a functional foot orthosis. Exclusion: clinical foot deformities that could cause an apropulsive gait.	IG wore functional foot orthoses and CG placebo orthoses	1. Foot pain 2. Disability	1. Painful foot joint count (JNTCNT8) 2. Total painful joint count (PANTOT8) 3. Foot pain (PAIN8) self-report 4. FFI: • Pain (PTOT1) • Disability (DTOT1) • Activity limitation (FTOT1) 5. Total disability (AIMS): subjective assessment with 12 items.
Cho et al, 2009 [11]	Korea	RCT	6	42 (IG: 22 and CG: 20). 34 completed the study (IG: 18 and CG: 16).	Exclusion: concomitant musculoskeletal disease, central or peripheral nervous system disease, endocrine disorders and severe cognitive impairment. Currently using foot orthoses, rigidly fixed foot deformities, and another medical disease potentially capable of causing foot problems.	IG wore an extra deep forefoot-rockered shoe with a custom-made semi-rigid insole and CG a ready-made simple soft insole. They wore shoe for at least 3 hours a day over six months.	1. Pain 2. Levels in blood	1. foot pain visual analogue scale (VAS) 2. Foot Function Index (FFI) 3. Erythrocyte sedimentation rate 4. C-reactive protein (CRP) 5. Amounts of medications (expressed as numbers of pills, at the time of evaluation) 6. Active joint counts
Wood-burn et al., 2002 [12]	England	RCT	30	98 (IG: 50 and CG: 48).	Valgus heel deformity. Normal range of motions at the joints. Exclusion: Concomitant musculoskeletal disease, central or peripheral nervous system disease, and endocrine disorders. Currently using foot orthoses or inappropriate footwear. Normal daily walking aids were permitted.	IG wore custom manufactured rigid foot orthoses under podiatry supervision. CG received foot orthoses only by prescribed medical care.	1. Foot pain 2. Disability	1. Foot Function Index (FFI) 2. Disease activity 3. Tolerance 4. Adverse reactions
Novak et al., 2009 [15]	Slovenia	RCT	6	40 (IG: 20 and CG: 20).	Community walker, Disease Activity Score 28 ≤ 5.1, intact skin surface of the feet, currently not using foot orthoses and/or orthopaedic shoes. Exclusion: valgus or varus heel deformation >5º, major foot injuries, diabetes, central or peripheral nervous system diseases, musculoskeletal pathology (sciatic pain, disc herniation, lower limb length discrepancy >0.5 cm). Patients whose arthritis worsened during the study were excluded.	IG receives functional foot orthoses and CG wore unshaped material.	1. Plantar pressure 2. Foot pain 3. Walking ability	1. F-scan system. 2. FFI. 3. 6 min walking test.

Risk of bias assessment

The risk of bias in the studies selected is represented in Figs. 5 and 6. Most studies had low quality in the blinding of participants and personnel, and uncertainty in blinding of outcome assessment and attrition bias.

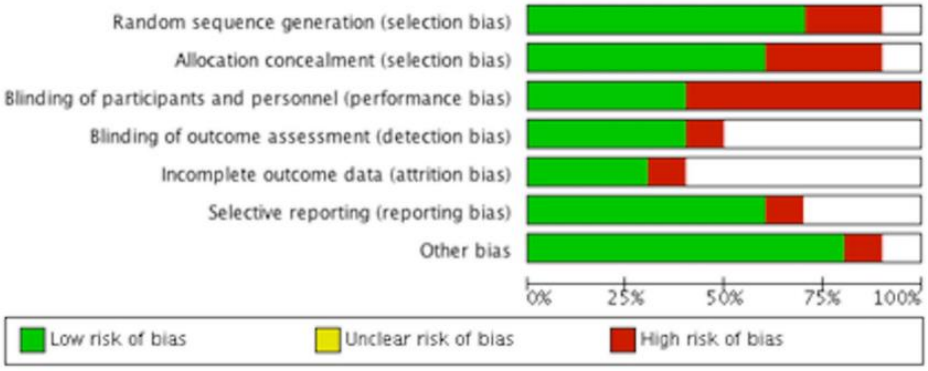

Figure 5. Risk of bias graph

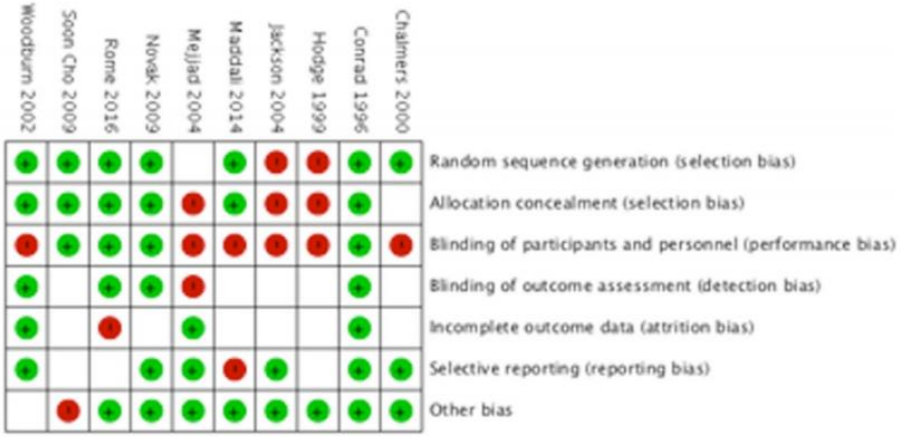

Figure 6. Risk of bias summary

Results by outcome measures

To accurately measure the impact of foot orthoses in terms of pain and disability, we established two types of results: those obtained in long-term and in short-term follow-up, defined as studies with >6 months' follow-up or ≤6 months' follow-up, respectively.

The meta-analyses were based on a calculation of the standardised difference of the means, with a random effects model, because some studies reported primary outcomes obtained by different evaluation or calculation methods.

- Pain

Foot pain was measured in all the studies included. Three of them (Cho, Rome and Novak) were classified as short-term follow-up, and two (Woodburn and Conrad) were classified as long-term follow-up.

Short-term follow-up

Although the three studies in this category reported improved foot pain outcomes in patients with foot orthoses, there were no statistically significant differences between the intervention and control groups. This conclusion was corroborated by our meta-analysis [0.03 (−0.58, 0.65)] (Fig. 7a). Due to the difference between the instruments used to measure foot pain (FFI and VAS), the standardised mean difference (SMD) was calculated.

Long-term follow-up

Although Conrad et al. (Conrad et al., 1996) recorded no significant differences between the groups, Woodburn et al. (Woodburn et al., 2002) did observe significant improvements in foot pain by the end of the follow-up period, although their results corresponded to AUC analyses. We tried to contact the authors to obtain raw data for our meta-analysis but received no response.

Nonetheless, we carried out a meta-analysis with the two studies, adjusting the Woodburn results by inferential extrapolation, calculating the difference of the means and the standard error to adjust the outcome to the confidence intervals reported. However, the results obtained were not statistically significant (Fig. 7b). Both studies used the FFI pain subscale to measure this outcome.

- Disability

Disability was measured in three of the studies, two of which (Conrad and Woodburn) were long term and one was short term (Rome). In all cases, the FFI was used.

Short-term follow-up

Because only one article (Rome) was included in this category, it was not possible to perform a meta-analysis. This paper reported a reduction in foot disability in both the intervention and the control groups, with no statistically significant differences between them [IG: 38.8 (24.2) vs. CG: 44.2 (20.2); P=0.12)].

Long-term follow-up

Although both studies observed reductions in foot disability, in both the intervention and the control groups, the differences between the groups were not significant at the end of follow-up. Nonetheless, a slight difference in this respect was detected in our meta-analysis (Fig. 7c).

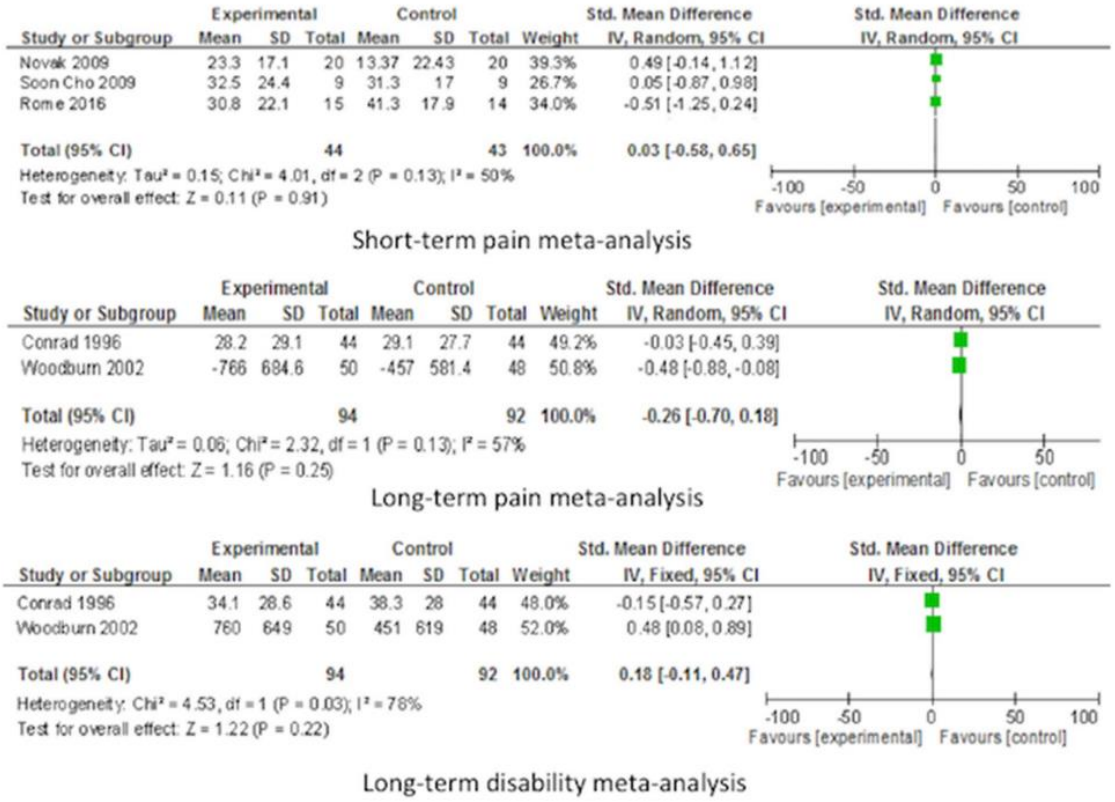

Figure 7. Short-term pain meta-analysis; long-term pain meta-analysis; long-term disability meta-analysis [(Woodburn et al., 2002) results correspond to 'area under curve' analyses]

Optimal information size analyses

We calculated the sample size that each study would have needed to obtain sufficient statistical power (>80%), considering the effect actually achieved in the primary outcome reported, not the initial estimate (Gordon H Guyatt et al., 2011). The recommendation for systematic reviews is that if the optimal information size (OIS) is not obtained, the result is considered imprecise, unless there is a large sample size for that result. If the OIS is met, the analyst should consider whether or not the confidence intervals exclude the desired effect. Table 6 shows that in all cases to obtain a statistical power of 80%, the OIS should exceed 50,000 patients.

Table 6. Optimal information size analysis.

	Mean	SD	*n*	Mean	SD	*n*	SMD	Power	OIS
Pain: short term									
Novak 2009	23.3	17.1	20	13.37	22.43	20	0.49	0.03	52,000
Rome 2016	30.8	22.1	15	41.3	17.9	14	−0.51	0.029	50,000
Soon Cho 2009	32.5	24.4	9	31.3	17.0	9	0.05	0.025	>75,000
Pain: long term									
Woodburn 2002	766.0	684.6	50	457.0	581.4	48	0.48	0.025	>75,000
Conrad 1996	28.2	29.1	44	29.1	27.7	44	−0.03	0.025	>75,000
Disability: long term									
Conrad 1996	34.1	28.6	44	38.3	28.0	44	−0.15	0.027	>75,000
Woodburn 2002	760.0	649.0	50	451.0	619.0	48	0.48	0.025	>75,000

SD standard deviation, *SMD* standard mean difference, *OIS* optimal information size

Discussion

The aim of this review is to determine the effectiveness of foot orthoses as a treatment for a patient with RA.

Our initial hypothesis was that the use of a foot orthosis could reduce disability, by reducing pain and increasing mobility in the foot and ankle of a person presenting this pathology. In view of the many studies related to this study aim, treatment with orthoses might be expected to produce improvements in these areas. However, our analysis of the articles selected for study shows that there are no significant differences, as regards outcomes, between using a foot orthosis and another insole or, indeed, a placebo. Nevertheless, this absence of significant impact could be accounted for by the small sample sizes of the studies in question, or by the limited sensitivity of the FFI questionnaire to detect such differences. On the other hand, it has been reported that the FFI presents more sensitive and validity for patients with RA (Madeley et al., 2012; Muradin & van der Heide, 2016).

To address this question appropriately, we must take into account various factors that influence the likelihood of obtaining a positive result from treatment so that the application of a foot orthosis can be proposed to the patient. In fact, most of the studies considered in our meta-analysis do not adopt the approach needed to certify that treatment with foot orthoses is effective. For example, according to the RevMan analysis, a triple-blind (randomized experiments in which the treatment or intervention is unknown to (a) the research participant, (b) the individual(s) who administer the treatment or intervention, and (c) the individual(s) who assess the outcomes) (Salkind, 2010) study should be performed to ensure that this

treatment is not biased. However, 78% of the studies considered did not do so, applying only single or double blinding, while the remaining 22% did not specify the type of blinding applied.

This same absence of rigour can be observed in many of the studies carried out to date, and so they provide a relatively poor basis on which to recommend foot orthoses treatment to persons with RA.

Not all the results of our analysis were unsatisfactory. Thus, certain areas are addressed correctly by almost all the articles considered, such as including all the clinically relevant data obtained from the patients comprising the study population.

Our analysis shows that the use of foot orthoses did reduce the foot pain suffered by patients with RA, although this effect did not reach the level of statistical significance, according to Mejjad et al. (2003), who analysed walking speed, cadence, step length, cycle duration and swing speed (Mejjad et al., 2004).

In 2014, Gibson et al. corroborated the view that the application of foot orthoses in a patient with RA reduces the foot pain suffered. The results presented in this study were supported by significant statistical evidence; most of the outcomes measured contained a zero, which confirms that this treatment is effective (Gibson et al., 2014). However, Rome et al. (2016) reported no significant difference in the treatment effect, although foot pain and disability were alleviated (Rome et al., 2017). The latter analysis was based on only 16 weeks of data, although any benefits achieved within this period would probably persist for a longer period.

The study by Woodburn et al. (Woodburn et al., 2002), which was among those scoring highest in our analysis, focused on the movement pattern presented by patients with RA, and compared two groups: those treated with foot orthoses and those who did not receive such treatment. The analysis of movement patterns produced surprising results; the application of foot orthoses was found to produce a statistically significant improvement in terms of a reduction in foot pain ($P=0.014$), foot disability ($P=0.016$), and functional limitation ($P=0.344$), and a better function of the whole foot in people with RA. These results are supported by Gibson et al. (Gibson et al., 2014), who studied, rather than movement patterns, the pressure peaks of each foot segment and the areas of contact. They compared higher-cost-, factory-based-, and centralized-manufactured orthoses with low-cost-, in-clinic-, and small-scale-manufactured ones, demonstrating that the higher cost were more effective ($P<0.006$). However, these results were not as statistically significant as those of Woodburn et al. (Woodburn et al., 2002). Although foot pain and disability were significantly alleviated, the

data used by Gibson et al. are complicated to interpret, due to the type of analysis performed and the heterogeneous measures used. Another reason for viewing these findings with caution is that the study design was in effect that of an open-label study, and the changes observed may reflect spontaneous changes in foot health status or merely a placebo effect. Furthermore, the study failed to recruit the desired number of patients and was, therefore, slightly underpowered. In 2009, Novak et al. studied plantar pressures in painful and non-painful joints, the redistribution of plantar pressure that took place and the correlation between foot pain and the application of fitted foot orthoses, in comparison with a control group of patients given unmodified orthoses. The results obtained were disappointing from a statistical standpoint; no major impact was recorded, simply a reduction in pain and a minor redistribution of plantar pressures (Novak et al., 2009).

Conrad et al. studied a group of patients with RA, considering painful joints, foot pain, the Foot Posture Index and disability (Conrad et al., 1996). After a 3-year follow-up of one group of patients given functional posted foot orthoses and another group with placebo orthoses, it was concluded that there were no statistically significant differences between the two groups, possibly due to the age of the participants,

the fact that the subjects of study were older males with a long duration of illness might involve that they would have adapted to their pain because of a long exposure to the disease, or because they might be reluctant to admit that they had pain. Similar results were obtained by Jackson et al., who studied contact areas, pressures and the relationship between pressure and time in the rheumatic foot, finding that only two of the four outcomes presented statistical reliability, and that there was no statistically significant difference (Jackson et al., 2004), significant reductions in mean peak plantar pressures over the central metatarsals were noted when using the insole and dome pad design [12% (33 kPa)] and the insole and bar pad design [21% (58 kPa)] compared with the shoe-only condition.

Cho et al. (Barn et al., 2014) evaluated patients provided with foot orthoses over a follow-up period of 6 months. Analysis of the FFI and the VAS of foot pain, together with an examination of mobile joints and of other outcomes, showed that this treatment produced positive results, although the difference did not reach statistical significance. At the 6-month review, the patients in both the intervention and the control groups had experienced an improvement, compared to the baseline, but there were no significant differences regarding the type of orthosis fitted or the anatomical location of the pathology (Cho et al., 2009).

Finally, the most recent study, conducted by Maddali et al. (Bongi et al., 2014), analysed pain, disability, functional limitation, the distribution of plantar pressures, and gait. In this study, the patients were divided into two groups: group A, initially given non-silicone orthoses which after 30 days were replaced with silicone-filled orthoses; and group B, given silicone-filled orthoses for the first 30 days and then non-silicone orthoses for a further 30 days. At the end of the study period, beneficial results were observed, although without sufficient statistical significance to affirm that this treatment produced an overall improvement for patients suffering from RA in the foot. In both groups, pain and disability were reduced, this effect being stronger in group A during the first 30-day period. However, there was no significant reduction in the functional limitation experienced.

Limitations

The main limitation in the present study is the small sample sizes of the included studies, which could reduce external validity of these results. Moreover, it cannot avoid the limited sensitivity of the FFI questionnaire to detect changes in pain and disability. Finally, another limitation is the difference in the materials used for foot orthoses, and intensity of the intervention (total time of use per day) of these devices among studies.

Future research

Future research should be undertaken with larger sample sizes (RA patients), including different interventions such as custom-made foot orthoses (CAD–CAM (Ki et al., 2008)) or Direct Modelling Technique (Gijon-Nogueron et al., 2013) placebo orthoses, custom-made orthoses with custom-design shoes (Cho et al., 2009) and/or shoes. Additionally, long-term follow-up (24–30 months) should be used to evaluate the effect of different interventions with the use of patient-reported outcome measures such as SEFAS (selfreported foot and ankle score) (Cöster et al., 2014).

Conclusions

Despite the poor methodological quality of most studies considered in this meta-analysis, it can be concluded that foot orthoses alleviate pain and disability in patients with RA. The absence of significant differences between the study groups may be due to the small sample sizes included in these studies. Another explanatory factor might be the insufficient sensitivity of the FFI to detect pain and disability. Further studies, with long-term follow-up, are needed to determine which type of foot orthosis should be provided, or whether conservative treatment is more effective in enhancing disability and reducing pain.

Clinical messages

1. It is a latest systematic review with update research.
2. This review can not determine that Foot Orthosis improve pain respect to RA.
3. Further studies, with long-term follow-up and big size, are needed.

4. SYSTEMATIC REVIEW OF THE PSYCHOMETRIC PROPERTIES OF PATIENT-REPORTED OUTCOME MEASURES FOR RHEUMATOID ARTHRITIS IN THE FOOT AND ANKLE.

Original Article

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Systematic review of the psychometric properties of patient-reported outcome measures for rheumatoid arthritis in the foot and ankle

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Abstract

Objective: To identify self-reported outcome measures specific to the foot and ankle in patients with rheumatoid arthritis and to investigate the methodological quality and psychometric properties of these measures.

Method: A systematic review focusing on patients with rheumatoid arthritis.

Setting: The search was conducted in the PubMed, SCOPUS, CINAHL, PEDro and Google Scholar databases, based on the following inclusion criteria: population (with rheumatoid arthritis) > 18 years; psychometric or clinimetric validation studies of patient-reported outcomes specific to the foot and ankle, in different languages, with no time limit. Two of the present authors independently assessed the quality of the studies located and extracted the relevant data. Terwee's criteria and the COSMIN checklist were employed to ensure adequate methodological quality.

Results: Of the initial 431 studies considered, 14 met the inclusion criteria, representing 7,793 patients (56.8 years). These instruments were grouped into three dimensions (pain, perceived health status and quality of life and disability). The time to complete any of the PROMs varies around 15 minutes. PROMs criterias with the worst scores by COSMIN, 92.85% and 85.71% were criterion validity, measurement error, internal consistency and responsiveness. 28.57% of PROMs were compared with the measurement properties.

Conclusion: the Self-Reported Foot and Ankle Score achieved the highest number of positive criteria (according to Terwee and COSMIN), and is currently the most appropriate for patients with Rheumatoid arthritis.

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SYSTEMATIC REVIEW OF THE PSYCHOMETRIC PROPERTIES OF PATIENT-REPORTED OUTCOME MEASURES FOR RHEUMATOID ARTHRITIS IN THE FOOT AND ANKLE.

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Review registration number: PROSPERO (CRD42018090594).

ABSTRACT

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Keywords: Rheumatoid arthritis, Foot, Ankle, Psychometrics, Methodological quality, Patient-reported outcome measures, Measure.

Introduction

In patients with rheumatoid arthritis, foot pain, joint stiffness, deformity and loss of foot function are the major determinants of problems in foot-health-related quality of life (Simon J. Otter et al., 2010; Oude Voshaar et al., 2011; Riskowski et al., 2011). The consequences of foot problems in rheumatoid arthritis can be measured in a variety of ways, including physical activity (Oude Voshaar et al., 2011), clinical status (Riskowski et al., 2011) and patient-reported outcome measures (Jia et al., 2017). The latter have the specific advantage of being meaningful to the individual patient, reflecting the issues that affect their health and lives. Existing patient-reported outcome measures differ in the foot-health concepts measured, but generally include pain (Budiman-Mak et al., 1991; R. L. Martin & Irrgang, 2007; Terwee et al., 2009; Walmsley et al., 2010), disability (Terwee et al., 2009; Walmsley et al., 2010), function (Bennett et al., 1998), activity limitation (Budiman-Mak et al., 1991), footwear and general foot health (Bennett et al., 1998).

In clinical practice, patient-reported outcome measures support physicians and patients, enabling them to co-create personalised care plans, taking into account patients' preferences and values. For this purpose, robust instruments with good psychometric properties are necessary. Whilst many instruments for the foot and ankle are available (Jia et al., 2017), few are specific to rheumatoid arthritis (R. L. Martin & Irrgang, 2007; Walmsley et al., 2010), and their validation remains unclear. Further evidence is needed to determine how best to summarise and interpret the research data obtained and to determine the conditions that must be met in order to make well-founded recommendations. Furthermore, the evidence derived from research may be specific to the characteristics of the patients involved and rigorous methods are needed to overcome the potential bias associated with the study of human subjects.

The main aims of this review were to identify patient-reported outcome measures specific to the effects of rheumatoid arthritis in the foot and ankle, and to evaluate the methodological quality and psychometric properties of these instruments.

Material and Methods

This systematic review was carried out to assess patient-reported outcome measures used for patients with foot and ankle pathologies associated with rheumatoid arthritis. The review protocol was registered at the International Prospective Register of Systematic Reviews (PROSPERO: CRD 42018090594) prior to the identification of articles and data extraction.

Search strategy

The following databases were searched: PubMed, Scopus, CINAHL, PEDro and Google Scholar from inception until February 2018. All databases were searched again at the first of June 2019. In PubMed, the search was conducted in accordance with the strategy described by Terwee et al. (Terwee et al., 2009) to detect the corresponding psychometric properties: construct search (patient-reported outcomes specific to the foot and ankle); population search (rheumatoid arthritis); instrument search (questionnaires, scales instrument) and measurement properties (filters).

The criteria applied for inclusion in the analysis were as follows:

- Participants: patients with rheumatoid arthritis, aged over 18 years. The studies should be specifically focused on the foot and ankle;
- Studies: psychometric validation studies of patient-reported outcomes, published in English or Spanish;
- Outcomes: psychometric or clinimetric properties based on criteria according to Terwee (content validity; internal consistency; criterion validity; construct validity; reproducibility (agreement and reliability); responsiveness; floor/ceiling effect; interpretability) or COSMIN (structural validity; internal consistency; reliability; measurement error; hypothesis testing for construct validity; cross cultural validity/measurement invariance; criterion validity and responsiveness).

The exclusion criteria were as follows:

- Studies: those based on questionnaires of orthopaedic injuries.

Quality appraisal

The updated COSMIN checklist was used to evaluate the methodological quality of studies investigating the measurement properties of a patient-reported outcome measure (Prinsen et al., 2018). This standard can be used either to assess the methodological quality of a study (Mokkink et al., 2010) or to compare the properties of various measurement instruments in a systematic review (Terwee et al., 2012). The measurement properties considered are divided into three domains: reliability, validity and responsiveness. Each property contains various items, evaluated on a 4-point Likert scale as poor, fair, good or excellent. The “worst score counts” approach was applied to derive a final rating for each patient-reported outcome measure considered (Terwee et al., 2012).

With respect to the psychometric properties proposed by Terwee (Terwee et al., 2007), each issue was rated as positive "+" (adequate description or value or measure or argument related to the psychometric property), negative "-" (inadequate or values below the accepted standards for the psychometric property), indeterminate "?" (doubtful methods or measures or design) or absent "0" (no information available about the psychometric property), except for responsiveness, which was rated only as present/absent.

Study selection

Two blinded reviewers (L.R.P. and P.C.G.) evaluated the search results. The reference lists were reviewed independently to observe fulfilment or otherwise of the inclusion criteria. Disagreements were resolved by discussion between the two evaluators, or if consensus was not possible, further opinion was sought (A.B.O.A., G.G.N., C.N. and J.M.M.A.).

Data extraction

Titles and abstracts were then reviewed independently by two reviewers (P.C.G. and L.R.P.) and relevant articles were then obtained in full text. The same reviewers undertook the second stage of screening by reading the full text of selected articles. The following data were extracted from each study, using a standardised template: full title, country, year of publication, dimensions and number of items, population used for the validation process, psychometric properties (Terwee's criteria with a positive rating), cross-cultural adaptation into the language of each questionnaire included, and methodological quality (according to COSMIN). In studies lacking any of these elements, the authors were contacted to obtain the necessary data. The studies were first grouped into broad themes (according to the items), and then narrowed down into three main categories: pain, perceived health status/quality of life and disability.

No meta-analysis was carried out due to the heterogeneity of the dimensions and outcomes included in these studies.

Results

An initial 431 studies were identified, but 63 were duplicated among the different databases. The remaining 368 were screened against our inclusion/exclusion criteria, using the titles, abstracts and key words. Fifty seven studies met the inclusion criteria. After quality appraisal, a further 43 were excluded, and so 14 studies remained in the final analysis. Figure 8 shows the PRISMA flow diagram for the studies included in the review (Liberati et al., 2009).

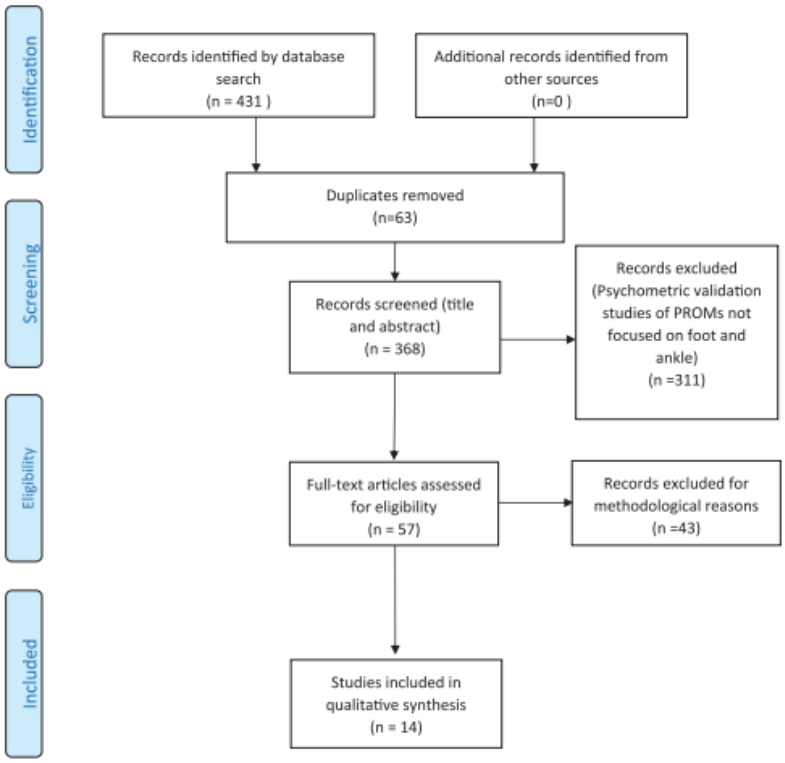

Figure 8. PRISMA flow diagram.

Population

A total of 7,793 participants were included in the 14 studies (61.4% female; 38.6% male, with a mean age of 56.8 years). The classification obtained for each measurement instrument is detailed in Table 7 (Yi et al., 2015).

Table 7. Instruments included.

	Author	**Year**	**Dimensions and items**	**Population used for validation**	**Psychometric properties**	**Cross-cultural adaptation**
FFI (Budiman-Mak et al., 1991) **Foot function Index**	E. Budiman-Mak et al.	1991	3 dimensions: pain, disability and activity restriction 23 items	87 patients with RA 77 males (89%) 10 females (11%) Mean age: 61 years (24-79)	Internal consistency: Cronbach´s alpha 0.96-0.73 (total: 0.9556) Test-retest reliability: (0.87 – 0.69). ICC= 0.87 4 factors: foot pain (1-9) disability (10-18) activity limitation (19-21) social issues (22-23)	8 Brazilian/Portuguese(Yi et al., 2015), Polish (Yi et al., 2015), Korean(Huh et al., 2016), Italian(Martinelli et al., 2014), Taiwan Chinese(Wu et al., 2008), French(Pourtier-Piotte et al., 2015), Spanish (Paez-Moguer et al., 2014), German(Naal et al., 2008)

AOS(Domsic & Saltzman, 1998) **Ankle Osteoarthritis Scale**	R T. Domsic and C L. Saitzman	1998	2 dimensions: pain and disability 18 items	562 patients 264 male (47%) 298 female (53%) Age 20-85 years	Test - retest analysis ICC of 0.97 (0.94-0.99)	1 French(Angers et al., 2016)
FHSQ(Bennett et al., 1998) **Foot Health Status Questionnaire**	P J. Bennett et al.	1998	4 dimensions: foot pain, foot function, footwear, and general foot health 13 items	111 patients 25 males (22.5%) Mean age 45 years 85 females (77.5%) Mean age 57 years	Internal consistency: Cronbach's α between 0.85 and 0.88 Construct validity: 4 factors from 0.0 to 1.0 Reliability: ICC between 0.740 and 0.915	2 Spanish(Cuesta-Vargas et al., 2013),Brazilian(Ferreira et al., 2008)

MFPDI(Garrow et al., 2000) **Manchester Foot Pain Disability Index**	A P. Garrow et al.	1999	2 dimensions: foot pain and disability 19 items	1078 patients 604 males (56%) 474 females (44%) Group 1 (RA) 45 Mean age 53 years (42-65) Group 2 (foot-related problem) 33 Mean age 61 years (41-76) Group 3 (survivor of foot disorders) 1000 Mean age 50 years (37-63)	Internal consistency: Cronbach's α= 0.99 Construct validity: 6.42 - 34.9 % Reliability: kappa values of 0.48, 0.50, and 0.17	3 Danish(Pedersen et al., 2013), Spanish(Gijon-Nogueron et al., 2014), Greek(Kaoulla et al., 2008)

ROFPAQ(Rowan, 2001) **Rowan Foot Pain Assessment Questionnaire**	K. Rowan	2001	3 dimensions: multi-dimensional pain (sensory-discriminative, motivational-affective and cognitive-evaluative). 39 items	17 patients 5 males (29%) 12 females (71%) Mean age 65 years (46-73)	Internal consistency: Cronbach's α between 0.8063 and 0.9030 Criterion validity: Spearman correlations with Headache scale from 0.154 to 0.489 Test-retest reliability: from 0.816 to 0.929	0
PHQ(Macran et al., 2003) **Podiatry Health Questionnaire**	S. Macran et al.	2003	7 dimensions: walking, hygiene, nail care, foot pain, worry/concern, quality of life and PHQ_{vas} 7 items	2073 patients 684 males (33%) 1389 female (67%) Mean age 72 years (18-96)	Criterion validity: Kendal correlation from -0.35 to 0.58 Floor effect: 86% in the nail care dimension	0

RAOS(Macran et al., 2003) **Rheumatoid and Arthritis Outcome Score**	A BI. Bremander et al.	2003	5 dimensions: Pain; other symptoms like stiffness, swelling, and range of motion; activities of Daily Living (ADL); sport and Recreational activities (Sport/Rec); and lower limb-related Quality of Life (QOL). 42 items	119 patients with inflammatory joint disease (51% RA) 32 males (27%) 87 females (73%) Mean age 56 years	Cronbach's alpha: from 0.78 to 0.95 ICC = 0.76 – 0.92 Floor effect: 37%	3 Turkish(Göksel Karatepe, Gürnaydin, et al., 2009) French (Duval et al., 2010) Persian(Negahban et al., 2015)

FAM-AAOS(Johanson et al., 2004) **Foot and Ankle Module of American Academy of Orthopaedic Surgeons**	N A. Johanson et al.	2004	5 dimensions: function, pain, stiffness and swelling, giving way and shoe comfort 25 items	205 patients 111 males (54%) 94 females (46%) Mean age 48 years (21-85) Group 1 (sport/knee diagnosis) n:59 Group 2 (hip and knee diagnosis) 43 Group 3 (foot and ankle diagnosis) n:70	Internal consistency: Cronbach's α between 0.7 and 0.95 Criterion validity: r between 0.49 and 0.95 Reliability: between 0.68 and0.99	1 Spanish(González-Sánchez et al., 2016)

FAAM (R. R. L. Martin et al., 2005) **Foot and Ankle Ability Measure**	R L. Martin et al.	2005	2 dimensions: activities of daily living (ADL) and sports. 21 items	1027 patients 391 males (38.1%) 629 females (61.2%) Gender not reported (0.7%) Mean age 42 years (8-83) Group 1 (Expected to change) 97 males (59.15%) 67 females (40.85%) Mean age 41.2 years Group 2 (Expected to remain stable)	Criterion validity: with SF-36 function subscale (r = 0.84, 0.78), physical component summary score (r = 0.78, 0.80), mental function subscale (r = 0.18, 0.11) and mental component summary score (r = 0.05, −0.02). Construct validity: one factor in Group 1 (80.46% of the variance and an eigenvalue of 16.90). Two factors in Group 2 (first factor 78.37% of the variance and an eigenvalue of 16.46; second factor 12.28% of the variance and an eigenvalue of 2.58)	11 French(Borloz et al., 2011), Japanese(Uematsu et al., 2015), Persian (Mazaheri et al., 2010), German (Nauck & Lohrer, 2011), Italian (Sartorio et al., 2014), Turkish (Çelik et al., 2016), Brazilian (Moreira et al., 2016), Spanish(Cervera-Garvi et al., 2017), Chinese (González-Sánchez et al., 2017), Thai (Arunakul Md et al., 2015) and Dutch(Weel et al., 2016)

				47 males (59.5%) 32 females (40.5%) Mean age 45.2 years	Agreement: minimal detectable change for the ADL subscale ±5.7. For the Sports subscale ±−12.3 points. Minimal clinically important diference for ADL 8 and for Sports subscale 9 points. Test-retest reliability: 4 weeks apart. 0.89 and 0.87 for the ADL and Sports subscales, respectively.	

BFS(Barnett et al., 2005) **Bristol Foot Score**	S. Barnett et al.	2005	5 dimensions: mobility, pain, footwear, foot health and disability, and perception of self as a result of foot problems 15 items	400 patients Pilot study 10 3 males (30%) 7 females (70%) Age 24 to 89 years Version 4 71 23 males (32%) 48 females (68%) Mean age 58 years (13-90)	Internal consistency: Cronbach's α= 0.9036 3 factors: feet pain (50%), footwear and general foot health (10%) and mobility (9%).	1 Spanish(Navarro-Flores et al., 2018)

LFIS(Helliwell et al., 2005) **Leeds Foot Impact Scale**	P. Helliwell et al.	2005	2 dimensions: impairment/shoe and activities/participation 51 items	192 patients with RA (yielded 148) 34 males (23%) 114 females (77%) Mean age 61.7 years (28-89)	Content validity: qualitative pilot study with 30 subjects Reliability: Impairment / shoes subscale ICC of 0.84 (95% CI 0.75–0.90); Activities / participation subscale ICC of 0.96 (95% CI 0.93–0.98).	3 Dutch(Woodburn et al., 2011) German Hungarian(Woodburn et al., 2012)
SAFE(Walmsley et al., 2012) **Salford Rheumatoid Arthritis Foot Evaluation**	S. Walmsley	2012	3 dimensions: impairment, disability and footwear 19 items	28 patients 7 males (25%) 21 females (75%) Mean age 58,5	Content validity: qualitative study Criterion validity: MFPDI 0.83 and LFIS 0.79	0

FAOS(Golightly et al., 2014) **Foot and Ankle Outcome Score**	Y M. Golightly et al.	2014	4 dimensions: pain, activities of daily living (ADL), sport and recreational function (sport/recreation), quality of life (QOL), other symptoms 42 items	1670 patients 541 males (32.4%) 1129 female (67.6%) Mean age 69 years (50-95) Group 1(pain) 1641 Group 2 (ADL) 1609 Group 3 (sport /recreation) 1454 Group 4 (QOL) 1632 Group 5 (other symptoms) 1670	Internal consistency: group 1 Cronbach's α= 0.95 – 0.97; group 2 Cronbach's α= 0.97-0.98; group 3 Cronbach's α= 0.94 – 0.96; group 4 Cronbach's α= 0.89 – 0.92; group 5 Cronbach's α= 0.72 – 0.82 Reliability: ICC=0.63 – 0.81	6 Persian(Vosoughi et al., 2016) Korean(K. M. Lee et al., 2013) Dutch(Van Den Akker-Scheek et al., 2013) German(Van Bergen et al., 2014) Thai(Angthong, 2016) Turkish(Göksel Karatepe, GünaydIn, et al., 2009)

SEFAS(Cöster et al., 2014) **Self-reported Foot and Ankle Score**	M. Cöster et al.	2014	3 dimensions: pain, function, and limitation of function 12 items	224 patients Group 1 (Forefoot disorders): 118 22 males (19%) 96 females (81%) Mean age 57 years (16– 87) Group 2 (midfoot, hindfoot or ankle disorders): 106 47 males (44%) 59 females (56%) Mean age 55 years (18–81)	Internal consistency: group 1 Cronbach's α = 0.84; group 2 Cronbach's α= 0.86, Criterion validity: Spearman rho with FAOS, SF-36, EQ-5D (0.6 – 0.8) Construct validity: 80% of predefined hypotheses confirmed Reliability: group 1 ICC = 0.92; group 2 ICC = 0.93 Floor/ceiling effect: group 1= 0%; group 2= 0%	1 German(Arbab et al., 2017)

RA Rheumatoid Arthritis; *N* number of patients; *ICC* Intraclass correlation coefficient; *ADL* Activities of Daily Living

Dimensions

The dimensions included in the different instruments were grouped as (Table 8):

- Pain (in the foot or ankle);
- Perceived health status and quality of life (overall, lower limb-related or foot-related);
- Disability (concerning activities of daily living, limitation of general function, limitation of sports/recreational function).

The range of dimensions were between two and seven. Four of the patient-reported outcome measures considered (the Ankle Osteoarthritis Scale, the Manchester Foot Pain and Disability Index, the Foot and Ankle Ability Measure and the Leeds Foot Impact Scale) had two dimensions, and one (the Podiatry Health Questionnaire) had seven dimensions.

Table 8. Assessment of the measurement properties of the questionnaires.

		Content validity	Internal consistency	Criterion validity	Construct validity	Reproductibility agreement	Reproductibility reliability	Responsiveness	Floor/ceiling effect	Interpretability	Final assessment
Pain	AOS	+	0	−	?	0	+	0	0	0	
	MFPDI[70]	+	−	?	−	?	−	0	0	0	
	ROFPAQ	+	+	+	−	0	+	0	0	0	
	SEFAS	+	+	−	+	?	+	?	+	?	V
Perceived health status and quality of life	FHSQ	+	+	?	+	0	+	0	0	?	V
	PHQ	+	0	−	0	0	0	0	−	?	
	BFS	+	+	?	−	?	?	?	0	?	
	FAOS	+	−	?	?	?	−	0	0	?	
Disability	FFI	+	+	0	?	0	−	?	0	?	
	RAOS	+	+	?	0	0	+	0	−	?	V
	FAAM	+	?	−	−	−	+	+	0	0	
	FAM AAOS	+	+	−	0	0	−	0	0	?	
	LFIS	+	0	?	0	0	+	0	?	?	
	SAFE	+	0	+	0	?	+	0	?	?	

Pain: AOS: Ankle Osteoarthritis Scale; MFPDI Manchester Foot Pain Disability Index; ROFPAQ: Rowan Foot Pain Assessment Questionnaire; SEFAS: Self-Reported Foot and Ankle Score.
Perceived Health Status and Quality of Life: FHSQ: Foot Health Status Questionnaire; PHQ: Podiatry Health Questionnaire; BFS: Bristol Foot Score; FAOS: Foot and Ankle Outcome Score.
Disability: FFI: Foot Function Index; RAOS: Rheumatoid and Arthritis Outcome Score; FAAM: Foot and Ankle Ability Measure; FAM-AAOS: Foot and Ankle Module of American Academy of Orthopaedic Surgeons; LFIS: Leeds Foot Impact Scale; SAFE: Salford Rheumatoid Arthritis Foot Evaluation.
Rating: +: positive; ?: indeterminate; −: negative; 0: no information available.

Structure

The shortest patient-reported outcome measure (the Podiatry Health Questionnaire) had seven items, and the longest (the Leeds Foot Impact Scale) had 51.

Psychometric properties

The psychometric properties of each patient-reported outcome measure are summarised in Tables 7 and 8, following Terwee's criteria. The Self-reported Foot and Ankle Score, included in the pain group, presented the best overall psychometric properties, with positive evidence for content validity (clear description of measurement aim, target population, item selection and reduction), internal consistency (Cronbach's alpha 0.70-0.95), construct validity (evidence from factor analysis to

confirm the study hypotheses), reproducibility/reliability (ICC>0.7), floor/ceiling effect (only described for the Self-reported Foot and Ankle Score (0%)). On the other hand, the evidence was indeterminate for three criteria (reproducibility: agreement, responsiveness and interpretability) and negative for one (criterion validity).

In the perceived health status/quality of life group, there was positive evidence for the Foot Health Status Questionnaire on four criteria: content validity, internal consistency, construct validity and reproducibility: reliability.

In the disability group, there was positive evidence for the Rheumatoid and Arthritis Outcome Score on three criteria: content validity, internal consistency and reproducibility/reliability.

With respect to criterion validity; reproducibility: agreement, responsiveness and interpretability, positive ratings were obtained in very few cases; most of the patient-reported outcome measures considered obtained an indeterminate or absent rating.

Cross-Cultural Adaptation

Neither the Rowan Foot Pain Assessment Questionnaire, the Podiatry Health Questionnaire nor the Salford Rheumatoid Arthritis Foot Evaluation considered the question of cross-cultural adaptation. The other patient-reported outcome measures had been translated or culturally adapted into diverse languages, including Arabic, Somali, Thai, Danish, Spanish, Hungarian, Polish and Greek. In this respect, the Foot and Ankle Ability Measure was the most widely adapted, being translated into eleven languages (French, Japanese, Persian, German, Italian, Turkish, Brazilian, Spanish, Chinese, Thai and Dutch).

Methodological Quality

The Self-reported Foot and Ankle Score and the Foot and Ankle Ability Measure were assessed by the COSMIN criteria for methodological quality (Table 9). The first of these patient-reported outcome measures had a positive rating for reliability, hypothesis testing for construct validity and responsiveness, a negative one for structural validity and criterion validity, and indeterminate ratings for internal consistency, measurement error and cross-cultural validity/measurement invariance. The second had a positive rating for reliability, measurement error and responsiveness, a negative one for structural validity, hypothesis testing for construct validity and criterion validity, and indeterminate ratings for internal consistency and cross-cultural validity/measurement invariance. Overall, both presented poor methodological quality.

Table 9. COSMIN rating

	Structural validity	Internal consistency	Reliability	Measurement error	Hypothesis testing for construct validity	Cross-cultural validity/Measurement invariance	Criterion validity	Responsiveness
FFI	+	+	−	?	?	?	?	?
AOS	−	?	+	?	?	?	−	?
FHSQ	−	?	+	?	−	−	?	−
MFPDI	−	?	−	?	?	−	?	?
ROFPAQ	−	?	+	?	?	?	−	?
PHQ	−	?	?	?	?	?	−	?
RAOS	−	?	+	?	?	?	−	?
FAM AAOS	−	?	−	?	?	?	−	?
FAAM	−	?	+	+	−	?	−	+
BFS	+	+	−	?	?	?	?	?
LFIS	−	?	+	?	?	−	?	?
SAFE	−	?	+	?	−	?	+	−
SEFAS	−	?	+	?	+	?	−	+
FAOS	−	?	−	?	?	−	?	?

Rating: '+': positive; '?': indeterminate; '–': negative.
FFI: Foot Function Index; AOS: Ankle Osteoarthritis Scale; FHSQ: Foot Health Status Questionnaire; MFPDI: Manchester Foot Pain Disability Index; ROFPAQ: Rowan Foot Pain Assessment Questionnaire; PHQ: Podiatry Health Questionnaire; RAOS: Rheumatoid and Arthritis Outcome Score; FAM-AAOS: Foot and Ankle Module of American Academy of Orthopaedic Surgeons; FAAM: Foot and Ankle Ability Measures; BFS: Bristol Foot Score; LFIS: Leeds Foot Impact Scale; SAFE: Salford Rheumatoid Arthritis Foot Evaluation; SEFAS: Self-Reported Foot and Ankle Score; FAOS: Foot and Ankle Outcome Score.

For the following properties, the other patient-reported outcome measures had few positive ratings, often presenting missing or unknown data: internal consistency (Cronbach's alpha not determined or dimensionality unknown), measurement error (patient-reported outcome measures not defined by minimally-important change), hypothesis testing (hypothesis not defined or results conflicting with the hypothesis), cross-cultural/measurement invariance (no important differences found between group factor or differential item functioning), criterion validity or responsiveness (no hypothesis defined, results conflicting with the hypothesis or area under the curve <0.70)

- *Methodological quality according to measurement properties*

In addition to the above, we evaluated the methodological quality of the best-rated patient-reported outcome measures, using COSMIN boxes to classify their quality as poor, fair, good or excellent. These details are shown in Table 10. In this respect, only the Foot Health Status Questionnaire, the Foot and Ankle Ability Measure, Salford Rheumatoid Arthritis Foot Evaluation and the Self-reported Foot and Ankle Score achieved a positive score according to COSMIN. In the context of the low overall score, the Foot and Ankle Ability Measure was rated highest, with excellent ratings for content validity, structural validity and criterion validity. None of these patient-reported outcome measures were evaluated for cross-cultural validity as the inclusion criteria limited the studies considered to those focusing on rheumatoid arthritis.

Table 10. Methodological quality per PROM property (COSMIN)[a].

	BOX A Internal consistency	BOX B reliability	BOX C Measurement error	BOX D Content validity	BOX E Structural validity	BOX F Hypothesis testing	BOX G Cross-cultural validity	BOX H Criterion validity	BOX I Responsiveness
FHSQ	Fair	Poor	Fair	Poor	Poor	Poor	–	Poor	Poor
FAAM	Poor	Poor	Good	Excellent	Excellent	Good	–	Excellent	Fair
SAFE	Poor	Poor	Poor	Excellent	Poor	Poor	–	Poor	Poor
SEFAS	Poor	Poor	Poor	Excellent	Poor	Fair	–	Poor	Poor

FHSQ: Foot Health Status Questionnaire; FAAM: Foot and Ankle Ability Measures; SAFE: Salford Rheumatoid Arthritis Foot Evaluation; SEFAS: Self-Reported Foot and Ankle Score.
[a]COSMIN checklist can be used to assess the quality of a study on one measurement instrument or to compare the measurement properties of a number of measurement instruments in a systematic review.

Discussion

The objective of this systematic review was to identify patient-reported outcome measures concerning the effects of rheumatoid arthritis on the foot and ankle, and to evaluate the methodological quality and psychometric properties of these measures. The Self-Reported Foot and Ankle Score presented the best overall psychometric properties and methodological quality. With respect to psychometric properties, the Self-Reported Foot and Ankle Score (Cöster et al., 2014) obtained the highest number of positive criteria, although it presented deficiencies in criterion validity, agreement, responsiveness and interpretability. This patient-reported outcome measure is relatively new and to date only one cross-cultural adaptation (into German) has been made (Arbab et al., 2017).

The patient-reported outcome measures analysed in this review had two to seven dimensions and were further categorised into three areas: pain, perceived health status and quality of life and disability, according to their main components. Similar categorisations have been performed by Jia et al. (Jia et al., 2017) and Oude Voshaar et al. (Oude Voshaar et al., 2011), both of whom combined patient-reported outcome measures with scales and other instruments measuring foot function, pain or foot-related disability.

Most of the patient-reported outcome measures analysed have been culturally adapted for use in other languages. Such transcultural adaptations are important, enabling health professionals in different societies and countries to have the same perspective and to obtain comparable data for patients with rheumatoid arthritis. On the other hand, if it is to be valid, any such cross-cultural adaptation must be performed with scientific rigour.

Most of the patient-reported outcome measures considered presented deficiencies regarding construct validity, responsiveness, floor/ceiling effect and interpretability. It is important to highlight these shortcomings, as they may have significant consequences in clinical and research contexts. Construct validation is an on-going process of learning, prediction and testing (Bandura, 1991). If it is not performed appropriately, the resulting conclusions on assisting patients in the development of self-management skills will be unreliable and discounted.

Another important question is that of the floor/ceiling effect. This parameter helps identify any redundant items it may include. Obviously, if a patient-reported outcome measure did not provide information about what (change in) score would be clinically meaningful, it would have little practical or theoretical value.

The study presents certain limitations. Importantly, some instruments were excluded from our analysis, namely, the Oxford Ankle Foot Questionnaire for Children (C. Morris et al., 2008) and the Juvenile Arthritis Foot Disability Index (André et al., 2004), due to our focus on patients aged over 18 years, therefore, our findings could only be related to adult rheumatoid arthritis population. Another limitation was the fact that some data were incomplete, despite our efforts to contact the original authors. Among its strengths, this study was based on a literature search of five medical databases, with a well-defined search strategy and no limitation on time. Moreover, all the studies included had been clinimetrically validated. The review we describe was based on a blinded quality appraisal following a well-established method, the COSMIN checklist.

The clinical implications of these results point out the gap regarding the dimension of self-care, prevention or treatment adherence specifically with respect to the foot and ankle. This issue is of major importance to patients with rheumatoid arthritis, as its impact on the foot and ankle often limits or prevents the activities of daily life. Instruments with these dimensions should be available for patients and clinicians.

On the other hand, the scarcity of responsiveness evaluation for most of the instruments implies a major shortfall for clinical practice. The criterion of responsiveness is of crucial importance, revealing the clinically important changes that must be observed and helping clinicians and patients monitor the condition. Moreover, this issue may jeopardize the outcome evaluation in longitudinal research.

Future research should address the structure of the questionnaires considered; the number of items varied widely among the patient-reported outcome measures, and response options were also heterogeneous, with some offering a simple yes/no choice, while others measured outcomes on a Likert-type scale. In future research, it would be useful to examine whether the number of items and

the response options provided correctly discriminate the interventions performed, the health status of the patients and the follow up procedures employed.

Clinical messages

1. On available evidence, the *Self-Reported Foot and Ankle Score* is currently the most appropriate patient-reported outcome measure available for patients with rheumatoid arthritis.
2. The most of patient-reported outcome measures have poor evidence of their psychometric properties and should be used with caution for patients with rheumatoid arthritis.
3. Robust methods should be designed and implemented to get higher quality instruments for patients with rheumatoid arthritis.

5. SYSTEMATIC REVIEW OF MEASUREMENT INSTRUMENTS FOR PATIENTS WITH JUVENILE IDIOPATHIC ARTHRITIS IN THE FOOT AND ANKLE.

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REVIEW

Systematic review of measurement instruments for patients with juvenile idiopathic arthritis in the foot and ankle

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ABSTRACT

INTRODUCTION: Juvenile idiopathic arthritis (JIA) is the most common rheumatic disease in childhood. The part of the body most commonly affected, and where cysts are most likely to form, is in the small joints of the foot. The aim of this review was to identify self-reported outcome measures specific to the foot and ankle in patients with JIA and to investigate the methodological quality and psychometric properties of these measures.

EVIDENCE ACQUISITION: A search was conducted for JIA in the PubMed, SCOPUS, CINAHL, PEDro and Google Scholar databases. The systematic review performed was based on the following inclusion criteria: population (with JIA) aged under 16 years; validation studies of patient-reported outcomes specific to the foot and ankle, in various languages, with no time limit. Two authors independently evaluated and assessed the quality of the studies, and extracted data using Terwee's criteria and the COSMIN checklist. No meta-analysis was carried out, due to the heterogeneity of the dimensions and outcomes included in each study.

EVIDENCE SYNTHESIS: Of the initial 67 studies considered, only five met the inclusion criteria for this review. Many of these studies presented significant methodological flaws, in areas such as construct validity, responsiveness, floor/ceiling effect and interpretability.

CONCLUSIONS: Despite the very low quality of the available evidence, the Italian-language adaptation of the Oxford Ankle Foot Questionnaire presents acceptable methodological quality. However, further studies, with greater methodological rigor, are required. A review of psychometric properties and methodological quality of evidence for each Patient Reported Outcome Measures specific for the foot and ankle affected by juvenile idiopathic arthritis is provided.

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KEY WORDS: Arthritis, juvenile; Foot; Ankle; Psychometrics; Patient reported outcome measures.

Introduction

Children's lives can be affected by a variety of foot and ankle problems. These include benign postural deformities, structural problems due or secondary to congenital conditions, acquired or inflammatory conditions, and trauma. Foot and ankle problems are common in pediatric orthopedics and rheumatology.[1]

Juvenile idiopathic arthritis (JIA) is the most common rheumatic disease in childhood, and its main consequences are sinovitis, pain, stiffness, deformity, growth disturbance and fatigue.[2] The International League of Associations for Rheumatology has identified seven subgroups of JIA.[3] Active JIA of any type may cause premature epiphyseal closure and subsequent local growth defects, typically of the knee.[4]

The part of the body most commonly affected by JIA, and where cysts are most likely to form, is in the small joints of the foot. The condition is also observed in the hip, knee and small joints of the hands.[5] The main consequences in the foot are inflammation (which may affect all the joints), limitation of motion and abnormal alignment. The most common abnormal alignments are valgus foot, cavovarus foot and varus heel position.[6] Children with JIA may

SYSTEMATIC REVIEW OF MEASUREMENT INSTRUMENTS FOR PATIENTS WITH JUVENILE IDIOPATHIC ARTHRITIS IN THE FOOT AND ANKLE

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Ethical approval: This systematic review is based on an analysis of anonymised information obtained from the PROSPERO database, and hence no ethical approval is required.

ABSTRACT

Introduction: Juvenile idiopathic arthritis (JIA) is the most common rheumatic disease in childhood. The part of the body most commonly affected, and where cysts are most likely to form, is in the small joints of the foot. The aim of this review is to identify self-reported outcome measures specific to the foot and ankle in patients with JIA and to investigate the methodological quality and psychometric properties of these measures.

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Conclusions: Despite the very low quality of the available evidence, the Italian-language adaptation of the Oxford Ankle Foot Questionnaire presents acceptable methodological quality. However, further studies, with greater methodological rigour, are required. A review of psycho- metric properties and methodological quality of evidence for each Patient Reported Outcome Measures specific for the foot and ankle affected by juvenile idiopathic arthritis is provided.

Key words: Arthritis, juvenile; Foot; Ankle; Psychometrics; Patient reported outcome measures.

Introduction

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Juvenile idiopathic arthritis (JIA) is the most common rheumatic disease in childhood, and its main consequences are sinovitis, pain, stiffness, deformity, growth disturbance and fatigue (Del Giudice et al., 2017). The International League of Associations for Rheumatology has identified seven subgroups of JIA (Petty et al., 2004). Active JIA of any type may cause premature epiphyseal closure and subsequent local growth defects, typically of the knee (Packham & Hall, 2002).

The part of the body most commonly affected by JIA, and where cysts are most likely to form, is in the small joints of the foot. The condition is also observed in the hip, knee and small joints of the hands (Spraul & Koenning, 1994). The main consequences in the foot are inflammation (which may affect all the joints), limitation of motion and abnormal alignment. The most common abnormal alignments are valgus foot, cavovarus foot and varus heel position (Truckenbrodt et al., 1994). Children with JIA may also present with enthesitis in the plantar fascia or Achilles tendon, flexion contractures, synovitis or muscle atrophy (Ravelli & Martini, 2006).

Although some patient-reported outcome measures (PROMs) have been developed to assess the consequences of JIA in the foot and ankle, such as disability or loss of function (Hunt et al., 2013), the majority have been developed for adult patients and have not been shown to be valid and reliable for use with children (R. L. Martin & Irrgang, 2007). The social context of children's lives differs from that of adults because of their dependence on their family, the relative importance of friends, experiences of school and play, and their aspirations for the future. These assessments do not capture the patients' perspectives and may not accurately reflect how children function in their usual environments, which puts children at risk of undergoing ineffective treatments and potentially wasting health service and family resources (Christopher Morris et al., 2010).

PROMs have become established as credible and useful instruments to evaluate the effectiveness of interventions both in research and as routine quality indicators. Criteria for assessing the utility of PROMs for a particular application are the appropriateness, reliability, validity, responsiveness, precision, interpretability, acceptability, and feasibility. Instruments must be shown to be valid for the population with whom they are to be used, and children pose a special case (Fitzpatrick et al., 1998).

The present review has two main aims: 1) to identify specific PROMs for children and adolescents with JIA in the foot and ankle; 2) to assess the methodological quality and psychometric properties of these instruments.

Evidence acquisition

Ethical approval:

This systematic review is based on an analysis of anonymised information obtained from the PROSPERO database, and hence no ethical approval is required.

Design

A systematic review was carried out to identify PROMs specific to the foot and ankle for patients with JIA and to assess the methodological quality and psychometric properties of these instruments.

Search strategy

The following databases were consulted: PubMed, Scopus, CINAHL, PEDro and Google Scholar. The only time limit imposed was that of the cut-off date, December 2018. Into PubMed database, the search strategy took into account the psychometric properties described by Terwee et al. (Terwee et al., 2009), namely construct search (patient-reported outcomes specific to the foot and ankle), population search (juvenile idiopathic arthritis), instrument search (questionnaires, scales and tests) and measurement properties, filters and criteria for exclusion.

The following search terms were used, together with the operators “OR” and “AND”: Juvenile idiopathic arthritis, patient-reported outcomes, foot, feet, ankle (Appendix A).

Inclusion criteria

- Types of participant: patients with JIA, aged under 16 years. The studies should be specifically focused on the foot and ankle
- Types of study: validation studies on patient-reported outcomes, whether original studies or cross-cultural adaptations.
- Types of outcome: psychometric or clinimetric properties based on Terwee criteria (content validity; internal consistency; criterion validity; construct validity; reproducibility: agreement, reliability; responsiveness; floor/ceiling effect; interpretability) or COSMIN criteria (structural validity; internal consistency; reliability; measurement error; hypothesis

testing for construct validity; cross cultural validity/measurement invariance; criterion validity and responsiveness).

Those using questionnaires without evidence supporting their validity or reliability, parent/patient-reported outcome measures and studies published in languages other than English or Spanish (the versions of the instrument could be published in the native language of the adapted version, but the paper should be in one of these two languages) were excluded.

Quality appraisal

The updated COSMIN checklist was used to evaluate the methodological quality of the studies undertaken to investigate the measurement properties of one or more PROMs (Prinsen et al., 2018). This standard can be used to assess methodological quality (Mokkink et al., 2010) and/or to compare the properties of various measurement instruments in a systematic review (Terwee et al., 2012). In our review, each of the properties observed was rated as sufficient ('+'), insufficient ('-') or indeterminate ('?').

We also applied Terwee's psychometric properties (Terwee et al., 2007) with respect to content validity, internal consistency, criterion validity, construct validity, reproducibility (agreement and reliability), responsiveness, floor/ceiling effects and interpretability. Each issue was rated as positive '+' (adequate description or value or measure or argument related to psychometric property), negative '-' (inadequate or values under the accepted standards in each psychometric property), indeterminate '?' (doubtful methods or measures or design) or absent '0' (no information available about a psychometric property), except for responsiveness, which was rated only as present/absent.

Study selection

All studies identified were screened using the eligibility criteria listed previously. The first stage, two blinded reviewers evaluated the title and abstracts. The same reviewers undertook the second stage of screening by reading the full text of selected articles. Disagreements were resolved by discussion between the two evaluators, or if consensus was not possible, further opinions were sought. If disagreements were not resolved successfully by the third and fourth reviewers, the intention was to contact the original authors of the paper in question, but in practice this measure was never required.

Data extraction

For each paper obtained, the Abstract was reviewed independently by two reviewers. Relevant articles were then obtained in full text. If any information was missing or uncertain, the study authors were contacted. The risk of bias, in each case, was rated independently by two reviewers.

The following parameters were extracted from each study using a standardised template: full title, author, country, year of publication, psychometric properties by Terwee´s criteria with a positive rating, and methodological quality by COSMIN.

No meta-analysis was carried out, due to the heterogeneity of the dimensions and outcomes included in each study.

Evidence synthesis

Application of the above search strategy produced an initial total of 67 studies, of which 46 were duplicated in the databases. After applying the inclusion/exclusion criteria and from reading the title and abstract, 16 were eliminated, leaving five studies for the final analysis. The flow of the process for study selection was based on the PRISMA statement for systematic reviews (Liberati et al., 2009) (Figure 9).

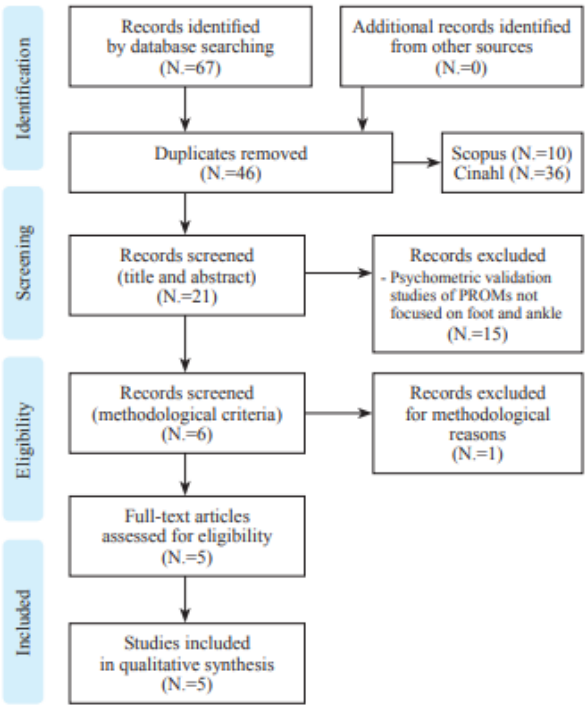

Figure 9. PRISMA flow diagram.

Domains

The PROMs included in this review are summarised in Table 11 (Burger et al., 2017; Martinelli et al., 2016; Martinkevich et al., 2015; C. Morris et al., 2008; Woo et al., 2004). They are composed of two original questionnaires: the Oxford Ankle and Foot Questionnaire for children (OAFQ) and the Juvenile Arthritis Foot Disability Index (JAFI).

These PROMs present a similar structure in terms of domains, but not in relation to the number of items contained. Fundamentally, they both focus on three domains: for the OAFQ, Physical, School and Play, and Emotional (15items. Each of the included statements are answered using a 5-point Likert: Never, Rarely, Sometimes, Very often and Always. It is graded in the opposite direction from the JAFI, from never (4) to always (0), so that a high score represents minimal impact); for the JAFI, Impairment, Activity Limitation and Participation Restriction (27items. Also using a Likert scale graded from Never, Occasionally, Sometimes, Frequently, Always and score from 0 to 4 respectively so that a high score represents marked impact).

The OAFQ has been culturally adapted into three different languages, but none of these adaptations incorporates a structure analysis (factor analysis) to group the items.

Table 11. Characteristic of included studies.

Acronym	Full title	Country	Year of Publication
JAFI (Woo et al., 2004)	Juvenile Arthritis Foot Disability Index	Sweden	2014
OAFQ (C. Morris et al., 2008)	Oxford ankle foot questionnaire	UK	2008
OAFQ Danish (Martinkevich et al., 2015)	Oxford ankle foot questionnaire in Danish	Denmark	2015
OAFQ Italian (Martinelli et al., 2016)	Oxford ankle foot questionnaire in Italian	Italy	2016
OAFQ Dutch (Burger et al., 2017)	Oxford ankle foot questionnaire in Dutch	Netherland	2017

Population

In the development and validation of the original questionnaires, OAFQ included 158 participants, all children and adolescents with JIA. JAFI included a smaller sample of participants, with only 73 children and adolescents, of whom 29 were healthy.

The transcultural adaptations of OAFQ (into Italian, Dutch and Danish) were obtained with respect to a total sample of 207 children/adolescents (48.79% girls and 51.20% boys), aged from 5 to 16 years.

Psychometric properties

The psychometric properties of the studies were rated in accordance with Terwee´s criteria, which are summarised in Table 12.

All the PROMs were rated positively for content validity, providing a clear description of measurement aim, target population, item selection and reduction. However, the score obtained for the other items was '-', '?' or '0', reflecting either an information deficit or the fact that the analysis required was not performed correctly. It is especially striking that in the criterion corresponding to Interpretability, all the studies obtained a rating of '?'.

According to the OAFQ Italian version, Reproducibility and Reliability have been assessed using Intraclass Correlation Coefficient (ICC), and they have come back with scores higher than 0.70 (0.87-0.99), reaching a positive score, which the original questionnaire does not achieve, because it does not use neither ICC nor Kappa.

In Responsiveness section of OAFQ Dutch version, some time comparations at 2 weeks and 4-6 weeks have been done, and any significative change has been shown. The hypothesis is confirmed; therefore, it achieves a positive score. On the contrary, in the original version of OAFQ, a time comparations at 2 weeks has been done, without any specification in term of changes or not, and the hypothesis is not confirmed.

Table 12. Assessment of the measurement properties of the questionnaires.

	Content validity	Internal consistency	Criterion validity	Construct validity	Reproducibil-ity agreement	Reproducibil-ity reliability	Respon-siveness	Floor and ceiling effects	Interpretability
JAFI	+	0	?	?	0	-	?	+	?
OAFQ	+	?	-	-	?	?	?	0	?
OAFQ Danish	+	-	-	?	-	-	-	-	?
OAFQ Italian	+	+	-	?	?	+	?	-	?
OAFQ Dutch	+	-	-	?	-	-	+	0	?

Rating: + Positive; ? Indeterminate; - Negative; 0 No information available.

Methodological quality

The methodological quality of the studies examined was assessed according to the COSMIN criteria. Among the PROMs analysed, the transcultural adaptation into Italian of the OAFQ questionnaire obtained a '+' score in more criteria than any other version. Table 13 details each of the items analysed, showing the rating awarded in each case.

Most of the PROMs analysed obtained a '+' score in the criteria corresponding to Hypothesis testing for construct validity and responsiveness. For the Measurement error criterion, on the other hand, all were rated as '?', since none of them defined the minimal important change parameter.

Table 13. COSMIN rating

	Structural validity	Internal consistency	Reliability	Measurement error	Hypotheses testing for construct validity	Cross-cultural validity	Criterion validity	Responsiveness
JAFI	-	?	-	?	+	+	?	+
OAFQ	?	?	?	?	-	?	-	-
OAFQ Danish	-	-	-	?	+	+	-	+
OAFQ Italian	-	+	+	?	+	-	-	+
OAFQ Dutch	-	-	-	?	+	+	-	+

Rating: + Positive; ? Indeterminate; - Negative.

Discussion

This systematic review has two main aims: first, to identify the PROMs specific to the foot and ankle in children and adolescents with JIA. Second, to analyse the psychometric properties and methodological quality provided by each of these instruments.

Only two original PROMs were identified: JAFI (Woo et al., 2004) and OAFQ (C. Morris et al., 2008), although three transcultural adaptations have been made of the latter, into Danish (Martinkevich et al., 2015), Italian (Martinelli et al., 2016) and Dutch (Burger et al., 2017). These questionnaires are all self-administered, and specifically designed for children and adolescents between the ages of 5 and 16 years, presenting JIA affecting the foot and/or ankle.

The PROMs analysed all contain three dimensions, although different denominations are used. However, there is no dimension referring to adherence to treatment, or concerning self-care of the foot and ankle and the prevention of JIA-related symptoms. Nevertheless, these areas of attention play an important role in alleviating functional limitations in daily life. Even, it could be able to provide information on how the child feels it makes a difference not only from a functional perspective, but also emotionally and socially(Burger et al., 2017). Therefore, in future research it would be advisable to take into account this perspective, especially with regard to children and adolescents. It would also be helpful for clinicians to identify the evolution and control of the disease, and to consider the most appropriate treatment option. Regarding the structure of the questionnaires, the response modes differ considerably, but this is not the case for the number of items within each one. None of the transcultural adaptations of the OAFQ incorporate a confirmatory factor analysis, and so there were no variations in the number of items within this instrument.

Most of the PROMs considered presented deficiencies regarding criterion validity, construct validity, responsiveness, floor/ceiling effect and interpretability. It is important to highlight these shortcomings, as they may have significant consequences in clinical and research contexts. Construct validation is an on-going process of learning, prediction and testing (Bandura, 1991). If it is not performed appropriately, the resulting conclusions on assisting patients in the development of self-management skills will be unreliable and should be discounted. The criterion of responsiveness is of crucial importance in clinical practice, revealing the clinically important changes that must be observed and helping physicians and patients monitor the condition. In research, it is important to design and conduct longitudinal studies so that changes can be evidenced, and treatment effectiveness optimised.

Another important question is that of the floor/ceiling effect. In performing a cross-cultural adaptation, this parameter helps identify any redundant items included. Obviously, if a PROM does not provide information about what (change in) score would be clinically meaningful, it has little practical or theoretical value.

At the generic level, there exist a large number of PROMs that can help assess the patient's clinical state of health or quality of life or detect important clinical changes (Oude Voshaar et al., 2011). Specific systematic reviews of PROMs for the foot and ankle have been performed, for example by Ortega-Avila et al. (A. Ortega-Avila et al., 2019), which included all the PROMs specific to the foot and ankle for patients with diabetes and Rheumatoid (A. B. Ortega-Avila et al., 2019). In another review, Jia et al. (Jia et al., 2017) included all the PROMs specific to the foot and ankle, but without specifying a specific pathology. In both cases, all the PROMs considered had been developed for use with an adult population, and therefore were not very suitable for children/adolescents, failing to reflect the interrelation of these patients with their environment. To our knowledge, the systematic review we present is the first to be carried out to identify PROMs to the foot and ankle in children/adolescents with JIA, and to determine the psychometric properties and methodological quality of these instruments.

Strengths and limitations of the study

The main strength of this study is the rigorous method applied to the systematic review, which included a blinded peer-review of quality appraisal using a standard method, COSMIN, and an exhaustive process for locating studies and versions of the instrument (this study was based on a literature search of five medical databases, with a well-defined search strategy and no limitation on time. Moreover, all the studies included had been clinimetrically validated). On the other hand, our

review also has certain limitations, due to the incompleteness of some of the data obtained, despite our attempts to contact the original authors and we only analysed PROMs in child/adolescent and not parent/patient report outcome measures.

We recommend that PROMs that present poor evidence of their psychometric properties should be used with caution. Future studies with robust methods should be developed to examine these lower-quality versions

Conclusions

Within the generally low methodological quality of the studies examined in this review, the Italian-language version of the Oxford Ankle Foot Questionnaire for children provides acceptable psychometric properties and methodological quality, according to the COSMIN criteria.

Key messages

4. Juvenile idiopathic arthritis is the most common rheumatic disease in childhood
5. A review of psychometric properties and methodological quality of evidence for each Patient Reported Outcome Measures specific for the foot and ankle affected by juvenile idiopathic arthritis is provided.
6. Based on available evidence, the Oxford Ankle Foot Questionnaire- Italian Language is the most appropriate Patient Reported Outcome Measures.

Appendix A. Searching Strategy

1	Juvenil Idiopathic Arthritis
2	Foot
3	Feet
4	Ankle
5	Ankle join
6	Lower extremity
7	Bones of lower extremity
8	2 OR 3 OR 4 OR 5 OR 6 OR 7
9	1 AND (2 OR 3 OR 4 OR 5 OR 6 OR 7)
10	Patient Reported Outcome Measures
11	Self-reported
12	Questionnaire
13	10 OR 11 OR 12
14	9 AND 13
15	Pain
16	Disab*
17	Funct*
18	15 OR 16 OR 17
19	14 AND 19

6. FOOT ORTHOSES FOR PEOPLE WITH RHEUMATOID ARTHRITIS, INVOLVING QUANTITATIVE AND QUALITATIVE OUTCOMES: PROTOCOL FOR A RANDOMISED CONTROLLED TRIAL.

Open access Protocol

BMJ Open

Foot orthoses for people with rheumatoid arthritis, involving quantitative and qualitative outcomes: protocol for a randomised controlled trial

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ABSTRACT

Introduction Rheumatoid arthritis (RA) involves changes to foot structure and function, and there is an association between RA and foot pain. This pain affects those patient's physical activity and experience of daily living. While there is clinical evidence for the value of foot orthoses (FO) on foot pain, there is a wide range of FO available and there is little evidence on the relative benefits of one orthoses type over another, especially in terms of their impact on physical activity and associated well-being. The aim of this study is to compare physical activity, general and foot health and foot health experiences in people with RA when wearing three different types of FO.

Methods and analysis A randomised controlled trial with three arms will compare the effects of (1) custom FO made using a direct adaptation technique, (2) custom FO made through a digital design and production process and (3) prefabricated orthoses. The primary outcome is physical activity measured using a GENEActiv bracelet. Secondary outcomes will be pain, function and disability and associated foot and general health evaluated using existing questionnaires. Semistructured interviews will identify patients' experiences of the orthoses and living with RA.

Ethics and dissemination The study has been approved by the Portal de Ética de la Investigación Biomédica de Andalucía ethical committee (SPAR-001). The results will be disseminated regardless of the magnitude or direction of effect.

Trial registration number NCT03170947; Pre-results.

Strengths and limitations of this study

- ► It is the first study that measures the effect of foot orthoses (FO) and the physical activity in patients with rheumatoid arthritis (RA).
- ► The combination of qualitative and quantitative data improves the overall knowledge of FO in patients with RA.
- ► The use of FO will be monitored by phone, but we cannot be sure that they use them everyday.

INTRODUCTION

The prevalence of foot involvement and foot pain in rheumatoid Arthritis (RA) is well documented, with an estimated 80%–90% of patients suffering foot pain in their lives.[1 2] The pain is due to structural and functional alterations associated with inflammation[3] and impacts on physical activity of patients with RA.[4 5] For example, Lee *et al* found that 42% of 176 patients with foot pain associated with RA failed to register any moderate/vigorous physical activity during a week-long evaluation.[6] Foot pain is strongly associated with a lack of physical activity.[7] Furthermore, there is good evidence that foot pain reduces a person's functional capacity and their quality of life[8 9] and qualitative studies concluded that there is a negative impact on emotions and social activities.[10 11]

Foot orthoses (FO) are used to reduce foot pain and preserve joint mobility and position, and through this their aim is to keep patients physically active.[12] It follows that the benefits of physical activity may be more accessible to patients using FO. A recent systematic review summarised the comparative effectiveness of the wide range of FOs suitable for patients with RA,[13] although differences in their effects were non-significant or data inconclusive. In addition, studies that assess foot biomechanics or foot conditions (eg, reduction of forefoot plantar pressure or pain) do not include any measure of physical activity and patients wider experience of living with RA.[14]

This trial was designed in response to gaps in the current evidence base concerning FOs effects and the expectation that patient physical activity and experience of living with RA is affected by FO use. Furthermore, there is a long-standing debate on the relative merits of different types of FO and this trial is a response to this debate.[15] We hypothesised that patients with RA and custom FO made

FOOT ORTHOSES FOR PEOPLE WITH RHEUMATOID ARTHRITIS, INVOLVING QUANTITATIVE AND QUALITATIVE OUTCOMES:

PROTOCOL FOR A RANDOMISED CONTROLLED TRIAL.

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Conflict of interest: All the authors declare that they have no conflict of interest derived from the outcomes of this study.

Ethical approval: Institutional review board that approved the protocol for the study: The study has been approved by the Portal de Ética de la Investigación Biomédica de Andalucía ethical committee (PEIBA)(SPAR-001). Clinicaltrials.gov identifier NCT03170947. Informed consent will be obtained prior to participation.

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ABSTRACT

Introduction: Rheumatoid arthritis (RA) involves changes to foot structure and function, and there is an association between RA and foot pain. This pain affects those patient´s physical activity and experience of daily living. While there is clinical evidence for the value of foot orthoses (FO) on foot pain, there is a wide range of FO available and there is little evidence on the relative benefits of one orthoses type over another, especially in terms of their impact on physical activity and associated well-being. The aim of this study is to compare physical activity, general and foot health and foot health experiences in people with RA when wearing three different types of FO.

Methods and analysis: A randomized controlled trial with three arms will compare the effects of (1) custom FO made using a direct adaptation technique, (2) custom FO made through a digital design and production process and (3) prefabricated orthoses. The primary outcome is physical activity measured using a GENEActiv bracelet. Secondary outcomes will be pain, function and disability and associated foot and general health evaluated using existing questionnaires. Semistructured interviews will identify patients' experiences of the orthoses and living with RA.

Ethics and dissemination: The study has been approved by the Portal de Ética de la Investigación Biomédica de Andalucía ethical committee (SPAR-001). The results will be disseminated regardless of the magnitude or direction of effect.

Trial registration number: Clinicaltrials.gov identifier NCT03170947.

Keywords: protocol, rheumatoid arthritis, foot, orthoses, interview.

Introduction

The prevalence of foot involvement and foot pain in rheumatoid Arthritis (RA) is well documented, with an estimated 80%–90% of patients suffering foot pain in their lives (Simon J. Otter et al., 2010; Van Der Leeden et al., 2008). The pain is due to structural and functional alterations associated with inflammation (Carroll et al., 2015) and impacts on physical activity of patients with RA (Inoue et al., 2018; Paolo et al., 2018). For example, Lee et al found that 42% of 176 patients with foot pain associated with RA failed to register any moderate/vigorous physical activity during a week-long evaluation (J. Lee et al., 2012). Foot pain is strongly associated with a lack of physical activity (Fenton et al., 2017). Furthermore, there is good evidence that foot pain reduces a person's functional capacity and their quality of life (Ramírez et al., 2015; Turesson et al., 2007) and qualitative studies concluded that there is a negative impact on emotions and social activities (Craig et al., 2019; Williams et al., 2007).

Foot orthoses (FO) are used to reduce foot pain and preserve joint mobility and position, and through this their aim is to keep patients physically active (Novak et al., 2009). It follows that the benefits of physical activity may be more accessible to patients using FO. A recent systematic review summarised the comparative effectiveness of the wide range of FOs suitable for patients with RA (Tenten-Diepenmaat et al., 2019), although differences in their effects were non-significant or data inconclusive. In addition, studies that assess foot biomechanics or foot conditions (eg, reduction of forefoot plantar pressure or pain) do not include any measure of physical activity and patients wider experience of living with RA (Reina-Bueno et al., 2019).

This trial was designed in response to gaps in the current evidence base concerning FOs effects and the expectation that patient physical activity and experience of living with RA is affected by FO use. Furthermore, there is a long-standing debate on the relative merits of different types of FO and this trial is a response to this debate (Gijon-Nogueron et al., 2018). We hypothesised that patients with RA and custom FO made either by direct adaptation technique or through a digital design and production process, will improve their activity level in comparison with patients with RA and prefabricated orthoses. Our null hypothesis is that we will not find any significant difference between results from each custom orthoses and prefabricated orthoses, related to improve their physical activity increasing the period time when the patient is standing or walking. The aim of this study is to compare physical activity, general and foot health, and foot health experiences in people with RA when wearing three different types of FO.

Methods and analysis

Study design and setting

The design is a randomised clinical trial with the parallel group, three-arm trial with 1:1:1 allocation ratio. A mix of quantitative and qualitative measures will be adopted to address the objectives.

Patients will be recruited from the Hospital Virgen de las Nieves, Granada (Spain) from December 2019 and randomised to one of the three groups, each receiving a different type of foot orthosis (online supplementary file 2). Randomisation will be achieved using software to generate the allocation sequence (Gerard E. Dallal. Randomization.com 2008.http://www.randomization.com) and allocation concealed in envelopes. An independent member of staff of Virgen de las Nieves hospital will perform the randomisation and allocation to groups.

Eligibility criteria

Patients aged 18 or over and satisfying 2010 RA classification criteria (approved by the American College of Rheumatology and the European League Against Rheumatism) (Aletaha et al., 2010) will be enrolled after giving informed written consent. Participants will be eligible if they have a history of bilateral subtalar and/or ankle and/or talonavicular pain, scoring at least 3.5 on a pain Visual Analogue Scale (VAS) (Boonstra et al., 2014).

Participants will be excluded if they present with concomitant musculoskeletal disease (eg, fibromyalgia), central or peripheral nervous system disease (eg, poliomyelitis) or endocrine disorders (eg, diabetes) and insensitivity to 10 g monofilaments applied to the medial and lateral plantar surfaces of the forefoot, and the plantar aspect of the great toe. Patients with a history of orthopaedic foot surgery, foot trauma in the last 6 months, those currently using FO or reliant on walking aids will be excluded.

Patients will be asked about the medication they use to monitor confounding variables during the period when using the FO.

Interventions

The systematic review by Healy et al concluded there is no gold standard type of foot orthosis for people with RA (Healy et al., 2018). The three different types of foot orthoses chosen for this trial reflect a range of orthoses used in practice (Nester et al., 2017). They are all made from materials and shapes that are intended to reduce forefoot pressure, support foot structures and thereafter benefit the wearer in terms of reduced foot pain and associated disability. The primary differences

between groups 1 and 2, and group 3, is the customisation of the foot orthoses to individual foot shape, and orthoses materials. The primary difference between groups 1 and 2 is the method by which the foot orthoses are designed and manufactured, and the materials used for the orthoses. There are also differences between the groups in the cost of the orthoses. Participants will use the orthoses for 12 months and must wear the orthoses for 70% of the time they are wearing shoes to remain in the trial. Use of the orthoses will be determinate through the phone calls every month, understanding that one of the limits of this study could be that patients may not give always a reliable answer.

Group 1:

Custom orthoses will be made using a direct adaptation technique that involves a polyester resin and a combination of 1.2 mm Podiaflex for the rear and midfoot, and 0.8 mm Podiaflex for the forefoot. There will also be a top layer of ethylene-vinyl acetate (EVA) (30 ShoreA) of 1.5 mm and polyurethane (22 ShoreA) over the entire foot.

The shape of the orthosis is determined by heat moulding the resin to 90°C with a vacuum machine that combines heat and vacuum and placing the material against the foot (which is protected with a sock) under vacuum process. While the resin cools it takes the shape of the foot, while the heel is held a position described as subtalar joint neutral and the metatarsal heads pushed upwards to dorsiflex the ankle to a position of resistance.(Gijon-Nogueron et al., 2013)(Gijon-Nogueron et al., 2015).

Group 2:

Custom-made orthoses will be made using a digital process and from 2 mm polypropylene with an EVA (30 ShoreA) of 1.5 mm and polyurethane (22 ShoreA) top layer.

The FO shape is determined by a three-dimensional (3D) scan (shape scan 100/IBV) of the feet, taken in a standing position. The FO shape is determined by a 3D scan (shape scan 100/IBV) of the feet, taken in a standing position. Each orthosis will be independently designed for left and right foot (Caravaggi et al., 2016).

Group 3:

Prefabricated orthoses will the OPCT-OC Comfort Standard (Podiatech, https://podiatech.es/). These full-length orthoses are available in increments of two European Union sizes and made from a base later of 5 mm EVA under the heel and arches, and 2.5 mm and 4 mm layers of EVA under

the heel/arch and forefoot areas respectively. A top layer consists of EVA (30 ShoreA) of 1.5 mm and polyurethane (22 ShoreA) (Figure 10).

The orthoses will not be modified through the process due to the nature of the study, as it is an assessment of 1 year and the FO will not change its structure or function much.

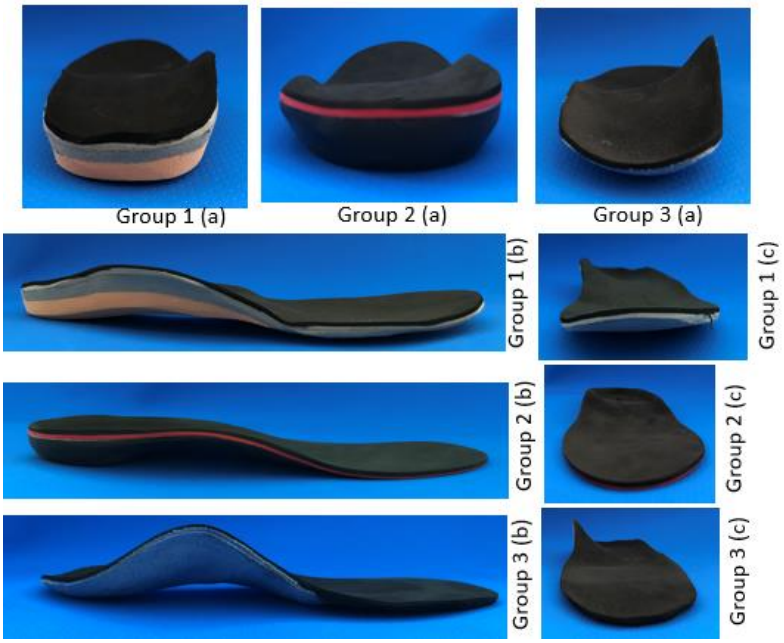

Figure 10. Foot orthoses included in the study. Group 1 (A) direct adaptation technique posterior view, group 1 (B) direct adaptation technique medial view, group 1 (C) direct adaptation technique anterior view. Group 2 (A) CAD/CAM foot orthoses posterior view, group 2 (B) CAD/CAM medial view, group 2 (C) CAD/CAM anterior view. Group 3 (A) prefabricated orthoses posterior view, group 3 (B) prefabricated orthoses medial view, group 3 (C) prefabricated orthoses anterior view. CAD, Computer-Aided Design; CAM, Computer-Aided Manufacturing.

If there were any discomfort during the delivery of the orthoses, the technician will make any necessary modifications, such as reduce the material under the arch.

Primary outcomes measures

The primary outcome measure is physical activity which will be measured using the actigraphy GENEActiv bracelet from Activinsights (info@geneactiv.co.uk). This combines a validated accelerometery technology with data on wear time, activity intensity and/or body position such as sitting or walking (Arvidsson et al., 2019).

Participants will wear the bracelet for a 7-day period on four different occasions: 1 week before orthoses first use, 6th week of orthoses use, and after 6 and 12 months of orthoses use. Adherence with accelerometer use will be tested through the accelerometer itself, which indicates the period when the participants are not wearing it. Accelerometer will be deactivated when the patient stops wearing it.

Secondary outcomes measures

Secondary outcomes will be measures of pain, function and disability, and associated foot and general health. These will be captured using the following tools:

- VAS to measure pain, with extremes labelled as “no pain” and “worst imaginable pain” (Collins et al., 1997).
- Foot and Ankle Ability Measure (FAAM). This is a questionnaire to measure changes in participant function and disability. It is designed to measure the effect of pathology and any associated deterioration of physical function. It has 29 items, with items 1-21 relating to “Activities of daily life” and 22 to 29 to “Sports” subscales. Each question is scored 0-4, where 0 is “unable to do” and 4 is able to achieve “without difficulty” (R. R. L. Martin et al., 2005).
- Foot-Health Status Questionnaire (FHSQ). This is a questionnaire which contains 13 items covering foot pain, foot function, footwear and general foot health (John Bennett et al., 1998).

The VAS will be completed before orthoses uses, after the first week of orthoses use and 6 and 12 months of orthoses use. The FAAM and FHSQ will be completed before orthoses uses and 6 and 12 months after orthoses use commences (Table 14).

Also, participants characteristics will be recorded.

Table 14. Participant timeline for outcome measurements.

	One week before orthoses first use	Fist day orthoses use	After 1 week of orthoses use	After 6 months of orthoses use	After 2 months of orthoses use
GENEActiv bracelet	x	x		x	x
VAS	x		x	x	x
FAAM and FHSQ	x			x	x
Interviews	x			x	x

Qualitative outcomes

To explore participant expectations and experiences of the orthoses use while having RA, qualitative data will be collected using unstructured interviews prior to, and after 6 and 12 months of orthoses use. The initial interview topic list is:

- Tell me about your feet.
- Tell me about your physical activity.
- How much do your foot problems affect your activity?
- How much do your foot problems affecting your activity levels?
- Have your feet and any problems affected your quality of life?
- How important are your foot problems to you?
- How do you feel about wearing orthotic insoles?
- Do the orthotic insoles affect or impact your activity life?

Blinding and monitoring

Participants will be blind as to which group, they are allocated to and will not see the other two orthoses designs.

Questionnaire data will be collected prior to the participant meeting clinician at each measurement point. Clinical appointments after first orthoses use will be at 6 and 12 months. All data will be entered into a database by a researcher independent of the clinician meeting participants, the process of making the orthoses and fitting the orthoses, and the researcher will be blind to group allocation because the research will not have access to the treatment selection.

Due to the aesthetics of the three orthoses, the clinician cannot be blind to group allocation, and the clinician will not take part in the data collection because the design, manufacturing, administration and modification of the orthoses are going to be done by three independent people. For the direct technique, a technician will undertake all design/manufacturing steps. For the digitally designed/manufactured orthoses, a technician will undertake all the necessary steps. One investigator will telephone participants once every 2 weeks to maintain contact, support good

compliance and record use of orthoses. Adverse events will be recorded as part of monitoring and appropriate safety measures. Statistical analysis will be performed by a statistician blinded to the study aims.

Sample size

The sample size will be determinate by application of the EPIDAT (https://www.sergas.es/Saude-publica/EPIDAT?idioma=es) program. Sample size calculation are based on an analysis of covariance adjusting for baseline of the outcome variable (GENEActiv bracelet), and assumen a between-person SD of 10! Of increase of walking in the main outcomes actigraphy GENEActiv bracelet (Pavey et al., 2016). Following, the study will be designed to detect changes exceeding 0.8 (high effect size) with a type I error of 0.05 and a type II error of 0.2. This is based on prior recommendation of 15 participants per arm for pilot studies to estimate outcome variance and allows for a predicted attrition rate of 20% with a precision of ±5% with 95% confidence level (Browne, 1995). Due to this, we will recruit 15 patients in each group during our pilot study.

Statistical analysis

Quantitative data will be assessed using SPSS (IBM SPSS Statistics: Version 24, USA). Outcomes will be evaluated at 3, 6 and 12 months of orthoses use. The primary time point will be the long-term follow-up 12 months. Quality of data will be assured by using range checks for data values. The database will be stored in a secure file that will be only accessed by encrypted login. Moreover, exploratory analyses will be carried out to check the integrity of data, and the normality of distributions, by evaluating the asymmetry and kurtosis, and the Kolmogorov-Smirnov test. Baseline data will be analysed to determine their distribution and potential differences between groups. If so, baseline data will be used to adjust the final analysis by multivariable analyses. For continuous outcomes, analysis of variance test will be used in case of homoscedasticity (it will be checked by the Levene's test). If homoscedasticity is not guaranteed, the Brown-Forsythe test will be used for hypothesis contrast. For qualitative outcomes, X^2 test will be used. Finally, a multivariable analysis will be carried out by using a linear regression model, introducing those factors that showed a significant association in the bivariant analysis, adjusted by baseline data.

The handle of missing data will be done across missing-data imputation process, to avoid pitfalls involved with listwise deletion. However, an analysis by intention to treat will be also performed, to compare the three analyses and to assess, in the absence of coincidence, the subgroups of patients who will not fulfil the study protocol, to identify possible causes of treatment dropout, before rejecting or accepting the null hypothesis

The qualitative data derived through interviews will be assessed using thematical analysis and supported by Nvivo (http://www.qsrinternational.com/nvivo-spanish)

This protocol will have some limitations due the nature of the study. Firstly, we cannot claim that all patients will be using their orthoses the whole period of our study. This is because the study will be undertaken in Spain, where there are very high temperatures in summer. This may make it difficult for the patients to wear close-toed shoes, thus limiting the orthoses use and interfering with the adherence to the treatment.

Secondly, according to the patients' condition, they may suffer a flare-up during the study, which can alter their physical activity independently of the orthoses use.

Any modifications to the protocol which may impact on the conduct of the study, may affect patient safety or potential benefit of the patient, including changes of study objectives, study design, sample sizes, patient population, study procedures, or significant administrative aspects will require a formal amendment to the protocol.

Patient and public involvement

No patients are involved in setting the research question or the outcome measures, nor are they involved in the design or conduct of the study. No patients are asked to advise on interpretation or writing up of results. There are no plans to disseminate the results of the research to study participants.

Strengths and limitations of this study

- The use of FO will be monitored by phone, but we cannot be sure that they use them every day.
- It is the first study that measures the effect of FO and the physical activity in patients with RA.
- The combination of qualitative and quantitative data improves the overall knowledge of FO in patients with RA.

7. A SYSTEMATIC REVIEW TO IDENTIFY THE EFFECTS OF BIOLOGICS IN THE FEET OF PATIENTS WITH RHEUMATOID ARTHRITIS PATIENTS FEET.

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Review

A Systematic Review to Identify the Effects of Biologics in the Feet of Patients with Rheumatoid Arthritis

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Abstract: *Background and Objective:* Ninety percent of patients with rheumatoid arthritis (RA) feel foot pain during the disease process. Pharmacological treatment of RA has a systematic effect on the body and includes: Nonsteroidal anti-inflammatory drugs, disease-modifying antirheumatic drugs (DMARDs) and biologics. The objective of our review was to examine the impact of biologics on patients with RA 'foot. *Methods and Material:* A systematic review of randomized control trials and observational studies that evaluated the efficacy of biologics against other pharmacological treatment, and included a foot outcome measure. The search covered MEDLINE Ovid, Pubmed, CINAHL, Cochrane Library, Evidence Search, and Web of Science. Risk of bias was evaluated using Cochrane guidance and the Newcastle Ottawa Scale adapted version. *Results:* A total of eight studies fully met the inclusion criteria: Three randomized control trials, and five observational studies were the basis of our review. A total sample of 1856 RA patients with RA treatment participated. The use of biologics was not associated as a risk factor for post-operative surgical site infection or delayed wound healing. The benefits of biologics, in terms of the disease evolution, were assessed using X-ray. *Conclusion:* Evidence suggests that the use of biologics is not a risk factor for post-operative surgical site infection or delayed wound healing. The use of biologics presents benefits in terms of the disease evolution assessed through X-ray.

Keywords: biologics; DMARDs; feet; rheumatoid arthritis; systematic review

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1. Introduction

Rheumatoid arthritis (RA) is a musculoskeletal disorder with a chronic inflammatory autoimmune condition that commonly affects foot joints, ankles, knees, and wrists [1]. It impairs normal daily life, affects body image and personal relationships, and therefore, also impacts the quality of life [2–4]. There is, consequently, a significant social and economic cost [4]. Foot involvement and foot joint pain are signature features of early RA and almost omnipresent during the progress of the disease, with subsequent physical and psychosocial impairment [5,6]. The prevalence of foot pain increases with disease duration, affecting 90% of people with RA at some stage [7,8]. The current strategy, as defined by the RA guidelines, is a treat-to-target strategy. The purpose of this strategy is to treat active RA to achieve a target of remission or lower disease activity in cases that remission cannot be achieved. The RA guidelines also state that it is important to always consider people's rights to be involved in discussions and make informed decisions about their care. The purpose is to provide pain relief, preserve physical activity, and quality of life [9,10]. Treatments include pharmacological agents, but also footwear, foot orthoses, and sometimes surgery [11].

A SYSTEMATIC REVIEW TO IDENTIFY THE EFFECTS OF BIOLOGICS IN THE FEET OF PATIENTS WITH RHEUMATOID ARTHRITIS PATIENTS FEET

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Review registration number: PROSPERO CRD42019137893.

ABSTRACT

Introduction: Ninety percent of patients with Rheumatoid Arthritis (RA) feel foot pain during the disease process. Pharmacological treatment of RA has a systematic effect on the body and includes: Nonsteroidal anti-inflammatory drugs, Disease-modifying antirheumatic drugs and biologics. The objective of our systematic review was to examine the impact of biologics on patients with RA 'foot.

Methods: A systematic review of randomized control trials and observational studies that evaluated the efficacy of biologics against other pharmacological treatment and included a foot outcome measure. The search covered MEDLINE Ovid, Pubmed, CINAHL, Cochrane Library, Evidence Search and Web of Science. Risk of bias was evaluated using Cochrane guidance and the Newcastle Ottawa Scale adapted version.

Results: A total of eight studies fully met the inclusion criteria. Three randomised control trials and five observational studies were the basis of our review. A total sample of 1,856 RA patients with RA treatment participated. The use of biologics was not associated as a risk factor for postoperative surgical site infection or delayed wound healing. The benefits of biologics, in terms of the disease evolution, were assessed using X-ray.

Conclusions**:** Evidence suggests that the use of biologics is not a risk factor for postoperative surgical site infection or delayed wound healing. The use of biologics presents benefits in terms of the disease evolution assessed through X-ray.

Keywords: biologics; DMARDs; feet; rheumatoid arthritis; systematic review.

Introduction

Rheumatoid arthritis (RA) is a musculoskeletal disorder with a chronic inflammatory autoimmune condition that commonly affects foot joints, ankles, knees and wrists (Raza et al. 2006). It impairs normal daily life, affects body image and personal relationships and therefore also impacts quality of life (Hill, Bird, and Thorpe 2003; Vamos, White, and Caughey 1990; Villamizar-Villamizar et al. 2015). There is consequently a significant social and economic cost(Villamizar-Villamizar et al. 2015). Foot involvement and foot joint pain are signature features of early RA and almost omnipresent during the progress of the disease, with subsequent physical and psychosocial impairment (S. J. Otter et al. 2010; Turner et al. 2003). The prevalence of foot pain increases with disease duration, affecting 90% of people with RA at some stage (Grondal et al. 2008a; Otter et al. 2011). The current strategy as defined by the RA guidelines is a treat-to-target strategy. The purpose of this strategy is to treat active RA to achieve a target of remission or lower disease activity in cases that remission cannot be achieved. The RA guidelines also state that it is important to always consider people's rights to be involved in discussions and make informed decisions about their care. The purpose is to provide pain relief, preserve physical activity and quality of life (Juan Mas 2008; NICE 2020). Treatments include pharmacological agents, but also footwear, foot orthoses and sometimes surgery (David L Scott, Frederick Wolfe and Lancet 2017).

Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used, but do not modify the disease evolution. In contrast, disease-modifying antirheumatic drugs (DMARDs) have the capacity to slow disease progression (including methotrexate (MTX), sulfasalazine (SSZ) and leflunomide (Lard et al. 2001)). These can alleviate patient symptoms and if used early in the RA process can enable better longer term outcomes (Nell et al. 2004). Biologics are a special type of DMARD, and they can help in terms of limiting radiological damage by inhibiting joint destruction and suppressing inflammation (Hirano et al. 2010; Saag et al. 2008; Sanmartí et al. 2015). However, some patients do not respond to pharmacological treatments or initial responses may reduce and efficacy changes over time. Regardless, any treatment has capacity as an anti-RA strategy if it inhibits hyperplasia of synovial cells (Okamoto et al. 2007; Scrivo et al. 2009). A previous systematic review concludes that compared with DMARDs alone, biologics in combination with DMARDs achieve a 50% reduction of joint destruction (Kornør et al. 2010). Regarding to biologics, they have shown significant contribution in aiding the reduction of inflammation and articular destruction (Taylor and Feldmann 2009), which may indicate clinical benefits in term of the feet of RA patients. A systematic review of the influence of biologics effects on RA patients in general pain, concluded that biologics are clearly effective in pain relief, improving functional status and preventing structural joint damage(Kulp et al. 2005). A prior qualitative study about foot impairments in RA

patients with biologics described a variety of participation limitations related to foot problems, such as foot impairments influencing work or foot obstacles in domestic life, (Björk et al. 2018) without any foot pain mentioned. However, the effect of biological treatments on the foot is not well-known since there are not many randomized control trials (RCTs).

A recent meta-analysis of evidence related to footwear and orthoses has evidenced their efficacy in relation to the reduction of foot pain and associated disability and increased quality of life (Gijon-Nogueron et al. 2018). A similar appraisal of the literature concerning pharmacological treatments has not been published. The objective of our systematic review was to explore biologics effects in patients with rheumatoid arthritis in terms of their feet.

Methods

Review registration number: PROSPERO CRD42019137893.

This review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Liberati et al. 2009).

Search

Studies were selected for analysis, in accordance with the PRISMA guidelines (Liberati et al. 2009), and a search completed from inception using the following databases: MEDLINE Ovid, Pubmed, CINAHL, Cochrane Library, Evidence Search and Web of Science. A previous scoping search was carried out to ensure that this aim had not been addressed by previous reviews, and PROSPERO and Cochrane Library were explored. The last search was run on 9th April 2020 by one reviewer. The following Mesh terms were used to identify relevant clinical trials: “Arthritis” [MeSH Terms], “Rheumatoid” [MeSH Terms], “Foot” [MeSH Terms], “biologics” [MeSH Terms], “biological therapy” [MeSH Terms] (appendix 1).

Eligibility criteria, study selection and data collection process:

We reviewed studies that assessed the efficacy of biologics therapy in terms of RA patients’ feet. All studies were conducted in accordance with the following PICO structure (Higgins JPT 2019).

- P (population) = Female and male patients with RA, aged>18 years.
- I (intervention) = efficacy of Biologics treatment in terms of RA patients’ feet.
- C (comparator) = Other type of pharmacological or conservative treatments.
- O (outcome) = Evaluation of biologics effects on RA patients ´feet, as the modified Sharp-van der Heijde (SvdH) score (Van Der Heijde 2000) or the use of the Guideline for the

Prevention of Surgical Site Infection (Mangram et al. 2000) or any aspect that directly affects the measurement of the foot.

No publication date, or publication status restrictions were imposed. Randomized control trials (RCT) and observational studies were included.

Studies focused on animals, lupus, juvenile or psoriasis arthritis were excluded. Studies that did not include biologics therapy or it was not compared with another pharmacological or conservative treatments, systematic reviews, non-focused on RA patients ´feet, case reports, skin cancer or studies in other languages rather than English were also excluded.

Study Selection

Study selection was carried out independently by 2 reviewers in an unblinded standardized manner. They extracted data from included studies and disagreements between them were resolved by consensus.

Data extraction and analysis

Two reviewers independently screened titles of potentially included studies to identify studies that may have met the inclusion criteria outlined above. Then, the studies were screened via their abstract. Finally, full texts of possibly eligible studies were investigated. Any disagreement between reviewers over the eligibility of studies was discussed with a third reviewer. The data extracted was study details (author, country and year of publication), sample size (gender, years of age, number of participants with), blinding, follow-up, intervention, measurement instrument used and results.

Whilst it was an aspiration at the start, due to the heterogeneity of studies and the varying outcomes, a meta-analysis was not appropriate

Risk of bias in individual studies:

Two reviewers worked unblinded to evaluate risk of bias in individual studies, using the Cochrane Handbook for Systematic Reviews of Interventions (CHSRI) (Higgins JPT 2019) to evaluate randomized control trials (RCT) and the Newcastle-Ottawa Scale (NOS) (Shea et al. 2012) for observational studies. NOS is a reliable and valid tool to evaluate the quality of any observational design that has an adapted version which has been used by previous systematic reviews (Bawor et al. 2015). The NOS adapted version assess risk of bias including 4 domains: selection bias, performance bias, detection bias and information bias. Those domains contain seven items, each item is scored from zero (high risk) to three (low risk) points. Therefore, a study is considered high

risk of bias with a total score from 0 to 6, moderate risk of bias from 7 to 13 and low risk of bias from 14 to 21.

Reviewers assessed each RCT taking in account the following domains from the (CHSRI): bias arising from the randomization process; bias due to deviations from intended interventions; bias due to missing outcome data; bias in measurement of the outcome and bias in selection of the reported result. Allocation, blinding, incomplete outcome data, selective reporting and other potential sources of bias are included in the table.

We used the Review Manager (RevMan) [Computer program]. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Results

Searches identified 180 articles, reduced to 155 after duplications were removed. These were screened by title and abstract and 118 were excluded. The remaining 37 were assessed and 8 carried forward. 29 studies were excluded due to differences in inclusion criteria, as no additional treatment for comparison or use of non-humans, meaning comparison of data would not be possible. Thus, only 8 studies fully met the inclusion criteria and were the basis of our review. Three randomised control trials and five observational studies (four retrospective studies and one prospective study). The PRISMA flow diagram is described in the Figure 11.

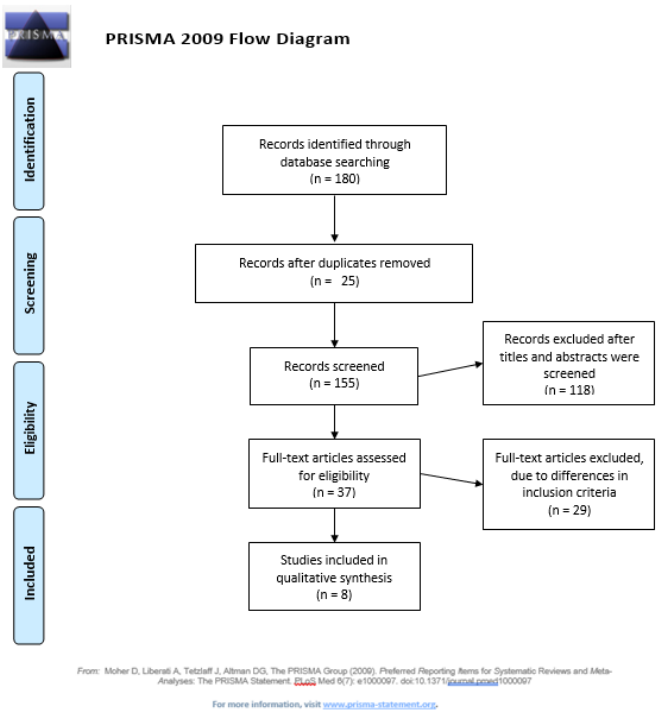

Figure 11. PRISMA flow diagram

They were published in English and between 2004 and 2016. The duration of the intervention was between 12 months and over 5 years. The total number of participants involved was 1,856. Five of the eight studies, include information about gender, showing that 965 participants (51.5%) were female. One of the RCT had blinded participants (Table 15).

Table 15. Study characteristics

Author and year	Country/ Study type	Sample size	Blinding	Follow-up	Intervention	**Foot outcome**	Results
Tada et al, 2016 (Tada et al. 2016)	Japan Retrospective study	227 patients with RA • Mean of age 65.0 • n female= 197 (86.7%) Rates of biologics and conventional synthetic DMARD (csDMARD) administration were 30.4 and 91.0 %, respectively.	No	Between 2006 and 2013	Orthopaedic surgeries. • DAS28	• Surgical site infection (SSI). (odds ratio [OR], 1.11; P = 0.045), • Wound healing (OR, 3.66; P= 0.003).	Biologics were not risk factors for postoperative SSI. Foot surgery was a risk factor for delayed wound healing due to the severe foot deformities, which causes swelling and increased skin turgor
Kadota et al, 2016 (Kadota et al. 2016)	Japan Retrospective study	204 foot and ankle surgeries in RA patients. 157 with biologics treatment and 47 with csDMARD treatment.	No	Between January 2004 and December 2012	Orthopaedic procedures.	• SSI (OR), 3.167; (CI), 1.256–7.986; P=0.015). • Delayed wound healing (DWH) (OR 1.004; CI, 1.000–1.007; P= 0.029)	SSI and DWH were identified in 8 cases (7 with csDMARD treatment) and 3 cases (2 with csDMARD treatment), respectively. Foot and ankle surgery were associated with an increased risk of SSI.
Van Herwaarden et al, 2015 (Van Herwaarde	Netherlands RCT	180 patients with RA: n= 121 with biologics and dose reduction • Mean of age 59	No	18 months	Biologics vs usual care in RA • DAS28 • Health assessment questionnaire–disability index (HAQ–DI).	• Radiological outcomes short lived flares (73% v 27%) and minimal	Biologics are non-inferior to usual care regarding outcomes

n et al. 2015)		• n female= 75 (61%) n= 59 without dose reduction (usual care). • Mean of age 58 • n female= 41 (69%)			• EuroQol-5D • Cumulative incidence of flares	radiographic progression (32% v 15%)	
Huizinga et al, 2015 (Huizinga et al. 2015)	Multicentre: Netherlands, UK, Spain, Germany, Israel, Brazil USA, Switzerland and France. RCT	From 556 randomised patients, n= 279 biologics tocilizumab (TCZ) + methotrexate (MTX) (add-on) and • n females= 227 (81.9%) • Mean of age 53 n= 277 TCZ + PBO (switch). • n females= 217 (78.6%) • Mean of age 53.6 Completed week 104: n= 222 TCZ + MTX (add-on) n= 201 TCZ + PBO (switch).	Yes	Over 24 months	Patients with active RA despite MTX were randomised to add TCZ to ongoing MTX (add-on) or switch to TCZ plus placebo (PBO) (switch). • Disease Activity Score (DAS28) • RA quality of life questionnaire • Tender joint count. • Swollen joint count. • HAQ–DI. • Patient's global assessment. • Physician's global assessment. • C-reactive protein	• Radiographs of hands/wrists and feet. 50.4% discontinued TCZ after achieving sustained remission and 5.9% achieved drug-free remission	Most patients demonstrated minimal progression of radiographic structural damage, with differences favouring the add-on group (p=0.034). Serious adverse events and serious infections per 100 patient-years were 12.2 and 4.4 in add-on and 15.0 and 3.7 in switch patients.
Kubota et al, 2014 (Kubota et al. 2014)	Japan Retrospective study	87 foot and ankle surgeries in RA patients. 50 with biologics and 37 with non-biologics.	No	Between January 2006 and December 2011.	Orthopaedic surgery.	• SSI (p=0.001), (OR)19.27; (CI) 4.67 – 79.45]. • Late infection	The use of biologics does not significantly increase the incidences of SSI and late infection after orthopaedic surgery
Van Vollenhoven et al, 2012 (Van Vollenhoven et	Sweden RCT	487 patients with RA and previous treatment with MTX. After 3-4 months, those who their treatment failed:	No	24 months	Addition of conventional disease modifying antirheumatic drugs (group A) vs addition of biologics (group B) VS • DAS28 • HAQ-DI	Radiological outcomes (mean 7·23 [SD 12·72] vs 4·00 [10·0]; p=0·009).	In group B good response was non-significantly greater than it was in group A. After 24 months, radiological disease progression was greater in patients in group A than it

al. 2012)		n= 130 (group A) with conventional treatment • Mean of age 52.9 • n female= 101 (78%) n= 128 (group B) with biologics. • Mean of age 51.1 • n female= 79 (76%)			• Health-economic outcomes		was in those in group B (p=0·009).
Kubota et al, 2012 (Kubota et al. 2012)	Japan Retrospective study	84 foot and ankle surgeries in RA patients. 47 with biologics and 37 with non-biologics	No	Between January 2006 and December 2010	Orthopaedic surgery.	• SSI (p=0.956) • Late infection (p = 0.55)	No statistically significant difference between groups. The use of biologics may not affect the incidence of postoperative wound healing and SSI.
Bibbo et al, 2004 (Bibbo and Goldberg 2004)	EEUU Prospective study	n= 28 females (90%) overall n= 16 biologics (group 1) n= 15 not receive biologics (group 2)	No	12 months	Risk for healing and infectious complications • smoking history	• Development of infectious/ healing complication (p = .033).	Group 1 demonstrated a lower complication rate (p = .033) in healing and infection.

All the studies included foot related outcomes, as radiographic disease progression, surgical site infection (SSI), development of infection or wound healing. General health status related, or RA assessment were also measured using the Health-Assessment Questionnaire (HAQ); the Disease Activity Score (DAS28) and the EuroQol-5D (EQ5D), which includes daily functioning, quality of life, radiographic progression, and adverse events. However, this systematic review is focused on foot outcomes, therefore this information was not included within our review.

Surgical site infection:

SSI was assessed in five (62.5%) of the included studies. SSI outcomes was diagnosed based on the Guideline for the Prevention of Surgical Site Infection (Mangram et al. 2000). By mutual agreement in all the studies, the use of biologics is not a risk factor for postoperative SSI (Bibbo and Goldberg 2004; Kadota et al. 2016; Kubota et al. 2012, 2014; Tada et al. 2016).

Delayed wound healing:

That outcome was quantified in 3 of the 8 included studies. Delayed wound healing was defined as either delayed suture removal or exhibit impaired healing, and this was judged by physicians (Mangram et al. 2000; Scanzello et al. 2006). All the studies concluded that biologics use is not a risk factor for delayed wound healing (Kadota et al. 2016; Kubota et al. 2012; Tada et al. 2016)

Radiographic progression:

Three studies included outcomes to measure the disease evolution assessed through X-ray to know biologics effects in terms of patients´ feet. Radiographs were assessed using the modified Sharp-van der Heijde (SvdH) score (range 0–448; higher scores indicate more joint damage). These values included subscores for erosion (range 0–280) and joint space narrowing (range 0–168)(Van Der Heijde 2000). Also, radiographs were assessed by applying the Genant-modified Sharp Score (GSS). Two different results were found in the included studies: relevant radiographic progression differences were not found between the groups (Van Herwaarden et al. 2015; Huizinga et al. 2015) and less radiological disease progression was found in patients with biologics (Van Vollenhoven et al. 2012).

Risk of bias

Risk of bias was evaluated using Cochrane guidance within RCT included studies is Figures 12 and 13. All RCTs had low quality in the blinding of participants and personnel, and most RCTs had uncertainty in allocation concealment and blinding of outcome assessment. The risk of bias assessment of observational studies is presented in Table 16, showing one moderate risk of bias study and four low risk of bias studies by NOS adapted version.

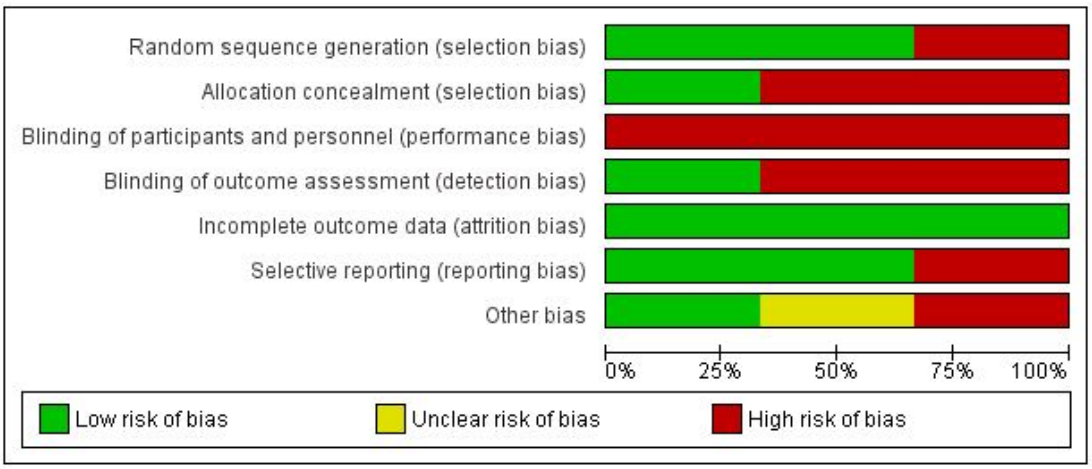

Figure 12. Risk of bias graph

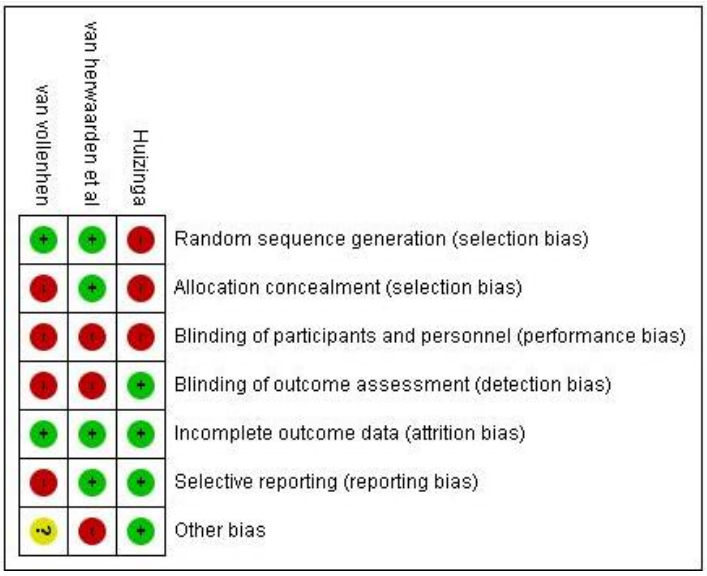

Figure 13. Risk of bias summary

Table 16. Risk of bias assessment for observational studies (NOS adapted version).

Study	Selection bias	Performance bias		Detection bias		Information bias		Total score
	A	B	C	D	E	F	G	
Tada et al(Tada et al. 2016)	3	2	0	3	3	3	3	17
Kadota et al(Kadota et al. 2016)	3	1	1	3	3	2	3	16
Kubota et al (Kubota et al. 2014)	2	1	2	2	3	2	3	15
Kubota et al (Kubota et al. 2012)	2	1	2	2	3	2	3	15
Bibbo et al(Bibbo and Goldberg 2004)	1	2	0	0	3	1	2	9

Note: A = Is the source population appropriate and representative of the population of interest?; B = Is the sample size adequate and is there sufficient power to detect a meaningful difference in the outcome of interest?; C = Did the study identify and adjust for any variables or confounders that may influence the outcome?; D = Did the study use appropriate statistical analysis methods relative to the outcome of interest?; E = Is there little missing data and did the study handle it accordingly?; F = Is the methodology of the outcome measurement explicitly stated and is it appropriate?; G = Is there an objective assessment of the outcome of interest?

Discussion

The main aim of our systematic review was to evaluate the evidence for changes in foot outcomes in patients with RA using biologics. From the review above, key findings emerged: longitudinal

analyses reported that the use of biologics may not be a risk factor for postoperative surgical site infection or delayed wound healing and there are no differences between biologics and non-biologics in terms of radiographic progression. Those are some important findings in the understanding of the biologics effect on RA patients´ feet.

Our initial hypothesis was that the use of biologics could benefit patients with RA in terms of their feet, such as reducing foot pain and therefore improving quality of life. Most patients with RA report foot symptoms during the process of the disease, foot pain being the most common (S. J. Otter et al. 2010).Whilst based on suitable studies, our analysis of eight studies involving almost 2,000 participants did not report any changes in terms of foot pain. Their outcomes are related to feet, including radiographic disease progression, SSI, development of infectious or wound healing. The included studies evaluated pain and quality of life from a holistic patient perspective. Those studies concluded that biologics can be used to improve patients' pain, but there was no specific indication about foot pain. A previous qualitative study explored the personal experiences of patients with RA in receipt of biologics, in terms of their feet. In this qualitative research, patients described that before biologics, they felt more pain and disabling symptoms. Also, patients declared that their function and mobility were restored. However, patients reported that foot pain remained, which could be explained by the established deformity or foot surgeries (Sanders et al. 2017).There is a lack of experimental studies focused on foot pain outcomes in RA patients receiving biologics.

Regarding the gender influence in our included studies, this information could not be found in all of them. Only five studies provide data related to sex difference, showing that most of the overall participants were female(Bibbo and Goldberg 2004; Van Herwaarden et al. 2015; Huizinga et al. 2015; Tada et al. 2016; Van Vollenhoven et al. 2012). This fact agrees with the previous findings about RA which identifies that the disease is more common in women than men (3:1) (Myasoedova et al. 2010). A prior review about gender influence in RA demonstrated that male and female approach their pathology differently. Presence of comorbidities, such as fibromyalgia, a different immune response, major depression, hormonal differences and osteoporosis, are more frequent in females (Favalli et al. 2019). It may influence the results; therefore, it is necessary to distinguish results from females and males in future research.

It has been suggested that patients with biologics have an extensive risk of post-operative infection (Kawakami et al. 2010), and the British Society for Rheumatology (BSR) have developed guidelines for the management of the biologic agent Tocilizumab. BSR claims that it is necessary to balance the risks of post-operative infection against the risks of a post-operative disease flare

(Malaviya et al. 2014). Some studies are investigating the risks associated with discontinuation of biologics vs the resultant infection risk after surgery. Our findings on post-operative infection suggest that the use of biological is not a risk factor for post-operative infection in foot and ankle surgery. Tada et al in 2016 (Tada et al. 2016), in their retrospective study among 227 patients with RA after 332 elective orthopaedic surgeries concluded that biologics were not risk factors for postoperative SSI. They concluded that the risk factor for postoperative SSI was foot surgery, due to the severe foot deformities which causes swelling and increased skin turgor. Kadota et al (Kadota et al. 2016) also found similar results, which provides support for the present findings. Therefore, surgeons and healthcare professionals who are involved in wound care need to be aware that foot surgery may be associated with SSI complications.

Previous studies reported that there is conflict related to continuing or stopping biologic drug therapy prior to orthopaedic procedures in terms of avoiding the possible side effects of these drugs in delayed wound healing (Diaper, Wong, and Metcalfe 2017). Previous in vivo studies, focused on the overall impact of biologics upon wound healing, showed that biologics suppress the promotion of key structural proteins, but help to collagen synthesis (Goldberg et al. 2007; Salomon et al. 1991). Nevertheless, a real environment is not considered in vivo studies. Included studies, within a real orthopaedic surgery process, concluded that biologics use is not a risk factor for delayed wound healing (Kadota et al. 2016; Kubota et al. 2012; Tada et al. 2016).

The assessment to determine bias within the observational studies which we included, demonstrated four low risk, and one moderate risk study. The studies also contained missing data such as activity remission, and the authors also showed a conflict of interest. The risk of bias within the randomized control trials included in this review, presented incomplete outcome data and a lack of blinding. There was a large difference between the number of included participants in the studies, the lowest of which being 31 (Bibbo and Goldberg 2004), and the highest being 556 (Huizinga et al. 2015). One of the strengths of this review is the use of specific review tools and checklists to evaluate risk of bias.

The clinical implications of our results may help in the therapy election for patients with RA in terms of their feet, considering the benefits in the feet radiographic progression. The applicability of these new results is also shown in the perioperative process.

The main limitation is that we have focused our review on biologics on foot outcomes instead of effectivity of all therapies for RA on patients' foot. Due to the nature of the study, groups were very heterogeneous, and sometimes information such as the types of surgery performed or if biologics were stopped peri-operatively, which may have an impact on SSI following surgery, were

not clear. Another limitation of the present study is the difficulty related to finding papers which relate to the topic of our study. This is due to the ambiguity in the studies related to RA, which mention feet however the aim of the study is not foot related. This makes it impossible to analyse the repercussion of biologics in term of feet patients.

Conclusions

The included studies suggest that the use of biologics slows the rate of foot joint erosion. Our review shows that biologics are not a risk for surgical site infection or delayed wound healing after foot and ankle surgery. However, as the included studies do not define if the use of biologics stopped prior to the surgery, results should be taken into consideration with caution. More research focused on biologics effect on foot pain is needed. We strongly suggest that biologics continue to be studied in experimental settings for the treatment of foot pathology in RA patients. Due to the diversity within the methodology of the included studies, results should be taken into consideration with caution. Thus, more rigorous and larger studies are needed.

Key points:

- To examine the impact of biologics on rheumatoid arthritis patients´ feet.
- Biologics do not increase risk of delayed wound healing.
- Biologics are not risk of surgical site infection after foot and ankle surgery.
- Biologics is an appropriate treatment option based on its good results on radiological disease progression.
- Foot and ankle surgery itself are risk factors of surgical site infection.

APPENDIX

Appendix 1. Search strategies.

Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) <1946 to April 08, 2020>

Search Strategy:

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1 exp Arthritis, Rheumatoid/ (111898)

2 exp Foot Joints/ or exp Foot/ (62425)

3 exp Biological Therapy/ (663983)

4 1 and 2 and 3 (18)

Database CINAHL:

rheumatoid arthritis AND foot AND (biologics OR biological therapy) (33)

Database Cochrane Library:

rheumatoid arthritis AND foot AND (biologics OR biological therapy) in Title Abstract Keyword (23)

Database Evidence Search:

rheumatoid arthritis AND foot AND (biologics OR biological therapy) (40)

Database Pubmed:

(((rheumatoid arthritis) AND (foot)) AND (biologics)) AND (biological therapy) (48)

Database Web of Science:

((rheumatoid) arthritis AND foot) AND (biologics) OR biological therapy)) (18)

8. A QUALITATIVE STUDY EXPLORING THE EXPERIENCES AND PERCEPTIONS OF PATIENTS WITH RHEUMATOID ARTHRITIS BEFORE AND AFTER WEARING FOOT ORTHOSES FOR 6 MONTHS.

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ORIGINAL ARTICLE

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A qualitative study exploring the experiences and perceptions of patients with rheumatoid arthritis before and after wearing foot orthoses for 6 months

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Abstract

Foot pathology in people with rheumatoid arthritis (RA) can have a psychosocial impact, but interventions such as foot orthoses can reduce foot pain, improving physical activity and quality of life. A previous meta-analysis concluded that foot orthoses can relieve pain and disability and enhance patient's well-being. The aim of this study was to explore the experiences of people with RA, before and after wearing foot orthoses for 6 months. Data were collected through digital recordings of semi-structured interviews carried out before and after wearing foot orthoses for 6 months. A thematic analysis of the transcripts was used to identify themes. Six female participants with RA wore foot orthoses for 6 months in Spain. The mean disease duration was more than 10 years. The findings showed three key themes emerged from the data: (1) improvement in physical activity; (2) footwear… a tricky situation and (3) social implications of RA feet. It is concluded that patients reported that wearing foot orthoses can have a positive impact on physical activity and improve general wellness and quality of life. However, to achieve the potential positive benefits, people with RA also needed to wear suitable footwear (defined as footwear which accommodates both the foot and the insole while maintaining the fit and function of the shoe). Despite the positive impact of wearing orthoses, participants stated that complexities of finding suitable footwear acted as a blocker.

KEYWORDS
foot, foot orthoses, pain, rheumatoid arthritis, self-care, thematic analysis

1 | BACKGROUND

Foot symptoms are almost pervasive in rheumatoid arthritis (RA), frequently severe and include foot pain, stiffness, swelling and numbness (Otter et al., 2010). Foot problems are associated with gait adaptations, reduced physical activity and quality of life, and have a potential negative impact on self-image because of changes in mobility and functional capacity (Carroll et al., 2015; Wickman et al., 2004; Williams et al., 2007). Indeed, almost every patient with RA presents with impairment of walking at some stage (Grondal et al., 2008) and this can affect social participation and thereafter quality of life (Wickman et al., 2004).

Foot pathology in people with RA therefore can have a psychosocial impact (Graham & Williams, 2016) and can persist despite good progress with treatments such as biologic drug therapy (Otter et al., 2010; Sanders et al., 2017). Therefore, foot pain remains a

A QUALITATIVE STUDY EXPLORING THE EXPERIENCES AND PERCEPTIONS OF PATIENTS WITH RHEUMATOID ARTHRITIS BEFORE AND AFTER WEARING FOOT ORTHOSES FOR 6 MONTHS.

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ABSTRACT

Foot pathology in people with rheumatoid arthritis (RA) can have a psychosocial impact, but interventions such as foot orthoses can reduce foot pain, improving physical activity and quality of life. A previous meta-analysis concluded that foot orthoses can relieve pain and disability and enhance patient's wellbeing. The aim of this study was to explore the experiences of people with RA, before and after wearing foot orthoses for 6 months. Data was collected through digital recordings of semi-structured interviews carried out before and after wearing foot orthoses for 6 months. A thematic analysis of the transcripts was used to identify themes. Six female participants with RA wore foot orthoses for 6 months in Spain. The mean disease duration was more than 10 years. The findings showed three key themes emerged from the data: 1) improvement in physical activity; 2) footwear…a tricky situation; 3) social implications of RA feet. It is concluded that patients reported that wearing foot orthoses can have a positive impact on physical activity and improve general wellness and quality of life. However, to achieve the potential positive benefits, people with RA also needed to wear suitable footwear, (defined as footwear which accommodates both the foot and the insole while maintaining the fit and function of the shoe). Despite the positive impact of wearing orthoses, participants stated that complexities of finding suitable footwear, acted as a blocker.

Keywords: foot orthoses; self-care; pain; foot; thematic analysis; rheumatoid arthritis.

Introduction

Foot symptoms are almost pervasive in rheumatoid arthritis (RA), frequently severe and include foot pain, stiffness, swelling and numbness (S. J. Otter et al. 2010). Foot problems are associated with gait adaptations, reduced physical activity and quality of life, and have a potential negative impact on self-image because of changes in mobility and functional capacity (Carroll et al. 2015; Wickman et al. 2004; Williams et al. 2007). Indeed, almost every patient with RA presents with impairment of walking at some stage (Grondal et al. 2008b) and this can affect social participation and thereafter quality of life (Wickman et al. 2004).

Foot pathology in people with RA therefore can have a psychosocial impact (Graham and Williams 2016) and can persist despite good progress with treatments such as biologic drug therapy (S. J. Otter et al. 2010; Sanders et al. 2017). Therefore, foot pain remains a common and disabling symptom, although foot care, footwear, patient education and foot orthoses are reported to offer relief (Deighton et al. 2009; Graham and Williams 2016).

Foot orthoses are an important conservative treatment option for RA-related foot problems and they are frequently prescribed in clinical practice (Marsman et al. 2013). Foot orthoses have been reported to have a positive effect on foot pain, disability, foot functionality, and quality of life, including both custom-made and standardised foot orthoses (Gatt, Formosa, and Otter 2016; Reina-Bueno et al. 2019). A meta-analysis concluded that foot orthoses relieve pain and disability and enhance patients quality of life (Gijon-Nogueron et al. 2018) and recommendations based on patients´ and professionals' views advocated use of custom-made foot orthoses to improve physical function and reduce pain (Tenten-Diepenmaat et al. 2018). Early and continuous interventions of foot orthoses in correctable deformities in RA provide a significant reduction in foot pain in the short-term, with reduction in disability and enhance foot health outcomes in long-term (Woodburn et al. 2010). Foot orthoses vary extensively in terms of their material, design and manufacturing method. This variation is further confounded by additions such as posting, wedges and pads (Payne, Oates, and Noakes 2003). Whilst this quantitative data supports use of orthoses the evidence based on largely clinical outcome measures, the evidence base is largely free of narratives capturing patient experiences of using orthoses and the benefits they allegedly offer.

Qualitative research and narrative based insights can offer an interpretation of any benefits of orthoses use and provides unique complementary evidence from which to understand outcomes in real rather than clinical trial terms. This advantage is created because qualitative research enables data capture taking into account a patients social perspective, and conceptualizes the individual real world settings within which the same intervention is used (Baixinho, Presado, and

Ribeiro 2019). It can thus add depth and richness to understanding of the outcomes from quantitative studies, and it may provide information around factors that influence patients with RA attitudes toward orthoses. One prior study of experience of people with RA using foot orthoses has been reported, finding that orthoses use was limited by footwear styles (Williams and Graham 2012). However, it did not illuminate further on experiences of foot orthoses use nor outcomes.

The aim of this study was to explore RA patients' experiences before and after wearing foot orthoses for 6 months.

Method

This study adopted a qualitative approach in order to collect the data and a thematic framework was used to analyse the data. The study has been awarded ethical approval from the committee of Portal de Ética de la Investigación Biomédica de Andalucía (PEIBA)(SPAR-001) and was registered at Clinicaltrials.gov identifier NCT03170947. This study was carried out in full accordance with the provisions of the Declaration of Helsinki regarding ethical principles for medical research involving human subjects and was approved by the Ethics Committee.

This qualitative study was embedded into a wider trial. The trial protocol can be found at https://bmjopen.bmj.com/content/10/7/e036433.long for the full details (Ramos-Petersen et al. 2020). The aim of the wider trial was to compare physical activity, general health, foot health and an in-depth understanding of the foot health experiences of people with RA when wearing three different types of foot orthoses. Therefore, a mixed methods approach was were adopted to address the objectives (Ramos-Petersen et al. 2020).

The research question that was addressed in this qualitative study was: what do people with RA experience before and after wearing foot orthoses for 6 months?

Population

Participants were recruited from the Hospital Virgen de las Nieves, Granada (Spain). They all agreed to take part in the study and provided informed and written consent. Interviews took place in September 2019 and again in March 2020.

Participants were dispensed randomly one of three foot orthoses types and were not aware of the other types of device dispensed to other participants. The principle aim of all three types of orthoses was to reduce forefoot pressure, support foot structures and reduce foot pain associated with RA.

The following inclusion and exclusion criteria were applied in relation to participant selection:

Participants aged 18 or over satisfied the 2010 Rheumatoid Arthritis Classification Criteria (approved by the American College of Rheumatology and the European League Against Rheumatism) (Aletaha, Neogi, Alan J. Silman, et al. 2010). All participants had a history of bilateral subtalar and/or ankle and/or talonavicular pain, scoring at least 3.5 on a pain Visual Analogue Scale (VAS)(Boonstra et al. 2014). Participants were excluded if they presented with concomitant musculoskeletal disease (e.g. fibromyalgia), central or peripheral nervous system disease (e.g. poliomyelitis), or endocrine disorders (e.g. diabetes) with clinical signs of neuropathy. Patients with a history of orthopaedic foot surgery, foot trauma in the last 6 months, those currently using foot orthoses or reliant on walking aids were also excluded.

Eligible patients were contacted by phone to ascertain willingness to participate in the qualitative part of the study before foot orthoses administration. Those who expressed an interest (n = 10) and sent a participant information sheet before the appointment to allow participants to consider their involvement in the study. Four of the ten female and male people that were approached did not respond. Six females agreed to participate, and interviews were conducted both pre and post orthoses prescription and use for a period of 6 months.

Foot orthoses intervention

The systematic review by Healy et al in 2018 concluded there is no gold-standard type of foot orthosis for people with RA. Therefore, three different types of foot orthoses were chosen for the trial reflecting a range of orthoses used in practice.

The three types of foot orthoses included were (1) custom foot orthoses made using a direct adaptation technique adapted by a trained podiatrist, (2) custom foot orthoses made through a digital design and production process, and (3) prefabricated orthoses. The main differences between groups 1 and 2, and group 3, are the customisation of the foot orthoses to individual foot shape and orthoses materials (groups 1 and 2 are customised and group 3 is off-the-shelf). There were also cost differences between each of the device types. All the orthoses had a full-length top layer of Ethylene-vinyl acetate (EVA) (30 ShoreA) of 1.5 mm and polyurethane (22 ShoreA) (appendix 1).

Data collection

Data was collected using semi-structured interviews employing open-ended questions to elicit in-depth responses in a clinical setting. The interviews were undertaken in two phases. The first interview took place before the participant had been issued with orthoses, and a second interview

was conducted after six months. Data collection was carried out between 2019 and 2020. Demographic information was collected through a questionnaire prior to the start of the interview. This information was collected again in the second interview six months for comparative purposes.

The interviews were conducted face to face, and they were recorded using a digital voice recorder. Field notes supplemented the data. The interviews were carried out by a researcher who had experience of foot orthoses and patients with RA from both a clinical and research context. The interviews and data analysis were conducted by the same researcher, and participants were made aware that the researcher was also a podiatrist (Richards and Emslie 2000).

The questions for the semi-structured topic guide were developed from a review of the literature on outcomes and measurement related to the use of foot orthoses.

The focus of the first set of interviews included the following questions. Those questions were based on a previous qualitative study in patients with RA (Williams et al. 2007):

- Tell me about your feet
- Tell me about your physical activity
- How much do your foot problems affect your activity?
- How much do your foot problems affecting your activity levels?
- Have your feet and any problems affected your quality of life?
- How important are your foot problems to you?
- How do you feel about wearing orthotic insoles?
- Do the orthotic insoles affect or impact your activity life?

The focus of the second set of interviews depended on their previous answer to keep exploring their experiences and perceptions before and after wearing foot orthoses for 6 months.

Data analysis

Thematic analysis (TA) (Clarke and Braun 2017) of the transcripts was carried out to analyse the data and to identify codes and themes. An inductive approach to TA was used to understand the experiences of people with RA before and after wearing foot orthoses for 6 months. TA is a systematic approach that transparently details the process of developing codes and themes. One researcher (LRP) undertook a line by line analysis of the transcribed experiences of each participant. From that work, all transcripts were read, and codes were developed. NVivo qualitative data analysis software was used to facilitate coding and analysis. Once codes had been

generated, themes and groups were developed iteratively. The findings were then scrutinised by a co-author (GGN).

Codes from the interviews undertaken prior to the issue of foot orthoses were generated first, followed by codes from the interviews conducted 6 months later. Finally, all codes were compared, and themes developed from the whole dataset. Particular attention was paid to both the frequency of emerging codes and their importance for multiple participants.

Findings

A total of 12 interviews were analysed thematically. All the participants were female and aged between 32 and 75 years old (mean 64 years old). The range of RA disease duration (at the first interview) was between 1.5 year to 45 years (mean 17.8 years).

Resulting themes were then agreed by the researcher and co-author (LRP and GGN), to enhance the validity of the data. Three themes were identified from the data:

1) Improvement in physical activity;
2) footwear…a tricky situation;
3) social implications of RA feet.

Theme 1 – "Improvement in physical activity"

Prior to wearing foot orthoses participants commented about the positive mental impact of participating in sport, but also how tired this made their feet and legs feel. Some reported changes in mobility as a result of their disease, for example driving instead of walking to reduce the amount of activity.

"I swim and I really feel its benefits. I feel that I am more flexible" "To dance gives me life." (Participant number 1)

"My legs… I feel so tired after I dance." (Participant number 1)

"I went hiking with my husband and my feet were shattered." (Participant number 2)

"I can´t be standing up for long… I have to look for a bench constantly." (Participant number 3)

After wearing the foot orthoses for 6 months, all participants declared that their physical activity levels had improved. They felt they could walk more safely, and this facilitated more physical activity. Some reported an improvement in their social life as a result of a reduction of symptoms of RA in their feet, connecting physical comfort with their activity levels, and associating perceived improvement in their physical activity and general wellness with improved quality of life.

Participants declared an increased social interaction, which improved their physical and mental wellbeing.

"I used to refuse going shopping with my daughter due to the pain. I love to spend time with her. But now my feet feel much better so the other day we went shopping together". (Participant number 3)

"Before the foot orthoses, I went (hiking), and the following day I felt awful…But this time I did everything without aches or pain the following day. Much better." (Participant number 2)

"I used to walk with foot pain, it felt like walking barefoot on a hard surface, even with good quality footwear. Now with the insoles I feel that I can walk better, more comfortably. Of course, I still have a huge foot deformity, but now I am not afraid to walk." (Participant number 4)

"…sport, it is good for me! A regular schedule of playing sports is awesome for me. I think that increasing the level of physical activity, I exercise my joints more, so I feel less pain. I am pretty clear about this." (Participant number 1)

"If I don´t walk I have pain. Sport is so good for me. Big time!" (Participant number 5)

"I thought I couldn´t go to the mountains with my family but I did it." (Participant number 2)

All the patients expressed associated benefits in their physical activity due to wearing foot orthoses. One declared that she struggled to adapt to using the orthoses but that the impact was significant.

"The difference is awesome with the insoles. The adaptation was not easy. But then the difference was huge." (Participant number 6)

Theme 2 – "Footwear…a tricky situation"

Participants expressed a dilemma in relation to footwear when they want to use orthoses, and this formed the second theme. Some participants expressed problems with their footwear prior to and during orthoses use, including limiting and adapting their choices.

Before orthoses intervention, patients claimed:

"I have to wear bigger shoes with a wider fitting to give my feet enough space". (Participant number 3)

"(after wearing heels for an event) … for a week or two afterwards I couldn't walk properly because my feet were so sore". (Participant number 1)

But some patients revealed that they have adapted to wearing their footwear to accommodate orthoses:

"*Sometimes I forget to take them off when I get home because now using orthoses, I am so comfortable that I don't realise they are there*." *(Participant number 6)*

During intervention, some people keep experienced problems with their footwear. Even after wearing the foot orthoses, footwear is still a problem for some participants. Some commented on difficulties finding shoes appropriate for wearing with orthoses. The cost, quality and aesthetics of the footwear meant that choices were limited and buying shoes to meet all their needs was difficult.

"It is hard to fit them (orthoses) in all my shoes, especially when I want to be more elegant." (Participant number 1)

"If I want to wear orthoses, I have to buy new shoes, and it means spending more money". (Participant number 5)

"Because of my toes, with the insole, my foot contacts with the toe box. So, on the one hand it relieves me but on the other hand, it gives me pain." (Participant number 4)

"In some shoes wearing insoles is not too bad, like trainers, big shoes or boots, because they don't show." (Participant number 5)

"It affects my choice of what kind of shoes I can and can't wear, and it limits me in that way." (Participant number 3)

Theme 3 – "Social implications of RA feet"

Prior to using the orthoses, patients explained that the symptoms in their feet limits their social life, making it necessary to adapt their social activity to their condition. That adaptation was unique to every participant. Some modified their social life, basing it in their own homes, and other patients chose to have less of a social life, which can result in isolation.

"I ask friends to come around to my house so that I can put my feet up and be more comfortable." (Participant number 4)

"They know that I have rheumatoid arthritis. That is it. They love me above anything else". (Participant number 3)

"I used to walk with some friends, but they always said: sit down a bit and then we will go on. But I didn´t feel comfortable about me being the centre of attention. So, I walked alone". (Participant number 2)

Beyond that, patients described the impact on their lives when interacting with others, feeling negative about how their feet influenced their decision to engage with others, and the burden and impact this had on themselves and others. Some patients felt embarrassed about their feet and felt anxious when someone looked at their feet, especially in summer. They claimed to feel sad every time they had to justify their foot morphology and footwear choice. This was more evident in young women.

"I feel that my friends change their plans depending on me, and I don´t like it". (Participant number 6)

"You can see it in their faces, like I don't want to look at your feet…feet phobia" (Participant number 4)

"I feel so ashamed of my feet when I´m with my friends… They are always better covered". "Why can´t I have (feet) as beautiful as my friends do?" (Participant number 1)

Also, a patient referred to the impact of her foot condition on her granddaughter:

"She was messing around with her feet after her bath. She placed her toes in a weird position and she said: look, they are like grandmas!". (Participant number 4)

Discussion

The aim of this study was to explore RA patients' experiences before and after wearing foot orthoses for 6 months, and whether and how the use of those foot orthoses impacted on physical activity participation, general wellness and quality of life. There is a paucity of qualitative research to explore patient´s feelings and opinions about feet and foot health. Therefore, there is a need to understand the experiences of people living with RA and its impact to inform practice and improve clinical guidance frameworks.

Participants felt that orthoses required time to adapt but were associated with improved comfort and decreased pain. Participants felt safer while walking and associated orthoses with increased physical activity levels, including time spent exercising or walking. This also had an impact on their social participation during these activities and had a positive impact on their wellbeing and interactions with friends, family and colleagues in some cases. Increased social interaction improved their physical and mental wellbeing. This is important because people with RA are at an

increased risk of stress and depression (López-lópez et al. 2018) and physical activity and social participation can be useful preventative or treatment strategies for this (White et al. 2017). Furthermore, this risk is greater in women and RA is most common in females (de Andrade et al. 2018; Kvien et al. 2006). Being physically active can also improve mental health and have an impact on body image.

Beside the initial discomfort and the pre orthoses use concern that some participants mentioned, all the participants felt that they had adapted to the orthoses after six months. One of the participants was prescribed foot orthoses as a child, for a 3 year period. Another participant was provided foot orthoses more than five years ago by the national service system, but she declared that she had not worn them due to discomfort. Those two participants, as well as other participants, claimed that they needed an initial period to get used to their foot orthoses. Participants recognised the advantage of wearing orthoses from a functionality point of view. Receiving the right wear, care and break in advice about the orthoses is an important aspect to give patients the correct information about the utility and use of the orthoses.

Our results agree with a previous metanalysis which concluded that foot orthoses can relieve pain and disability and enhance the lives of patients with RA (Gijon-Nogueron et al. 2018). Participants felt that orthoses seems to alleviate foot pain and it has been demonstrated that pain relief is the main reason why patients look for treatment (Chalmers et al. 2000). By reducing pain and improving foot function due to orthoses, patients can improve their physical functioning (Tenten-Diepenmaat et al. 2018). Participants expressed that reducing their pain level, they were willing to increase their physical activity on their own, with their family and friends or in a team.

A prior qualitative study about foot care for people with RA reported that foot orthoses use was limited by the footwear styles that participants liked to wear, which stops some participants using them (Williams and Graham 2012). But there is a lack of qualitative research focus on patients with RA and their experiences of wearing foot orthoses.

Participants expressed strong feelings toward their feet, the importance of footwear aesthetics and the problems associated with buying footwear that is both suitable and acceptable. Suitable footwear is defined as footwear which accommodates both the foot and the insole while maintaining the fit and function of the shoe. Tehan et al (2019) concluded (Tehan et al. 2019) that there is a constant compromise for people with RA, between achieving comfort, their feelings about their appearance and how they feel others perceive them. This suggests that footwear plays an important role for people with RA and we found that when footwear was uncomfortable it can

limit mobility and thereafter daily living and other physical activities. These outcomes are often associated with dissatisfaction and even depression among the population affected.

The use of foot orthoses has a significant impact on footwear options. Furthermore, as RA develops the impact and progression of the condition may not be symmetrical in both feet, and this can add further complexity to footwear options and decision making. Prior work indicates that people with RA often use footwear which may contribute to foot pain, for example selecting footwear that is too small, and this is strongly associated with disability(Tovaruela-Carrión et al. 2018). Participants often describe difficulties finding suitable footwear (Hendry et al. 2015) in terms of improving their foot pain, but also to improve their physical image in front of others (such as family, friends and colleagues) (Naidoo et al. 2010). The use of foot orthoses adds to this already difficult issue and further limits footwear options. A previous literature review has concluded that footwear interventions are associated with reductions in disability and mental health improvement (Frecklington et al. 2018). As a result, patients should be aware of how important it is to choose the right footwear that is both comfortable and supportive, and able to accommodate foot orthoses, such that any addition benefits from the orthoses is accessible to them.

The results demonstrate the complexities associated with footwear for those who's feet are affected by RA. Considerations include whether to choose therapeutic or retail footwear whilst also achieving a balance of cushioning, a flexible sole, that are easy to put on and take off, and are also aesthetically acceptable for their particular circumstances. This research exposes how the effectiveness of foot orthoses is strongly related with the patients ´footwear choice, and sometime patients prioritise aesthetic features, making foot orthoses adaptations more difficult. Furthermore, footwear also needs to be both comfortable and affordable. Footwear is an important part of a person's identity, and therapeutic footwear can have a negative impact on how a person feels about themselves and how they feel others might perceive them (Netten et al. 2012; Williams et al. 2007). Also, we must consider the financial implications. All of these factors could influence whether or not a person with RA will wear footwear that is both good for their foot health and will accommodate orthoses.

Another important finding is the implications for practice and managing expectations as some participants took a while to get used to the device, so they had to persevere. If expectations are not managed some people may give up on orthoses before they have had chance to adapt to them. Therefore, it is important for clinicians to make this clear in consultation with their patients that the gains may not be immediate. This finding is important for podiatrists to help their patient

understand what they can expect, and this encourages people to stick with it. Key markers are discomfort and/or pain after the technician has made all the necessary modifications, such as reducing the material under the arch. If the problems are due to the patient´s footwear choice, the first option is to assess the footwear to ascertain if it is suitable for the patient or not. Suitable footwear is defined as footwear which accommodates both the foot and the insole while maintaining the fit and function of the shoe. Future research in terms of advice that clinicians can provide to their patients is required.

This study has several limitations: the sample could be strengthened by the addition of men as there was a lack of men happy to be enrolled in a qualitative study. For this reason, only females responded to recruitment, which may influence responses about shoe selection and its social repercussions. Furthermore, it is possible that difficulty in adapting to wearing the device may be related to the extent of customisation of the specific device that was issued to the participant. Another limitation is that only participants from the wider trial who expressed an interest were included. Participants who were not interested in participating in the qualitative part, may have other experiences with the use of foot orthoses that would enrich knowledge but remains concealed. Finally, it is impossible to know if the participant reported accurately how often they wore the device and their experience of it.

It can be concluded that this study is the first qualitative research study that focuses on illuminating both the impact of, and attitudes towards the use of foot orthoses for people with RA in their feet, and how that use has impacted on physical activity participation, general wellness and quality of life.

Participants reported that wearing foot orthoses has a positive impact on comfort, pain and physical activity and associated this with improved general wellness and quality of life. However, barriers to use and negative aspects of experiences relate to footwear choices, which might already be limited and an issue for people whose feet are affected by RA and who might benefit from foot orthoses.

Key messages:

- Some people take a while to get used to their foot orthoses, so they had to persevere.
- Podiatrists need to help their patient understand what they can expect in terms of foot orthoses, encouraging people to stick with it.
- Wearing foot orthoses has a positive impact on comfort, pain and physical activity, which is associated with improved general wellness and quality of life.

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10. LIMITATIONS AND FUTURE RESEARCH

The main limitation in the systematic review and meta-analysis to determine the effectiveness of foot orthoses as a treatment for a patient with RA is the small sample sizes of the included studies. This could reduce external validity of these results. Moreover, it cannot avoid the limited sensitivity of the FFI questionnaire to detect changes in pain and disability. Finally, another limitation is the difference in the materials used for foot orthoses, and intensity of the intervention (total time of use per day) of these devices among the studies.

Certain limitations are presented in the systematic review which identifies PROMs concerning the effects of RA on the foot and ankle and evaluates the methodological quality and psychometric properties of these measures. Importantly, some instruments were excluded from our analysis due to our focus on patients aged over 18 years, therefore, our findings could only be related to the adult RA population. Another limitation was the fact that some data was incomplete, despite our efforts to contact the original authors.

Some limitations are presented in the systematic review that identifies the PROMs specific to the foot and ankle in children and adolescents with JIA and analyses the psychometric properties provided by each of these instruments. Those limitations are due to the incompleteness of some of the data obtained (despite our attempts to contact the original authors) and only PROMs in child/adolescent were analysed (not parent/ patient report outcome measures).

The protocol to compare physical activity, general and foot health, and foot health experiences in people with RA when wearing three different types of FO may have some limitations due the nature of the study. First, we cannot claim that all patients will be using their orthoses the whole period of our study. This is because the study will be undertaken in Spain, where there are very high temperatures in summer. This may make it difficult for the patients to wear close-toed shoes, thus limiting the orthoses use and interfering with the adherence to the treatment. Secondly, according to the patients' condition, they may suffer a flare-up during the study, which can alter their physical activity independent of orthoses use.

The main limitation of the systematic review and meta-analysis to evaluate the evidence for changes in foot outcomes in patients with RA using biologics is that we have focused our review on biologics on foot outcomes instead of effectivity of all therapies for RA on patients' feet. Due to the nature of the study, groups were very heterogeneous, and sometimes information such as the

types of surgery performed or if biologics were stopped peri-operatively, which may have an impact on SSI following surgery, were not clear.

The qualitative study to explore RA patients' experiences before and after wearing foot orthoses for 6 months has several limitations. The sample could be strengthened by the addition of men as there was a lack of men happy to be enrolled in a qualitative study. For this reason, only females responded to recruitment, which may influence responses about shoe selection and its social repercussions. Furthermore, it is possible that difficulty in adapting to wearing the device may be related to the extent of customisation of the specific device that was issued to the participant. Finally, it is impossible to know if the participant reported accurately how often they wore the device and their experience of it.

Future research should address several subjects that are presented below:

- Studies undertaken with larger sample sizes of RA patients and long-term follow-up (24–30 months) to evaluate the effect of different interventions with the use of PROMs such as SEFAS.
- Studies that address the following structure for questionnaires: number of items varied widely among PROMs and heterogeneous response options, with some offering a simple yes/no choice, while others measured outcomes on a Likert-type scale.
- Studies to examine whether the number of items and the response options provided correctly discriminate the interventions performed, the health status of the patients and the follow up procedures employed.
- Studies with robust methods to replace the lower-quality versions of PROMs that present poor evidence of their psychometric properties.
- It is necessary to continue studying biologics in an experimental setting for the treatment of foot pathology in RA patients.

The main future research that we will carry out is the randomized controlled trial that was described in the published protocol which is attached in this thesis. A study undertaken with larger sample sizes of RA patients, including different interventions of foot orthoses: custom foot orthoses made using a direct adaptation technique, custom foot orthoses made through a digital design and production process and prefabricated orthoses. This study had stared before a worldwide pandemic (COVID 19), therefore during the ongoing pandemic, we have been unable to recruit patients and continue with the study until the situation becomes stable and safe.

11. CONCLUSIONS

Patients with RA suffer several changes in their feet. Those changes involve some consequences that need to be assessed to determine the patient's status. This evaluation can be carried out through patient-reported outcome measures and interviews. Also, feet changes in patients with RA can be managed with the use of conservative treatments, such as foot orthoses.

After determining the effectiveness of foot orthoses in patients with RA related to disability and pain with a systematic review and meta-analysis, it can be concluded that despite the poor methodological quality of most studies considered in the meta-analysis, foot orthoses alleviate pain and disability in patients with RA. The absence of significant differences between the study groups may be due to the small sample sizes included in these studies. Another explanatory factor might be the insufficient sensitivity of the Foot Function Index to detect pain and disability.

The systematic review of the psychometric properties of patient-reported outcome measures for RA in the foot and ankle concluded that the Self-Reported Foot and Ankle Score achieved the highest number of positive criteria (according to Terwee and COSMIN), and is currently the most appropriate for patients with RA.

The systematic review of measurement instruments for patients with juvenile idiopathic arthritis in the foot and ankle concluded that despite the very low quality of the available evidence, the Italian-language adaptation of the Oxford Ankle Foot Questionnaire presents acceptable methodological quality.

The systematic review and meta-analysis to evaluate the evidence for changes in foot outcomes in patients with RA using biologics concludes that the use of biologics provides good results on foot joint erosion. Biologics are not a risk of surgical site infection or delayed wound healing after foot and ankle surgery.

The qualitative study to explore RA patients' experiences before and after wearing foot orthoses for 6 months concludes that wearing foot orthoses has a positive impact on comfort, pain and physical activity and is associated with improved general wellness and quality of life. However, barriers to use the foot orthoses were found, such us the footwear choice. This study is the first qualitative research study that focuses on illuminating both the impact of, and attitudes towards the use of foot orthoses for people with RA in their feet, and how that use has impacted on physical activity participation, general wellness and quality of life.

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13. APPENDIX

Appendix 1: CERTIFICADO PEIBA

JUNTA DE ANDALUCIA

CONSEJERÍA DE IGUALDAD, SALUD Y POLÍTICAS SOCIALES
Dirección General de Calidad, Investigación, Desarrollo e Innovación
Comité Coordinador de Ética de la Investigación Biomédica de Andalucía

DICTAMEN ÚNICO EN LA COMUNIDAD AUTÓNOMA DE ANDALUCÍA

D/Dª: Juan Morales Arcas como secretario/a del CEI de Granada

CERTIFICA

Que este Comité ha evaluado la propuesta de (No hay promotor/a asociado/a) para realizar el estudio de investigación titulado:

TÍTULO DEL ESTUDIO:	Clasificación del grado de afectación del pie en Artritis Reumatoide. ,(Clasificación del grado de afectación del pie en Artritis Reumatoide.)
Protocolo, Versión:	PAR-01
HIP, Versión:	PAR-01
CI, Versión:	PAR-01

Y que considera que:

Se cumplen los requisitos necesarios de idoneidad del protocolo en relación con los objetivos del estudio y se ajusta a los principios éticos aplicables a este tipo de estudios.

La capacidad del/de la investigador/a y los medios disponibles son apropiados para llevar a cabo el estudio.

Están justificados los riesgos y molestias previsibles para los participantes.

Que los aspectos económicos involucrados en el proyecto, no interfieren con respecto a los postulados éticos.

Y que este Comité considera, que dicho estudio puede ser realizado en los Centros de la Comunidad Autónoma de Andalucía que se relacionan, para lo cual corresponde a la Dirección del Centro correspondiente determinar si la capacidad y los medios disponibles son apropiados para llevar a cabo el estudio.

Lo que firmo en GRANADA a 07/07/2017

D/Dª. Juan Morales Arcas, como Secretario/a del CEI de Granada

Código Seguro De Verificación:	e85b1e5dc971f35359091 84c090728ba3e17f05	**Fecha**	07/07/2017
Normativa	Este documento incorpora firma electrónica reconocida de acuerdo a la Ley 59/2003, de 19 de diciembre, de firma electrónica.		
Firmado Por	Juan Morales Arcas		
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CERTIFICA

Que este Comité ha ponderado y evaluado en sesión celebrada el 26/06/2017 y recogida en acta 7/2017 la propuesta del/de la Promotor/a (No hay promotor/a asociado/a), para realizar el estudio de investigación titulado:

TÍTULO DEL ESTUDIO:	Clasificación del grado de afectación del pie en Artritis Reumatoide. ,(Clasificación del grado de afectación del pie en Artritis Reumatoide.)
Protocolo, Versión:	PAR-01
HIP, Versión:	PAR-01
CI, Versión:	PAR-01

Que a dicha sesión asistieron los siguientes integrantes del Comité:

Presidente/a
D/Dª. Fidel Fernández Quesada

Vicepresidente/a
D/Dª.

Secretario/a
D/Dª. Juan Morales Arcas

Vocales
D/Dª. FRANCISCO LUIS MANZANO MANZANO
D/Dª. Juan Ramón Delgado Pérez
D/Dª. Berta Gorlat Sánchez
D/Dª. José Darío Sánchez López
D/Dª. José Cabeza Barrera
D/Dª. José Uberos Fernández
D/Dª. Enrique Lopez Cordoba
D/Dª. MARIA ESPERANZA DEL POZO GAVILAN
D/Dª. ESTHER OCETE HITA
D/Dª. MAXIMILIANO OCETE ESPINOLA
D/Dª. Joaquina Martínez Galán
D/Dª. Paloma Muñoz de Rueda
D/Dª. Esther Espinola Garcia
D/Dª. MIGUEL LÓPEZ GUADALUPE
D/Dª. MARÍA DEL PILAR GONZÁLEZ CARRIÓN
D/Dª. JUAN ROMERO COTELO
D/Dª. Juan de Dios Luna del Castillo
D/Dª. Pilar Guijosa Campos
D/Dª. José Luis Martín Ruiz

Que dicho Comité, está constituido y actua de acuerdo con la normativa vigente y las directrices de la Conferencia Internacional de Buena Práctica Clínica.

Lo que firmo en GRANADA a 07/07/2017

Código Seguro De Verificación:	e85b1e5dc971f35359090184c090728ba3e17f05	Fecha	07/07/2017
Normativa	Este documento incorpora firma electrónica reconocida de acuerdo a la Ley 59/2003, de 19 de diciembre, de firma electrónica.		
Firmado Por	Juan Morales Arcas		
Url De Verificación	https://www.juntadeandalucia.es/salud/portaldeetica/xhtml/ayuda/verificarFirmaDocumento.iface/code/e85b1e5dc971f35359090184c090728ba3e17f05	Página	2/2

Appendix 2: CERTIFICADO CEUMA

UNIVERSIDAD DE MÁLAGA

ANDALUCÍA TECH
Campus de Excelencia Internacional

Vicerrectorado de Investigación y Transferencia
Comité Ético de Experimentación de la Universidad de Málaga
(CEUMA)

Nº: 301	Nº de Registro CEUMA: 91-2015-H

INFORME DEL COMITÉ ÉTICO DE EXPERIMENTACIÓN DE LA UNIVERSIDAD DE MÁLAGA

CEUMA

Reunido el Comité Ético de Experimentación en Málaga, el 9 de diciembre de 2015 ha evaluado la solicitud del proyecto denominado: **"Clasificación del grado de afectación del pie en la Artritis Reumatoide"**, cuyo investigador principal es **D. Gabriel Antonio Gijón Nogueron**.

Una vez examinada la documentación presentada y verificados aquellos aspectos relacionados con la ética y la legislación en materia de investigación que se indican:

-Se cumplen los requisitos necesarios de idoneidad del protocolo en relación con los objetivos del estudio y están justificados los riesgos y molestias previsibles para el sujeto, teniendo en cuenta los beneficios esperados.

- El procedimiento para obtener el consentimiento informado, incluyendo la hoja de información al sujeto son correctos.

- La idoneidad del procedimiento experimental, especialmente la posibilidad de alcanzar conclusiones válidas de acuerdo con los objetivos establecidos.

- La capacidad del investigador principal y sus colaboradores los medios y las instalaciones previstas son apropiados para llevar a cabo dicho estudio.

- El alcance de las compensaciones y motivaciones previstas no interfiere con el respeto a los postulados éticos.

Acuerda por consenso emitir Informe Ético **FAVORABLE** para dicho proyecto.

Para que así conste Dña. MARÍA VALPUESTA FERNÁNDEZ, Vicerrectora de Investigación y Transferencia y Presidenta del Comité Ético de Investigación de la Universidad de Málaga lo firma en Málaga a 9 de diciembre de 2015.

Fdo: María Valpuesta Fernández

Una vez instruido el procedimiento, y en base a lo dispuesto en el artículo 84 de la Ley 30/92, de 26 de noviembre, de Régimen Jurídico de las Administraciones Públicas y Procedimiento Administrativo Común, se le da audiencia para que en un plazo de 10 días, contados a partir de la recepción/publicación del presente informe, pueda formular alegaciones y presentar los documentos y justificaciones que estime pertinentes.

EFQM AENOR

Pabellón de Gobierno, planta 3ª. Campus El Ejido. 29071. Tel.: 952 13 42 04
E-mail- ceuma@uma.es

Appendix 3: CUADERNO DE CAMPO

Doctorado: *Efectos de los soportes plantares en pacientes con artritis reumatoide mediante la medición de calidad de vida y actividad física.*
Tutor *Dr. Gijón Noguerón, Gabriel A.*
Doctoranda *Ramos Petersen, Laura*
Jefe de Servicio Reumatología: *Caliz Caliz, Rafael A.*
Facultad Ciencias de la Salud, Universidad de Málaga
Hospital Universitario Virgen de las Nieves de Granada
Servicio Reumatología

Proyecto de investigación: *Efectos de los soportes plantares en pacientes con artritis reumatoide mediante la medición de calidad de vida y actividad física*

Este documento se le proporciona para darle información suficiente para que pueda entender los posibles riesgos y beneficios derivados de su participación en este proyecto.

Objetivo primario:

Observar las diferencias con respecto a la calidad de vida y actividad física entre los siguientes grupos que serán generados aleatoriamente entre los voluntarios que participaron en el anterior proyecto de investigación ARC0001.

1. Grupo control, el cual se compone de pacientes con Artritis Reumatoide (AR) con plantillas estandarizadas.
2. Grupo de actuación TAD, que se compone de pacientes con Artritis Reumatoide (AR) con plantillas realizadas con la Técnica de Adaptación en Directo (TAD)
3. Grupo de actuación CAD-CAM que se compone de pacientes con Artritis Reumatoide (AR) con plantillas realizadas con la técnica Computer Aided Desing- Computer Aided Manufaturing (CAD-CAM).

Objetivos secundarios:

1. Observar las diferencias con respecto el número de kilómetros recorridos entre los grupos control y de actuación.
2. Observar las diferencias entre los tres grupos seleccionados aleatoriamente definidos anteriormente.
3. Observar las diferencias con respecto el número de horas en pie entre tres grupos seleccionados aleatoriamente definidos anteriormente.

Metodología empleada

El estudio en el que usted participara, ha sido diseñado en la Universidad de Málaga, Facultad de Ciencias de la Salud, departamento de Enfermería Podología, área de Ortopodología, por la Doctoranda Laura Ramos Petersen, dirigido por el Dr Gabriel Gijón Noguerón.

Será llevado a cabo en el Hospital Universitario Virgen de las Nieves, bajo la tutorización clínica del Dr Rafael Caliz Caliz, Jefe de Servicio de Reumatología y el enfermero Andrés Reinoso Cobo.

Los tres tipos de plantillas que se utilizan en el estudio, en el cual usted va a participar, han sido seleccionadas por el equipo de investigación, basándose en las necesidades a cubrir que se han observado en el estudio *"Clasificación del grado de afectación del pie en Artritis Reumatoide"*, en el cual usted participo entre los meses de enero y junio de 2018.

El estudio en el que usted participara se le proporcionaran unas plantilla ortopédicas y se comprometerá a llevarlas durante un año, tiempo requerido para realizar el estudio completo.

El material que se le proporcionara en el estudio es subvencionado por la Universidad de Málaga, Facultad Ciencias de la Salud.

- Firmando este documento se compromete a devolver al equipo de investigación las pulseras Active Graph.
- Sin embargo las plantillas que se le entreguen al inicio del estudio se las puede quedar, sin necesidad de pago alguno, ya que la Universidad de Málaga se hace cargo de los gastos.

En todo momento podrá contar con la ayuda del personal de investigación y con la posibilidad de aclarar cualquier duda que se le presente, llamando a los teléfonos que se le proporcionaran para el control y seguimiento.

Usted siempre tendrá la opción de abandonar el estudio revocando su consentimiento en cualquier momento que lo considere, nunca se ha de sentir obligado a continuar, ni ofrecer explicaciones del motivo.

Ha de saber que su decisión voluntaria de participación o no en el proyecto de investigación, NO condicionara en NINGUN momento la asistencia médica que se le proporciona en el Hospital Universitario Virgen de las Nieves.

Los **BENEFICIOS** que esperamos obtener con dicho estudio, son determinar cuales son los mejores tipos de plantillas ortopédicas que cubran las necesidades de pacientes con Artritis Reumatoide (AR), en la mejora de la calidad de vida de los pacientes con Artritis Reumatoide (AR) y así poder elaborar y recomendar tratamientos ortopocológicos más eficientes para los pacientes con Artritis Reumatoide (AR), y trasladar los resultados a la practica clínica.

También informarle que NO apreciamos **RIESGOS** potenciales para los voluntarios que participen en dicha investigación, al no ser preciso realizar ninguna técnica invasiva, ni procedimiento que ponga en peligro la integridad del paciente.

También le informamos de la confidencialidad y protección de datos de carácter personal, de acuerdo a la Ley que se describe a continuación:

A partir del 25 de mayo de 2018 es de plena aplicación la nueva legislación en la UE sobre datos personales, en concreto el Reglamento (UE) 2016/679 del Parlamento Europeo y del Consejo de 27 de abril de 2016 de Protección de Datos (RGPD). Por ello, es importante que conozca la siguiente información:

- *Además de los derechos que ya conoce (acceso, modificación, oposición y cancelación de datos) ahora también puede limitar el tratamiento de datos que sean incorrectos, solicitar una copia o que se trasladen a un tercero (portabilidad) los datos que usted ha facilitado para el estudio. Para ejercitar sus derechos, diríjase a los investigadores principales del estudio Dr. Rafael Cáliz Cáliz (rcalizcaliz@gmail.com) y/o Gabriel A. Gijón Noguerón (gagijon@uma.es) . Le recordamos que los datos no se pueden eliminar aunque deje de participar en el ensayo para garantizar la validez de la investigación y cumplir con los deberes legales y los requisitos de autorización de medicamentos. Así mismo tiene derecho a dirigirse a la Agencia de Protección de Datos si no quedara satisfecho.*
- *Tanto el Centro como el Promotor son responsables respectivamente del tratamiento de sus datos y se comprometen a cumplir con la normativa de protección de datos en vigor. Los datos recogidos para el estudio estarán identificados mediante un código, de manera que no se incluya información que pueda identificarle, y sólo su médico del estudio/colaboradores podrá relacionar dichos datos con usted y con su historia clínica. Por lo tanto, su identidad no será revelada a ninguna otra persona salvo a las autoridades sanitarias, cuando así lo requieran o en casos de urgencia médica. Los Comités de Ética de la Investigación, los representantes de la Autoridad Sanitaria en materia de inspección y el personal autorizado por el Promotor, únicamente podrán acceder para comprobar los datos personales, los procedimientos del estudio clínico y el cumplimiento de las normas de buena práctica clínica (siempre manteniendo la confidencialidad de la información).*
- *El Investigador y el Promotor están obligados a conservar los datos recogidos para el estudio al menos hasta 25 años tras su finalización. Posteriormente, su información personal solo se conservará por el centro para el cuidado de su salud y por el promotor para otros fines de investigación científica si usted hubiera otorgado su consentimiento para ello, y si así lo permite la ley y requisitos éticos aplicables.*
- *Si realizáramos transferencia de sus datos codificados fuera de la UE a las entidades de nuestro grupo, a prestadores de servicios o a investigadores científicos que colaboren con nosotros, los datos del participante quedarán protegidos con salvaguardas tales como contratos u otros mecanismos por las autoridades de protección de datos. Si el participante quiere saber más al respecto, puede contactar al investigador principal del proyecto Dr. Rafael Cáliz Cáliz (rcalizcaliz@gmail.com) y/o. Gabriel A. Gijón Noguerón (gagijon@uma.es)*

Si precisa de alguna aclaración que no se recoja en este documento o de cualquier duda que le suponga, podrá dirigirse al personal de referencia.

Atentamente

Gijón Noguerón, Gabriel A

Doctorado: *Efectos de los soportes plantares en pacientes con artritis reumatoide mediante la medición de calidad de vida y actividad física.*
Tutor *Dr. Gijón Noguerón, Gabriel A.*
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Jefe de Servicio Reumatología: *Caliz Caliz, Rafael A.*
Facultad Ciencias de la Salud, Universidad de Málaga
Hospital Universitario Virgen de las Nieves de Granada
Servicio Reumatología

CONSENTIMIENTO INFORMADO POR ESCRITO DEL PACIENTE O PARTICIPANTE

Título del estudio: *Efectos de los soportes plantares en pacientes con artritis reumatoide mediante la medición de calidad de vida y actividad física*

Yo el abajo firmante:

Nombre:	Apellidos:

Firma:	A fecha: ____/____/_____
	DNI:

He sido informado por algún miembro del equipo de investigación que se han recogido en este documento.

He leído la hoja de información que se me ha entregado.

He podido hacer preguntas sobre el estudio.

He recibido suficiente información sobre el estudio.

Comprendo que mi participación es voluntaria.

Comprendo que puedo retirarme del estudio:

- Cuando quiera.
- Sin tener que dar explicaciones.
- Sin que esto repercuta en mis cuidados médicos.

Presto libremente mi conformidad para participar en el estudio.

También doy mi autorización para que los miembros del equipo de investigación autorizados por el Hospital Universitario Virgen de las Nieves puedan utilizar los datos recogidos en su historia clínica referentes a la enfermedad de estudio, Artritis Reumatoide, siempre de forma anónima como exige la actual y vigente legislación.

Se me ha informado que todos los datos obtenidos en este estudio serán confidenciales y se tratarán conforme establece la Ley Orgánica de Protección de Datos de Carácter Personal 15/99 y por la legislación en la UE sobre datos personales, en concreto el Reglamento (UE) 2016/679 del Parlamento europeo y del Consejo de 27 de abril de 2016 de Protección de Datos (RGPD).

Se me ha informado de que la información obtenida sólo se utilizará para los fines específicos del estudio.

Yo como investigador/miembro del equipo de investigación me comprometo y garantizo que los datos obtenidos en este estudio solo serán utilizados para los fines específicos del mismo.

Nombre:	Apellidos:

Firma profesional responsable:	A fecha: ____/____/_____
	DNI:

REVOCACIÓN CONSENTIMIENTO INFORMADO

Mediante la firma del presente documento declaro la revocación del consentimiento informado firmado en el que consentí participar en el estudio *"Efectos de los soportes plantares en pacientes con artritis reumatoide mediante la medición de calidad de vida y actividad física"*

Nombre:	Apellidos:

Firma:	A fecha: ____/____/_____
	DNI:

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Departamento de Enfermería y Podología
Facultad de Ciencias de la Salud

FAAM

Por favor, responda a cada una de las preguntas con la respuesta que mejor describa su estado dentro de la última semana. Si la actividad en cuestión se limita por algo más que el pie o el tobillo, marcar *no aplicable*.

Actividades	No dificultad	Leve dificultad	Moderada dificultad	Extrema dificultad	No se puede hacer	No aplicable
1. Estar de pie	4	3	2	1	0	
2. Caminar sin zapatos	4	3	2	1	0	
3. Caminar cuesta arriba	4	3	2	1	0	
4. Caminar cuesta abajo	4	3	2	1	0	
5. Subir escaleras	4	3	2	1	0	
6. Caminar por terreno irregular	4	3	2	1	0	
7. Subir y bajar bordillos	4	3	2	1	0	
8. Estar en cuclillas	4	3	2	1	0	
9. Levantar los dedos	4	3	2	1	0	
10. Empezar a andar	4	3	2	1	0	
11. Andar15 minutos o mas	4	3	2	1	0	

A causa de su pie y tobillo, qué dificultad tiene usted con:

Actividades	No dificultad	Leve dificultad	Moderada dificultad	Extrema dificultad	No se puede hacer	No aplicable
12. Inicio tareas domesticas	4	3	2	1	0	
13. Actividades de la vida diaria	4	3	2	1	0	
14. Leve a moderado trabajo (estar de pie, andar)	4	3	2	1	0	
15. Actividades recreativas	4	3	2	1	0	

¿Cómo calificaría su nivel actual de función durante sus actividades habituales de la vida diaria de 0 a 100 siendo 100 el nivel de la función antes de su problema de pie tobillo y 0 es la incapacidad para realizar cualquiera de sus actividades diarias habituales? _____%

Complete la siguiente sección sólo si usted está involucrado en los deportes, de lo contrario omita esta sección y firme abajo.

A causa de su pie y tobillo, qué dificultad tiene usted con:

Actividades	No dificultad	Leve dificultad	Moderada dificultad	Extrema dificultad	No se puede hacer	No aplicable
16. Correr	4	3	2	1	0	
17. Saltar	4	3	2	1	0	
18. Descenso	4	3	2	1	0	
19. Empezar y para rápidamente	4	3	2	1	0	
20. Movimientos laterales cortos	4	3	2	1	0	
21. Actividades de bajo impacto	4	3	2	1	0	
22. Capacidad para realizar la actividad con su tecnica normal	4	3	2	1	0	
23. Capacidad para participar en su deporte deseado todo el tiempo que quisiera	4	3	2	1	0	

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DE MÁLAGA
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Facultad de Ciencias de la Salud

¿Cómo calificaría su nivel actual de función durante sus actividades habituales de la vida diaria de 0 a 100 siendo 100 el nivel de la función antes de su problema de pie tobillo y 0 es la incapacidad para realizar cualquiera de sus actividades diarias habituales? _____%

En general, ¿cómo calificaría su nivel actual de la función?

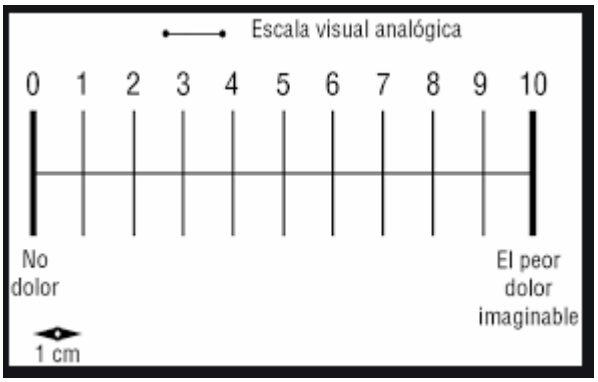
Normal Casi Normal Anormal severamente anormal

_____ _____
Firma de la persona que realiza el formulario Fecha

_____ _____ _____
Entrevistador Fecha Hora

FAAM Puntuación: _____ / 60 FAAM Deportes Puntaje: _____ / 32

Valore su dolor con respecto a los pies según esta escala:



CUESTIONARIO SOBRE EL ESTADO DE SALUD DEL PIE FHSQ

Versión 1.03
Gracias por dedicar parte de su tiempo en rellenar este importante cuestionario.
Las respuestas que nos proporcione ayudarán a su podólogo a atender los problemas de su pie.
Es muy sencillo rellenar el cuestionario y no existen respuestas correctas o incorrectas.
Solamente necesitará 10 minutos para completarlo.

Instrucciones

- Este cuestionario versa sobre la percepción que usted tiene de la salud de su pie
- Lo único que debe hacer es trazar un círculo en cada pregunta alrededor de la respuesta que estime más correcta.
- Si no está seguro sobre cómo responder a alguna pregunta, por favor, dé la respuesta que considere más acertada.

Las siguientes preguntas tratan sobre el dolor que sufrió en el pie durante la semana pasada.

1. ¿Qué tipo de dolor tuvo durante la semana pasada?

(Haga un círculo en el número)

Ninguno	1
Muy leve	2
Leve	3
Moderado	4
Fuerte	5

(redondee un número por cada pregunta de las siguientes)
DURANTE LA SEMANA PASADA…

1-Nunca
2-De vez en cuando 3-Bastantes veces
4-Muy a menudo 5-Siempre

2. ¿Con qué frecuencia sintió dolor en el pie?

1 2 3 4 5

3. ¿Con qué frecuencia le dolían los pies?

1 2 3 4 5

4. ¿Con qué frecuencia sentía dolores fuertes en los pies?

1 2 3 4 5

Con estas preguntas se pretende averiguar de qué manera sus pies interfieren en las actividades que realizaría en un día normal. (redondee un número por cada pregunta de las siguientes)

DURANTE LA SEMANA PASADA…

1-No mucho
2-Levemente
3-De forma moderada
4-Bastante
5-Mucho

5. ¿Le han causado sus pies dificultades en su trabajo o actividades?

1	2	3	4	5

6. ¿Se ha sentido limitado en su trabajo a causa de sus pies?

1	2	3	4	5

7. ¿Cuánto le limita la salud de su pie a la hora de caminar?

1	2	3	4	5

8. ¿Cuánto le limita la salud de su pie al subir escaleras?

1	2	3	4	5

9. ¿Cómo calificaría la salud global de su pie? (Haga un círculo alrededor de un número)

Excelente	1
Muy buena	2
Buena	3
Regular	4
Delicada	5

Las siguientes preguntas tratan sobre los zapatos que utiliza. Por favor, haga un círculo alrededor de la respuesta que más se aproxime a su situación.

1-Muy de acuerdo
2-De acuerdo
3-Indiferente
4-En desacuerdo
5-Muy en desacuerdo

10. Me resulta difícil encontrar zapatos que no me hagan daño en los pies.

1	2	3	4	5

11. ¿Tengo problemas para encontrar zapatos que se me ajusten al pie?

1	2	3	4	5

12. Estoy muy limitado/a en la cantidad de zapatos que puedo utilizar.

1	2	3	4	5

13. En líneas generales, ¿en qué condición diría que se encuentran sus pies?

(Haga un círculo alrededor de un número)

Excelente	1
Muy buena	2
Buena	3
Regular	4
Delicada	5

Por favor, escriba aquí algún comentario sobre el estado actual de sus pies:
……
……
……
……

14. En general, señale cómo calificaría su salud:

Muy buena	1
Regular	2
Delicada	3

15. Las siguientes preguntas versan sobre las actividades que realizaría un día normal. ¿Le limita su salud en estas actividades? Si es así, ¿en qué medida?

Sí, muy limitado	1
Sí, algo limitado	2
No, no estoy limitado	3

ACTIVIDADES

a. **Actividades que requieran esfuerzo físico** como correr, levantar objetos pesados o (si lo desea) su capacidad para participar en deportes que produzcan agotamiento físico

1 2 3

b. **Actividades moderadas** como limpiar la casa, levantar una silla, jugar al golf o nadar 1 2 3

c. Levantar o transportar bolsas de la compra: 1 2 3

d. Subir una cuesta empinada: 1 2 3

e. Subir **un** tramo de la escalera: 1 2 3

f. Levantarse si se encuentra sentado/a: 1 2 3

g. Caminar **más de un kilómetro:** 1 2 3

h. Caminar **cien metros:** 1 2 3

i. Ducharse o vestirse: 1 2 3

16. Mediante la siguiente pregunta se pretende averiguar hasta qué punto su salud física o sus problemas emocionales han interferido en las actividades sociales habituales con su familia, amigos, vecinos o grupos sociales.

(Haga un círculo alrededor de un número)

En absoluto	1
Ligeramente	2
De manera moderada	3
Bastante	4
Mucho	5

17. La finalidad de estas preguntas es averiguar cómo se "siente" y qué le ha sucedido durante el último mes. Para cada pregunta dé la respuesta que más se aproxime a lo que ha estado "sintiendo". Durante cuánto tiempo de las últimas 4 semanas:

1-Todo el tiempo
2-La mayor parte del tiempo 3-Algunas veces
4-Casi nunca 5-Nunca

a. ¿Se ha sentido cansado? 1 2 3 4 5

b. ¿Ha tenido mucha energía? 1 2 3 4 5

c. ¿Ha sentido agotamiento físico? 1 2 3 4 5

d. ¿Se sentía con vitalidad? 1 2 3 4 5

18. Durante las últimas 4 semanas, ¿en qué medida sus problemas emocionales o su salud física han interferido en sus actividades sociales (como visitar a los amigos, familiares, etc.)?

(Haga un círculo alrededor de un número)

En Ningún momento	1
En algún momento	2
De manera regular	3
Bastante veces	4
Todo el tiempo	5

19. Indique si las siguientes afirmaciones son VERDADERAS o FALSAS desde su perspectiva.

(Redondee un número en cada línea)

1-Verdadero o mayoritariamente verdadero 2-No losé
3-Falso o mayoritariamente falso

a. Parece que tiendo a enfermar con más facilidad que otras personas 1 2 3

b. Me siento tan bien de salud como las personas que conozco 1 2 3

c. Imagino que mi salud empeorará: 1 2 3

d. Tengo una salud excelente: 1 2 3

Por favor, complete los siguientes datos:

24. Señale si se encuentra actualmente bajo algún tratamiento por prescripción médica debido a alguno de los siguientes casos:

Por favor marque la casilla adecuada)

Diabetes ☐ Depresión ☐

Osteoartritis ☐ Terapia de Reemplazo Hormonal ☐

Tensión sanguínea ☐ Colesterol alto ☐

Enfermedades del corazón ☐ Dolor de espalda ☐

Enfermedades de los pulmones ☐ Artritis reumatoide ☐

Si está tomando alguna medicación por otras causas, por favor indíquelas:

_____

_____

En las siguientes preguntas, marque **SÍ** o **NO**

	Sí	No
25. ¿Es Vd. pensionista o poseedor de la tarjeta de asistencia sanitaria?	☐	☐
26. ¿Es Vd. fumador?	☐	☐
27. ¿Realiza normalmente algún tipo de ejercicio físico	☐	☐
28. ¿Tiene seguro médico privado?	☐	☐
29. ¿Ha obtenido algún certificado o título de enseñanza desde que acabó el colegio?	☐	☐