Morpho-structural characteristics of feet in patients with rheumatoid arthritis in relation with the years of disease

UNIVERSITY OF MALAGA

SCHOOL OF HEALTH SCIENCES

PHD PROGRAM IN HEALTH SCIENCE

Malaga, January 2022

Presented by
Pekka Anttila

Supervised by

Dr Gabriel Antonio Gijón Noguerón

UNIVERSIDAD
DE MÁLAGA

AUTOR: Pekka Anttila

https://orcid.org/0000-0003-0405-0657

EDITA: Publicaciones y Divulgación Científica. Universidad de Málaga

DECLARACIÓN DE AUTORÍA Y ORIGINALIDAD DE LA TESIS PRESENTADA PARA OBTENER EL TÍTULO DE DOCTOR

D./Dña PEKKA ANTTILA
Estudiante del programa de doctorado CIENCIAS DE LA SALUD de la Universidad de Málaga, autor/a de la tesis, presentada para la obtención del título de doctor por la Universidad de Málaga, titulada: MORPHO-STRUCTURAL CHARACTERISTICS OF FEET IN PATIENTS WITH RHEUMATOID ARTHRITIS IN RELATION WITH THE YEARS OF DISEASE

Realizada bajo la tutorización de JOSE MIGUEL MORALES ASENCIO y dirección de GABRIEL GIJON NOGUERON (si tuviera varios directores deberá hacer constar el nombre de todos)

DECLARO QUE:

La tesis presentada es una obra original que no infringe los derechos de propiedad intelectual ni los derechos de propiedad industrial u otros, conforme al ordenamiento jurídico vigente (Real Decreto Legislativo 1/1996, de 12 de abril, por el que se aprueba el texto refundido de la Ley de Propiedad Intelectual, regularizando, aclarando y armonizando las disposiciones legales vigentes sobre la materia), modificado por la Ley 2/2019, de 1 de marzo.

Igualmente asumo, ante a la Universidad de Málaga y ante cualquier otra instancia, la responsabilidad que pudiera derivarse en caso de plagio de contenidos en la tesis presentada, conforme al ordenamiento jurídico vigente.

En Málaga, a 25 de ENERO de 2022

o.: Doctorando/a	Fdo.: JOSE MIGU Tutor/a
Director/es de tesis	

UNIVERSIDAD DE MÁLAGA

Facultad de Ciencias de la Salud

D. Gabriel Antonio Gijón Noguerón, Doctor por la Universidad de Málaga, Profesor Titular de Universidad del Departamento de Enfermería (Podología) de la Universidad de Málaga.

Certifica que el trabajo presentado como Tesis doctoral por D. Pekka Anttila. "Morpho-structural characteristics of feet in patients with rheumatoid arthritis in relation with the years of disease", ha sido realizado bajo mi dirección y considera que reúne las condiciones apropiadas en cuanto a contenido y rigor científico para ser presentado a trámite de lectura.

Y para que conste donde convenga firmo el presente en Málaga a 17 de Enero de dos mil veintidos.

Fdo. Dr. Gabriel Antonio Gijón Noguerón

Table of contents

Tables

Figure

Abbreviations

ACPA: Anti-CCP is the citrullinated cyclic antipeptide antibody

ACR: American College of Rheumatology

AID: arginine deiminase enzyme, participates in the citrullination process of the amino acid arginine

NSAIDs: Non-steroidal anti-inflammatory drugs.

ALI: Internal longitudinal arch of the foot.

Anti-TNF-α: the inhibitors of tumour necrosis factor α

APC: Antigen presenting cells, in Spanish CPA

Joints of the foot:

• AAE: Talar-scaphoid joint

• ACaCu: Calcaneocuboid articulation

• ACCu: Cuneocuboid joint

• ACM: Cuneometatarsal joint

• ACuM: Cuboid-metatarsal joint

• AEC: Scapho-cuneal articulation

• AECu: Scapho-cuboid joint

• AIC: Intercuneal joints

• AIF: Interphalangeal joints

• POINT. Intermetatarsal joints

• AMTF: Metatarsophalangeal joints

• ASA: Subtalar joint

• ATPA: Tibioperoneal talar joint

• MTT: Metatarsals

RA: Rheumatoid arthritis

SD: Standard deviation

DMARD: Disease-modifying antirheumatic drugs, see FARMS

DMARD: Synthetic disease-modifying antirheumatic drugs

DMARDb Biologic disease-modifying antirheumatic drugs

EULAR: European League Against Rheumatism

FARM: Disease modifying antirheumatic drug

HLA gene: Gene responsible for the human leukocyte antigen

GM-CSF: Granulocyte and macrophage colony stimulating factor

HAV: Hallux abductus valgus

HDA: High disease activity

IL: Interleukins

IC: Internal consistency

ICC: Interclass correlation coefficient

LDA: Low disease activity

MDA: Moderate disease activity

PF: Plantar Fascia

RF: Rheumatoid Factor

Evaluation methods:

• OSA: Ankle Osteoarthritis Scale

• CDAI: Index of clinical activity of the disease

• DAS28: Disease Activity Score

• VAS: Visual scale to assess pain, usually from 0 to 10

• EQ-5D: EuroQol 5 dimensions

• FAAM: Foot and Ankle Ability Measure

• FFI: Foot Function Index

• FHSQ: Foot Healing Status Questionnaire

• FPI: Foot Posture Index

• LFIS: Leeds Foot Impact Scale

• HAQ: Health Assessment Questionnaire

• MFPDI: Manchester Foot Pain Disability Index

• MHAV: Manchester Hallux Abductus Valgus Scale

• PAS: Patient Activity Score

• RAPID3: Routine evaluation of patient index 3 data

• SDAI: Simplified Disease Activity Index

• SEFAS: Self-reported Foot and Ankle Score.

• SF12: Abbreviated form 12 of the Medical outcome study

• SF36: Short form 36 of the Medical outcome study

• SJC28: Count of swollen joints (in Spanish NAD) (out of 28)

• TJC28: Swollen joint count (NAT in Spanish) (out of 28)

MHC: Major histocompatibility complex (in Spanish it corresponds to HLA)

MTX: Methotrexate

RANGE: Nuclear factor kappa beta receptor (acronym)

RANKL Activating receptor ligand for nuclear factor kappa beta, belongs to the TNF group (acronym in English)

NF-κβ: Nuclear factor kappa beta

PAD: Peptidyl arginine deiminated enzyme, participates in the citrullination process of the amino acid arginine

CRP: C Reactive protein

REM: Remission

NMR: Nuclear magnetic resonance

TNF-α: Tumour necrosis factor α (acronym)

CT: Computed Axial Tomography

Extrinsic tendons of the foot:

• EN: Achilles tendon

• EC: Common extensor tendon

• EH: Extensor hallux tendon

• FC: Common flexor tendon

• FH: Flexor hallux tendon

• PLC: Short peroneal tendon

• PLL: Long peroneal tendon

• TA: Anterior tibial tendon

• TP: Posterior tibial tendon

ESR: Erythrocyte sedimentation rate

Chapter I

Summary

Abstract:

Objective: The aim of this study was to evaluate and classify the types and incidences of foot deformities in patients with Rheumatoid Arthritis (RA).

Methods*:* A cross-sectional study with a convenience sample was obtained of 220 patients with foot pain and RA classification criteria (approved by the American College of Rheumatology and the European League Against Rheumatism in 2010). A series of outcomes were assessed to measure the morphological characteristics of the feet. The Foot Posture Index (FPI), the Manchester Scale of Hallux Valgus and the Nijmegen classification of forefoot disorders were assessed.

Results**:** The most common foot posture according to the FPI assessment are the pronated position in the left foot (32.7% of participants) and the neutral position in the right foot (34.1% of participants). The disease progression causes more advanced and serious foot deformities. 1.82% of patients present a severe level of Hallux Valgus before 10 years of disease evolution whereas 4.09% of patients present a severe level of Hallux Valgus after 10 years of disease evolution.

Conclusions**:** The most common foot type in patients with RA is the pronated foot type with deformities in the MTP joints without Hallux Valgus. However, a percentage of patients with RA presents supinated foot type. The evolution of the disease shows some morphological changes in terms of patient's feet. The presence of more developed foot deformities is increased, such us Hallux Valgus or MTP joints deformity (Grade 3 in the Nijmegen classification scale).

Chapter II

Spanish Summary

Resumen

La artritis reumatoide (AR) es una enfermedad inflamatoria crónica y progresiva que puede causar limitaciones y dificultades en las actividades de la vida diaria (AVD) y dolor. Como resultado, los pacientes pueden presentar alteraciones de la marcha y dificultades para el autocuidado (1). La prevalencia de la artritis reumatoide (AR) se establece entre el 0,5 y el 1% de la población general, con una relación de predominio femenino de 3/1. La prevalencia también tiene una variabilidad asociada con poblaciones genéticamente diferenciadas donde las poblaciones del norte aumentan esta predisposición. La incidencia estimada anual es de 16,5 casos por cada 100.000 habitantes en los países del sur de Europa y de 29 en los del norte de Europa. Hay un pico de incidencia en mujeres de 50 a 60 años, donde se diagnostican el mayor numero de casos, aunque no es de extrañas encontrar población mas joven, sobre todo en mujeres con antecedentes familiares . Las tasas de incidencia de la AR en España son de 135 por 100.000 mujeres y 46,7 por 100.000 hombres (2016). Aunque se ha observado que en los últimos 30 años la incidencia ha disminuido gracias en parte a los nuevos tratamiento farmacológicos como son los biológicos, que actúan en la enfermedad, disminuyendo o en algunos casos frenando los casos mas severos de brotes y dolor en estos pacientes(2).

Para el diagnostico de la enfermedad la Asociación Americana de Reumatología junto a Asociación Europea de Reumatología crean unos criterios en 1987, que son modificados por un comité de expertos en 2010, siendo los siguientes (Criterios ACR/EULAR 2010)
– Presentar al menos 1 articulación con sinovitis clínica, es decir, al menos 1 articulación inflamada y además que dicha sinovitis no se pueda explicar por otra enfermedad.
– Tener una puntuación igual o superior a 6 según el sistema de puntuación donde se encuentren tanto articulaciones denominadas pequeñas como la de manos y pies, y articulaciones grandes como son la de la rodilla, cadera o hombro y que tiene en cuenta los siguientes parámetros:
1) La afectación articular. (distribución y cuantificación).
2) Serología (FR y/o ACPA, y de los reactantes de fase aguda)
3) La duración debe ser igual o superior a 6 semanas
Estos criterios también serán de aplicación para hacer el diagnóstico en pacientes que presenten una AR evolucionada siempre que:
- Presenten erosiones típicas de AR.
- Presenten una enfermedad (activa o inactiva) de larga evolución y cuyos datos retrospectivos de la historia clínica permitan la clasificación según los criterios mencionados.
O también en aquellos pacientes con artritis de muy reciente comienzo, que no cumplan en un momento dado dichos criterios pero que los cumplan a posteriori con la evolución de la

enfermedad.

Existen múltiples afectaciones en el miembro superior e inferior (3), así como la calidad de vida de los pacientes con AR se ve muy afectada desde el comienzo de la enfermedad (4) , la aparición de fatiga es uno de los primeros síntomas de la misma, donde reflejan mas de 70% de los pacientes que debutan con esta patología (5). La AR se asocia con un dolor significativo y deformidades, donde los individuos continúan realizando actividades con restricción de la capacidad funcional. La fatiga y la discapacidad funcional sobrevienen con la progresión de la enfermedad (6), lo que precede a la limitación de movimiento y al empeoramiento de las capacidades biopsicosociales del paciente.

Existe una alta prevalencia de afectación del pie en la AR y más del 90% de los pacientes informan dolor en el pie durante el curso de la enfermedad (7). Se ha sugerido que pueden ocurrir cambios erosivos en las articulaciones de las manos y los pies, particularmente en las articulaciones metatarsofalángicas (MTP), donde la afectaciones son mas graves por el aumento de la carga mecánica que soporta estas articulaciones debido al proceso de la deambulación (8). La inflamación de las articulaciones del pie y los tejidos sinoviales provoca daño articular y deformidades estructurales. Las deformidades más comunes del pie en pacientes con AR incluyen subluxación dorsal de las articulaciones MTP menores, hallux valgus (HV), metatarsus primus varus (MPV), hallux rigidus, retropié valgus, pie plano (PP) y extensión del antepié (SF) (9), todo ello unido a marchar antialgicas que pueden provocar dolores en otras articulaciones de la extremidad inferior debido a las desalineaciones producidas por estas alteraciones antes mencionadas.

Además, existe afectación del trofismo cutáneo con lesiones como formación de callos y úlceras que se asocian a las desviaciones antes mencionadas. Se estima que la ulceración del pie afecta a 10 a 13% de los pacientes con AR durante el curso de su enfermedad, sobre todo a nivel de los dedos, por dedos en garra o en martillo, o en la zona plantar a nivel de las cabezas metatarsales, ya que son los puntos de mas presión debido a las deformidades y luxaciones provocadas por estas alteraciones. Además, el 47% de los pacientes afectados experimentan múltiples episodios de ulceración que afectan a numerosos sitios del pie (10). Sin embargo, se desconocen las deformidades y la estructura morfológica de los pies en los pacientes con AR.

La artritis reumatoide perjudica la vida diaria normal, afecta la imagen corporal y las relaciones personales y, por lo tanto, también afecta la calidad de vida, el simple hecho de condicionar el uso de un calzado standard a este tipo de paciente, disminuye los niveles de autoestima, y si a eso unimos que el porcentaje de estos pacientes son

mujeres, dificulta de una manera exponencial el uso de calzado genérico. Por ello hay un costo social y económico significativo, las visitas constantes al podólogo, o la compra de calzado ortopédico por parte del paciente merma la economía de la misma, uniéndose a la incapacidad en muchos casos de poder trabajar. La afectación del pie y el dolor articular del pie son características distintivas de la AR temprana y casi omnipresentes durante el progreso de la enfermedad, con el consiguiente deterioro físico y psicosocial. La estrategia actual es una estrategia de tratar al objetivo, tratando la AR activa para lograr un objetivo de remisión o menor actividad de la enfermedad en los casos en que no se pueda lograr la remisión. El propósito por tanto es proporcionar alivio del dolor, preservar la actividad física y la calidad de vida

El factor de riesgo genético más importante para la aparición de AR está asociado al complejo mayor de histocompatibilidad (MCH), especialmente al "Antígeno Leucocitario Humano" (HLA), al que se le atribuye entre el 30% y el 50% del riesgo genético total (6).

-Edad: El punto de máxima incidencia en mujeres es a los 55-64 años y en hombres a los 65-75 años. El aumento de la edad los hace más susceptibles a desarrollar AR. Del mismo modo, existe una mayor severidad de la AR a medida que aumenta la edad de aparición de la AR (7).
-Hormonal: En las mujeres, la AR se desarrolla con frecuencia durante los períodos de tiempo en los que las hormonas esteroides fluctúan mucho, como el posparto y la perimenopausia (8).
-Ambiental: Hay ciertas infecciones que pueden causar AR, como infecciones por parvovirus y rubéola. Estos pueden activar la AR en ciertos individuos, pero es una pequeña proporción de la prevalencia . También parece haber un alto riesgo de enfermedad en individuos después de una transfusión de sangre (2).

La artritis reumatoide es una de las enfermedades en las que es más común la afectación articular, su forma de presentación típica es una poliartralgia de inicio gradual, con afectación articular simétrica, especialmente en manos y pies, y con degeneración erosiva articular, afectándose las articulaciones sinoviales independientemente de su tipo y su tamaño (2). La inflamación sinovial o sinovitis crónica provoca a corto plazo, dolor articular, tumefacción, rigidez articular matinal (de al menos 1 hora de duración

antes de mejorar), y a largo plazo, con la evolución de la enfermedad, conlleva una progresiva destrucción articular con presencia de deformidades anatómicas que deterioran y limitan la funcionalidad de dichas articulaciones. Otros signos y síntomas que pueden aparecer son: malestar general, astenia, fiebre o febrícula, dolores musculares, anorexia y/o pérdida de peso, que son muy inespecíficos y comunes también en otras patologías (6)

Objetivos

El objetivo principal

- El objetivo de este estudio es evaluar y clasificar los tipos de pies y la frecuencia de las deformidades de los pies en pacientes con AR.

Objetivos secundarios

- Determinar la relación de la postura del pie con los años de evolución de la enfermedad
- Determinar la relación de las desviaciones del Hallux valgus con la evolución de la enfermedad
- Determinar la relación de las desviaciones de los radios menores con la evolución de la enfermedad
-

Materiales y métodos

Aprobación ética: Comité de revisión institucional que aprobó el protocolo del estudio: Comité de Ética en Investigación Médica de la Universidad de Málaga (CEUMA-91-2015-H) y PEIBA Andalucía (ARC0001), España.

Diseño: un estudio transversal

Participantes: Se obtuvo una muestra de conveniencia de 237 pacientes con dolor de pie y criterios de clasificación de AR (aprobados por el American College of Rheumatology y la European League Against Rheumatism en 2010) (11), de los cuales 17 posteriormente declinaron participar por falta de tiempo (el cuestionario del estudio requirió 30 minutos para completar). Los pacientes fueron inscritos en clínicas ambulatorias hospitalarias de enero a diciembre de 2018. Todos los participantes incluidos en el estudio eran adultos (mayores de 18 años) que tenían antecedentes de dolor subastragalino y / o tobillo y / o talonavicular o retropié, no hacer uso diario de ayudas para caminar, y fueron capaces de lograr el rango normal de movimientos en el tobillo, las articulaciones subastragalina y mediotarsiana (incluso si no se pudo producir la máxima dorsiflexión, pronación o supinación en estas articulaciones, se logró un rango de movimiento suficiente ajustar la dinámica, por ejemplo, reduciendo la longitud de

la zancada) (12). Los criterios de exclusión aplicados fueron presentar una enfermedad musculoesquelética concomitante, enfermedad del sistema nervioso central o periférico y / o trastornos endocrinos (especialmente diabetes mellitusLos pacientes que cumplían los criterios de inclusión fueron abordados por miembros del servicio de reumatología del Hospital Virgen de la Nieves (Granada, España), entregados una ficha informativa e invitados a participar. Los participantes que estuvieron de acuerdo fueron entrevistados y se les dio más detalles del estudio. Todos los participantes dieron su consentimiento por escrito antes de comenzar las entrevistas.

Recolección de datos

Características demográficas y clínicas

Las características demográficas registradas incluyeron la edad, el sexo, la duración de la enfermedad y la terapia actual del paciente. Los datos clínicos registrados para evaluar el estado de la enfermedad de los pacientes fueron la escala analógica visual para el dolor (dolor EVA) La escala analógica visual para el dolor (VAS pain) (13) es una medida subjetiva validada para el dolor agudo y crónico. Los puntajes se registran haciendo una marca escrita a mano en una línea de 10 cm que representa un continuo entre "sin dolor" y "el peor dolor" (13), esta es la manera mas utilizada en la literatura científica para recoger los datos , la puntuación de actividad de la enfermedad-28 (DAS28) Este índice fue desarrollado para medir el grado de actividad de la enfermedad durante los años 80 y posteriormente fue publicado en 1990 por Van der Heijde et al. DAS utilizaba en origen la valoración de 44 articulaciones en su recuento, posteriormente algunos autores consideraron que tanto las articulaciones de tobillo como las del pie, debido a su localización y por la presencia en el pie de signos o síntomas de otras patologías que pudieran inducir a error en el recuento articular, presentaban una mayor dificultad para ser evaluadas, por lo que propusieron una versión simplificada de sólo 28 articulaciones (14) Los rangos de puntuación resultantes se interpretan:

•Menos de 2,6: Remisión de la enfermedad.

•De 2,6 hasta < 3,2: Actividad de la enfermedad BAJA.

•Entre 3,2 y 5,1: Actividad de la enfermedad MODERADA.

•Mayor de 5,1: Actividad de la enfermedad ALTA.

y el índice de actividad de la enfermedad simplificado (SDAI) El SDAI es un método cuantitativo de evaluación de la enfermedad que tiene en cuenta además del recuento de la presencia de dolor e inflamación en 28 articulaciones seleccionadas, una valoración global de la actividad de la enfermedad utilizando para ello una escala EVA percibida tanto por el profesional como por el propio paciente y por último los valores analíticos de la proteína C reactiva (PCR).

Fórmula: SDAI = SJC(28) + TJC(28) + PGA + EGA + PCR (15).

Se evaluaron una serie de resultados para medir las características morfológicas de los pies. El índice de postura del pie (FPI) es un instrumento confiable para este propósito (16). Además, se evaluó la Escala de Manchester de Hallux Valgus (17) y la clasificación de Nijmegen de los trastornos del antepié (9).

Procedimiento

Dos investigadores (ARC y GGN) entrevistaron de forma independiente a los pacientes para obtener los datos del estudio. La entrevista clínica se llevó a cabo en una sala, donde se pidió a los pacientes que completaran las características demográficas. En una habitación separada, se midió la postura del pie de cada paciente.

Para ello, se evaluó el FPI (coeficiente de correlación intraclase (CCI) para el clínico, 0,94-0,96). Es un criterio para la medición de la postura del pie , determinando si se considera un pie neutro, pronado , supinado o altamente pronado os supinado. Para ello se mide mediante una escala liker, cada criterio se calificó como -2, -1, 0, +1 o +2, donde los valores positivos se asocian con pies pronados, mientras los valores negativos se relacionan con pies supinados , la suma de los 6 items evaluados dentro del pie 1.Palpacion de la cabeza del astrágalo, 2 Curvatura infra y supra maleolar, 3 Angulo de calcáneo, 4. Espacio retromaleolar, 5. Curvatura del arco longitudinal interno y 6. Signo de mas menos dedos , estos se valoran tanto en sus planos sagital, frontal y transversal, como en las unidades funcionales de antepie, mediopie y retropié.. Se utilizaron los siguientes puntos de corte del FPI, que definen la categoría de tipo de pie: a) muy supinado de −12 a −4, b) supinado de −3 a 0, c) neutro de 1 a 6, d) pronado de 6 a 10 y e) muy pronado de 11 a 12 (18).

La presencia / ausencia de hallux valgus se determinó de acuerdo con la Escala de Manchester de Hallux Valgus (ICC para el instrumento, 0,93-0,97). Es una herramienta clínica que consiste en fotografías de pies con cuatro niveles de hallux valgus: ninguno, leve, moderado y severo (17). Se realiza una fotografía del pie en su cara dorsal, y se compara con las originales del autor Adam Garrow, que comparo dichas fotografías con ángulos radiológicos de esos mismos pies, determinando una excelente correlación del instrumento. Como limitación de esta herramienta, decir que al ser un elemento visual el periodo de entrenamiento debe ser de mínimo 30 sujetos. Para este estudio el. Mismo observador fue quien midió todos los participantes, con ICC de 0,92-0,96, por lo que se considero valido como evaluador.

La clasificación de Nijmegen de los trastornos del antepié es un sistema de clasificación que se puede utilizar para clasificar la gravedad de la deformidad del antepié. El antepie es una de las unidades del pie que mas se afectan en los pacientes con AR. Presenta cuatro niveles diferentes para evaluar la deformidad: Grado 0. Sin cambios clínicos en las articulaciones metatarsofalángicas (MTP), cambios radiográficos leves o nulos; Grado 1. Disminución de la movilidad de una o más de las articulaciones, particularmente de la flexión plantar, con la capacidad de reducir los tejidos blandos plantares debajo de las cabezas de los metatarsianos, y con una calidad adecuada de los tejidos blandos plantares y / o cambios radiográficos erosivos (Larsen 2- 5) o cambios intraarticulares evidentes; Grado 2. Pérdida de la flexión plantar en una o más de las articulaciones MTP (hasta 00) y pérdida de la capacidad de reducir los tejidos blandos plantares debajo de las cabezas de los metatarsianos y / o con calidad inadecuada de los tejidos blandos plantares A. con un hallux valgus de más de 20º B. sin un hallux valgus de más de 20º; Grado 3. Contractura profunda en una o más articulaciones MTP, con o sin subluxación o luxación radiográfica A. con hallux valgus de más de 20º. B. sin hallux valgus de más de 20º (9) (CCI para el médico, 0,83-0,87).

Análisis estadístico

El análisis bivariado se realizó con la prueba t de Student y la prueba no paramétrica de Wilcoxon; para la asociación de variables cualitativas se utilizó la prueba de chi-cuadrado para la comparación de proporciones. El nivel de significancia se fijó en $p < 0,05$. Todos los análisis estadísticos se realizaron utilizando el software estadístico SPSS v. 24.0 (SPSS Inc., Chicago, IL, EE. UU.).

Resultados

En total, se analizaron 220 pacientes con AR (promedio de duración de la AR en años, 15,44, DE 10,54 años), 173 pacientes eran mujeres. Los valores de mediana de edad y rango intercuartílico (RI) fueron 59 y 16 años para los pacientes con AR. Los valores medianos de altura y peso fueron 162 cm (RI: 10) y 65 kg (RI: 15). Los pacientes con AR fueron tratados con fármacos antirreumáticos modificadores de la enfermedad biológicos (bDMARD) (42%), metotrexato (35%) o fármacos antiinflamatorios no esteroideos (AINE) / corticosteroides (20%). DAS 28 2,77 (SD 1,27) y SDAI 10,10 (SD 7,88)

La postura del pie más común según la evaluación del FPI son la posición pronada en el pie izquierdo (32,7% de los participantes) y la posición neutra en el pie derecho (34,1% de los

participantes). En pacientes con menos de 10 años de AR en pacientes que fueron diagnosticados hace menos de 10 años, el pie derecho ha mostrado una posición supinada (13,64% de los participantes). Por otro lado, en pacientes después de los 10 de evolución de la AR, lo más común es que el pie derecho tenga una postura neutra (19,55% de los participantes). En el pie izquierdo se muestran diferentes resultados. En pacientes después de 10 de evolución de la AR, el pie izquierdo se encuentra en posición pronada (19,55% de los participantes). Se encontraron diferencias no estadísticamente significativas usando la prueba de chi-cuadrado en pies de botas ($p = 0.098$ y$p = 0.257$)

Con respecto a la deformidad en hallux valgus, la progresión de la deformidad en general se ve agravada por la deformidad en hallux valgus. El 1,82% de los pacientes presenta un nivel severo de Hallux Valgus antes de los pacientes después de 10 de evolución de la AR, mientras que el 4,09% de los pacientes presenta un nivel severo de Hallux Valgus después de los pacientes después de 10 de evolución de la AR. No se encontraron diferencias estadísticamente significativas utilizando la prueba de chi-cuadrado en el pie derecho ($p = 0.573$), sin embargo, se encontraron diferencias estadísticamente significativas en el pie izquierdo ($p = 0.024$).

En cuanto a las deformidades metatarsofalángicas menores, se presentan diferencias estadísticamente significativas en ambos pies ($p = 0,013$ y$p = 0,007$). El Grado 3 aumenta su porcentaje en ambos pies en pacientes con más que en pacientes después de 10 de evolución de la AR.

Discusión

El objetivo de este estudio transversal fue evaluar y clasificar los tipos y la frecuencia de las deformidades del pie en pacientes con AR. Para el propósito de este estudio, se evaluó el tipo de pie definido por FPI, la Escala de Manchester de Hallux Valgus (17) y la clasificación de Nijmegen de los trastornos del antepié en pacientes con AR. Como resultado, se describió la prevalencia del VHA, las deformidades del antepié y el tipo de pie.

En estudios anteriores, donde se mencionaron diferentes deformaciones estructurales en el pie, no se describió el método cuantitativo utilizado para demostrar estos cambios estructurales (19,20). En nuestro estudio, para evitar el mismo sesgo, se han incluido resultados validados del pie, excepto la clasificación de Nijmegen. Nuestros resultados se pueden comparar con los resultados de Biscontini et al. en 2009 (21), donde tras utilizar el FPI y el Manchester Hallux Valgus concluyeron que los pacientes con AR pueden presentar frecuentemente hallux valgus y pie en pronación.

Ambos estudios coinciden en que los pies de los pacientes con AR padecen patología en valgo y deformidad en el antepié. Sin embargo, varios estudios han demostrado que aparecen algunas alteraciones musculoesqueléticas en los miembros superiores, como atrofia muscular, rotura de tendones, disminución del rango de movimiento articular, inestabilidad articular, rigidez, dolor y deterioro biomecánico. Todas esas alteraciones no están asociadas a la deformación osteoarticular del pie (22,23). Además, nuestro estudio aporta datos de evolución del proceso con la diferenciación entre pacientes que presentan AR antes y después de los 10 años. A diferencia de estudios anteriores. como Lee S.W. et al., que analizaron la incidencia de afectación de pie y tobillo en pacientes con una evolución media de la enfermedad de solo 8 años, cuantificando el número de articulaciones afectadas con dolor, inflamación y alteraciones radiológicas en pie y tobillo (20).

Si tenemos en cuenta la evolución de la enfermedad, podemos distinguir tres procesos clínicos diferenciados (23): 1) Evolución progresiva, en la que se produce un aumento progresivo de la afectación articular, es el patrón más frecuente. 2) Evolución intermitente, en la que existen periodos de remisión total o parcial, y en periodos sucesivos se va incrementando el número de articulaciones afectadas. 3) Evolución remitente, en la que existen largos períodos de remisión de la enfermedad.
Es por ello que en enfermedades como la AR, la evaluación frecuente y continuada de los pacientes nos va a permitir valorar la evolución enfermedad, la respuesta del paciente al tratamiento, así como la aparición de posibles efectos adversos, donde el pie debe ser parte de estas revisiones, ya que actualmente no esta contemplado esa opción .
En este sentido las revisiones del paciente deberían realizarse en intervalos más cortos cuando la actividad de la enfermedad sea de moderada-grave (intervalo de revisión de 1 a 2 meses), para valorar posibles cambios de tratamiento que permitan el control de la inflamación y en pacientes en remisión o con baja actividad se podrían espaciar las visitas hasta 3-6 meses (2), parte de nuestro estudio determina que las deformidades podría estar asociada a la evolución de la enfermedad, lo que reitera la importancia del pie dentro de la enfermedad.

Como se ha descrito en nuestro estudio, una gran cantidad de pacientes, especialmente mujeres, con AR padecen hallux valgus y deformidades menores en los dedos como disminución de la movilidad de una o más de las articulaciones MTP, reducción de los tejidos blandos debajo de las articulaciones MTP y / o cambios erosivos radiográficos. Se ha discutido en estudios anteriores que los síntomas del pie son casi omnipresentes entre los pacientes con AR y con frecuencia son graves, a pesar del progreso excepcional en los tratamientos de la AR (2).

Sin embargo, Yano et al. Solo se analizó la incidencia de pacientes que presentaban alteraciones en el pie al momento del diagnóstico, sin reportar la prevalencia de deformaciones del pie (19) .Las primeras manifestaciones del pie suelen ser en el antepié, y estas deformidades del pie empeoran con el tiempo (2). Esto concuerda con nuestros resultados que muestran que los pacientes con AR presentan niveles más altos de Hallux Valgus grave en pacientes después de los 10 años de evolución de la AR que antes de los 10 años de evolución. El desarrollo del VHA en pacientes con AR ocurre en un período de tiempo más corto que en la población general debido a las siguientes alteraciones estructurales del pie: aumento de la presión medial en el antepié; sinovitis en la primera articulación MTP, que provoca laxitud e inestabilidad de la cápsula articular; erosión articular que ayuda a la desviación en el plano transversal de la primera articulación MTP y aumento de la laxitud del ligamento de Lisfranc aumentando el ángulo intermetatarsiano (24,25).

Los resultados del FPI de los participantes incluidos mostraron que los pacientes con AR presentan una amplia variedad de tipos de pie, incluida la postura neutra, en pronación, sobrepronación y supinación del pie. La postura del pie más común fue la posición neutra y en pronación, mostrando una intención de valores más altos en el FPI después de 10 años de evolución de la enfermedad, lo que significa postura del pie en pronación. Estos resultados concuerdan con estudios previos que concluyeron que el retropié se encuentra frecuentemente en posición de valgo en pacientes con AR. La presencia de una alteración en la alineación articular, una reducción de la movilidad y un cambio en la distribución de la presión en la cara medial del pie progresan en una deformación en valgo (24–26).

Fortalezas y debilidades del estudio:

Las fortalezas de este estudio incluyen; medidas de resultado y cuestionarios validados y fiables utilizados para evaluar los tipos de pie y la frecuencia de las deformidades del pie en pacientes con AR. Todos los participantes presentaron una mayor duración de la enfermedad de más de 10 años, lo que sirvió para establecer una clasificación antes y después de los 10 años de evolución. Además, se ha seguido un protocolo con cada paciente. Las limitaciones asociadas con este estudio deben reconocerse al interpretar los resultados. Primero, todos los participantes eran principalmente mujeres, lo que se correlacionó con la información de que la AR se encuentra con mayor frecuencia en mujeres en Europa. En segundo lugar, se debería haber evaluado la influencia del tratamiento biológico para diferenciar los efectos de los tratamientos en los tejidos blandos (ligamentos y músculos). El tratamiento biológico puede influir en los tejidos blandos según el tiempo de uso del tratamiento. Como resultado, el tratamiento biológico puede influir en la apariencia del tipo de pie en pronación.

Investigación futura:

En estudios posteriores, es necesario analizar tamaños de muestra más homogéneos, ya que un tamaño de muestra no homogéneo puede influir en los resultados. Además, se requieren estudios con resultados que permitan establecer una relación entre el dolor, la pérdida de funcionalidad y/o calidad de vida y la deformidad de los pies.

Es necesario aumentar el conocimiento sobre el impacto de la AR en los pies y desarrollar tratamientos podológicos que consideren los años de evolución de la enfermedad. Adicionalmente, el desarrollo de un sistema que dé seguimiento a los pacientes cada 6 meses sobre su enfermedad y los cambios producidos en sus pies ayudaría a determinar de manera más efectiva el procedimiento para tratamientos farmacológicos y no farmacológicos.

Limitaciones:

Las limitaciones asociadas con este estudio deben reconocerse al interpretar los resultados. Primero, todos los participantes eran principalmente mujeres, lo que se correlacionó con la información de que la AR es más común en mujeres en Europa. En segundo lugar, se debería haber evaluado la influencia del tratamiento biológico para diferenciar los efectos de los tratamientos sobre los tejidos blandos (ligamentos y músculos). El tratamiento biológico puede influir en los tejidos blandos dependiendo de cuánto tiempo se haya utilizado el tratamiento. Como resultado, el tratamiento biológico puede influir en la aparición de tipos de pie en pronación, la deformación mas frecuente encontrada en nuestro trabajo, determina que el pie pronado será una de las consecuencias mas determinantes en el pacientes, y se debería analizar una evolución longitudinal, limitación que no se abordado desde este estudio, pero que seguirá analizándose por parte del equipo de investigación sobre AR.

Conclusiones

1. El tipo de pie más frecuente en pacientes con AR es el pie en pronación, con deformidades en las articulaciones metatarsofalángicas sin Hallux Valgus. Sin embargo, un porcentaje de pacientes con AR presentan un pie en supinación.

2. La evolución de la enfermedad muestra algunos cambios morfológicos en cuanto a los pies del paciente. Se presenta una evolución de estadios más severos de las deformidades del pie, como Hallux Valgus o Grado 3 de las articulaciones MTF en la escala de clasificación de Nijmegen.

3. Los pies de pacientes con AR y más de 10 años de evolución aumentan su grado de pronación según el

Foot Posture Index.

4. El grado de severidad de la deformidad del hallux está aumentado según la escala de Manchester en pacientes con AR de más de 10 años de evolución.

5. El grado de severidad de la deformidad de la articulación metatarsofalángica por categorías de la clasificación de Nijmegen aumenta en pacientes con más de 10 años de evolución

Chapter III

Introduction

1. Introduction

1.1 Rheumatic diseases

Rheumatic diseases are a set of health disorders that affect the locomotor system (bone, joints, muscles, tendons, ligaments), and connective tissue (collagenases, connective tissue diseases, systemic diseases), as well as more than 250 diseases.

a. Inflammatory connective tissue diseases and vasculitis:

- Rheumatoid arthritis
- Systemic lupus erythematosus
- Scleroderma
- Dermatomyositis / Polymyositis
- Sjögren's syndrome
- Other inflammatory connective tissue diseases
    - Recurrent polychondritis
    - Primary antiphospholipid syndrome

b. Connective tissue overlap syndromes. Mixed connective tissue disease

c. Juvenile Chronic Arthritis. Adult Still's disease

d. Vasculitis

- Panarteritis nodosa
- Wegener's granulomatosis
- Churg-Strauss disease
- Temporal arteritis
- Polymyalgia rheumatica

- Takayasu arteritis
- Hypersensitivity vasculitis
- Schonlein-Henoch disease
- Behçet's disease
- Kawasaki disease

e. Inflammatory Spondyloarthropathies:

- Ankylosing spondylitis
- Reactive arthritis
- Reiter syndrome
- Psoriatic arthritis

f. Osteoarthritis:

- Peripheral joint osteoarthritis
- Hip osteoarthritis
- Interphalangeal osteoarthritis
- Knee osteoarthritis

g. Infection-related arthritis:

- Rheumatic fever
- Lyme's disease

h. Microcrystalline Arthropathies:

- Acute gout
- Calcium pyrophosphate deposition arthropathy

i. Extra-articular Rheumatisms: Regional and general painful syndromes

- Fibromyalgia, soft tissue rheumatism
- Ligament hypermobility

1.2 Rheumatoid arthritis

Rheumatoid arthritis is a chronic, systemic, autoimmune, inflammatory, symmetric, and degenerative disease, and its symptoms being unpredictable and fluctuating. Foot involvement is estimated in approximately 90% of patients. Joint deterioration in the foot causes an imbalance that causes frequent deformations of the foot in patients with rheumatoid arthritis.

The scales and forms of measurement used in studies of the foot in patients with rheumatoid arthritis usually analyse the functionality, pain, joint deterioration, the number of affected joints, or scales designed for the evaluation of another pathology are used.

In 1987 the American College of Rheumatology (ACR) selected the criteria that allow healthcare professionals to differentiate RA from other arthropathies with similar pathologies. The importance of predictive markers such as ACPA was not yet known, and only RF and radiographic changes (joint erosion, loss of periarticular bone density) were included. The objective in 1987 was purely to avoid errors in the diagnosis of RA (11,27).

Seven criteria were defined and established that a patient could have RA if he or she fulfilled at least 4 criteria. One of the criteria, as we see in the following table (see table 1), corresponds to bone erosion and periarticular osteopenia characteristic of the disease, but it is not typical of the early stages, therefore it is not valid for a premature diagnosis (11).

Criterion	Definition
1. Morning stiffness	Morning stiffness in and around the joints, lasting at least 1 hour before maximal improvement
2. Arthritis of 3 or more joint areas	At least 3 joint areas simultaneously have had soft tissue swelling or fluid (not bony overgrowth alone) observed by a physician. The 14 possible areas are right or left PIP, MCP, wrist, elbow, knee, ankle, and MTP joints
3. Arthritis of hand joints	At least 1 area swollen (as defined above) in a wrist, MCP, or PIP joint
4. Symmetric arthritis	Simultaneous involvement of the same joint areas (as defined in 2) on both sides fo the body (bilateral involvement of PIPs, MCPs, or MTPs is acceptable without absolute symmetry)
5. Rheumatoid nodules	Subcutaneous nodules, over bony prominences, or extensor surfaces, or in juxtaarticular regions, observed by a physician
6. Serum rheumatoid factor	Demonstration of abnormal amounts of serum rheumatoid factor by any method for which the result has been positive in
7. Radiographic changes	Radiographic changes typical of rheumatoid arthritis on posteroanterior hand and wrist radiographs, which must include erosions or unequivocal bony decalcification localized in or most marked adjacent to the involved joints (osteoarthritis changes alone do not qualify)

Table 1 1987 the American College of Rheumatology (ACR) criteria (https://pubmed.ncbi.nlm.nih.gov/20872595/)

In the last decade there have been a series of changes, some of them minor and not very perceptible, in the RA scenario. The changes in the end have led us to a completely different scenario from the one that was present in 1987, when the classification criteria used until now was formed. Among these changes can be emphasized the changes in the available treatments (appearance of new synthetic pharmaceuticals [leflunomide] and especially the appearance of biological pharmaceuticals), changes in RA biomarkers (appearance and standardization of ACPA [anti-citrullinated peptides antibodies]), changes in the therapeutic objectives (search for remission or at least low disease activity), changes in the therapeutic strategy (using DMARDs early and especially rapidly escalating MTX) and changes in the recommendations of treatment such as that carried out by EULAR, where they recommended starting DMARD treatment in those patients at risk of developing a persistent or erosive disease even before they met criteria for an established disease5. This new scenario requires a change in the classification criteria that would allow the different advances to be applied systematically and objectively, especially early treatment. That is why EULAR and ACR have joined forces to develop a new set of criteria, that when applied to a group of patients with recent onset synovitis, allows the identification of the subgroup of patients with the highest risk of presenting persistent and/or erosive disease and consequently detect those patients who can benefit from the initiation of DMARD treatment early, while still identifying and classifying those patients who present with a more advanced disease2.

1.2.1 Methodology for the development of the new criteria

Developing new criteria has been challenging due to the lack of an easy gold standard to define RA to start with. The use of the 1987 definition of RA as a gold standard was rejected due to the inherent complexity that this would produce, so a 3-phase study was proposed.

The objective of the first phase was to identify the contribution of the different clinical and laboratory variables used during the daily clinical practice in the diagnosis of RA6. The data was obtained from cohorts of patients selected, based on the publications made of these cohorts, and on the ease of obtaining the data through their principal investigator. Thus, 9 cohorts were selected, 6 of which (Amsterdam, Austria, ESPOIR, Manchester, Norway, and REACH) were used as the basis of the analysis and 3 (Leeds, Leiden, and Toronto) were used as validation of the data obtained.

The first obstacle was defining the gold standard definition of RA. The group of experts defined that a particular patient would be diagnosed with RA if he or she started treatment with MTX within 12 months after the first visit to the rheumatologist. Despite the possible biases produced by this definition, such as substituting the diagnosis of a disease at the beginning of a certain

treatment (not specific) for the disease, and with the risk of including as RA patients affected by other inflammatory arthropathies such as psoriatic arthritis and, to a lesser extent, other connective tissue diseases, it was decided to use this definition in to avoid complexity with the 1987 RA classification criteria.

The importance of the variables in the diagnosis of RA was determined (start of MTX in the 12 months following the first visit) by conducting an analysis on 3,115 patients belonging to the previously mentioned cohorts. The analytical process aimed to identify the independent contribution of each of the studied variables by performing a univariate regression model of all the demographic, clinical and analytical variables included in the analysed cohorts. Subsequently, the main variables of the univariate regression model were analysed (those that presented a significant odds ratio) and a multivariate regression model was constructed to identify the independent contribution of each of the variables identified as independent.

The second phase consisted of producing a clinical judgment on the relative contribution of each of the variables identified in phase 1 on the diagnosis of RA7. A panel of experts made up of 12 European rheumatologists and 12 North American rheumatologists with extensive experience in the diagnosis and treatment of RA was created. Members of the panel were presented with a series of scenarios based on real cases of patients with undifferentiated arthritis with a low or high probability of developing RA, asking them to identify the factors and categories among the factors that were important in determining the probability of developing RA. The relative importance or weight of each of the factors was determined by using a specific program called 1000Minds (http://www.10000minds.com) in an interactive and iterative process. This process allowed the calculation of an individual weighing of each of the parameters identified in the first phase.

The objectives of the third phase were to use the results obtained in the first two phases and to develop a scoring system and define the optimal cut-off point that, applied to patients with recent-onset undifferentiated arthritis, would allow them to be identified with a high probability of developing a persistent or erosive RA.

The new criteria for rheumatoid arthritis

The new RA criteria will only be applied to a certain target population that must have the following characteristics:

-Present at least 1 joint with clinical synovitis (at least one inflamed joint) and that said synovitis cannot be explained by suffering from another disease.

-Have a score equal to or greater than 6 in the scoring system presented in Table 2, which considers the distribution of joint involvement, serology of rheumatoid factor (RF) and / or ACPA, increase in acute phase reactants, and duration equal to or greater than 6 weeks.

Target population (Who should be tested?): Patients who	
1) have at least 1 joint with definite clinical synovitis (swelling)*	
2) with the synovitis not better explained by another disease†	
Classification criteria for RA (score-based algorithm: add score of categories A–D;	
a score of ≥6/10 is needed for classification of a patient as having definite RA)‡	
A. Joint involvement§	
1 large joint¶	0
2−10 large joints	1
1−3 small joints (with or without involvement of large joints)#	2
4−10 small joints (with or without involvement of large joints)	3
>10 joints (at least 1 small joint)**	5
B. Serology (at least 1 test result is needed for classification)††	
Negative RF *and* negative ACPA	0
Low-positive RF *or* low-positive ACPA	2

High-positive RF *or* high-positive ACPA	3
C. Acute-phase reactants (at least 1 test result is needed for classification)‡‡	
Normal CRP *and* normal ESR	0
Abnormal CRP *or* abnormal ESR	1
D. Duration of symptoms§§	
<6 weeks	0
≥6 weeks	1

* The criteria are aimed at classification of newly presenting patients. In addition, patients with erosive disease typical of rheumatoid arthritis (RA) with a history compatible with prior fulfilment of the 2010 criteria should be classified as having RA. Patients with longstanding disease, including those whose disease is inactive (with or without treatment) who, based on retrospectively available data, have previously fulfilled the 2010 criteria should be classified as having RA.

† Differential diagnoses vary among patients with different presentations, but may include conditions such as systemic lupus erythematosus, psoriatic arthritis, and gout. If it is unclear about the relevant differential diagnoses to consider, an expert rheumatologist should be consulted.

‡ Although patients with a score of <6/10 are not classifiable as having RA, their status can be reassessed, and the criteria might be fulfilled cumulatively over time.

§ Joint involvement refers to any *swollen* or *tender* joint on examination, which may be confirmed by imaging evidence of synovitis. Distal interphalangeal joints, first carpometacarpal joints, and first metatarsophalangeal joints are *excluded from assessment*. Categories of joint distribution are classified according to the location and number of involved joints, with placement into the highest category possible based on the pattern of joint involvement.

¶ "Large joints" refers to shoulders, elbows, hips, knees, and ankles.
# "Small joints" refers to the metacarpophalangeal joints, proximal interphalangeal joints, second through fifth metatarsophalangeal joints, thumb interphalangeal joints, and wrists.
** In this category, at least 1 of the involved joints must be a small joint; the other joints can include any combination of large and additional small joints, as well as other joints not specifically listed elsewhere (e.g., temporomandibular, acromioclavicular, sternoclavicular, etc.).
†† Negative refers to IU values that are less than or equal to the upper limit of normal (ULN) for the laboratory and assay; low-positive refers to IU values that are higher than the ULN but ≤3 times the ULN for the laboratory and assay; high-positive refers to IU values that are >3 times the ULN for the laboratory and assay. Where rheumatoid factor (RF) information is only available as positive or negative, a positive result should be scored as low-positive for RF. ACPA = anti-citrullinated protein antibody.
‡‡ Normal/abnormal is determined by local laboratory standards. CRP = C-reactive protein; ESR = erythrocyte sedimentation rate.
§§ Duration of symptoms refers to patient self-report of the duration of signs or symptoms of synovitis (e.g., pain, swelling, tenderness) of joints that are clinically involved at the time of assessment, regardless of treatment status.

Table 2 The 2010 American College of Rheumatology/European League Against Rheumatism classification criteria for rheumatoid arthritis

1.2.2 Rheumatoid arthritis epidemiology

The prevalence of rheumatoid arthritis (RA) is established between 0.5 and 1% of the general population, with a 3/1 female preponderance ratio. The prevalence also has a variability associated with genetically differentiated populations (28–35).

The estimated incidence annually is 16.5 cases per 100,000 people in southern European countries, and 29 in northern European countries. There is a peak in the incidence in women aged 50 to 60 years (33,35–37).

The incidence rates of RA in Spain are 135 per 100,000 women and 46.7 per 100,000 men (2016). We observe that in the last 30 years the incidence has decreased (Figure 1) (36).

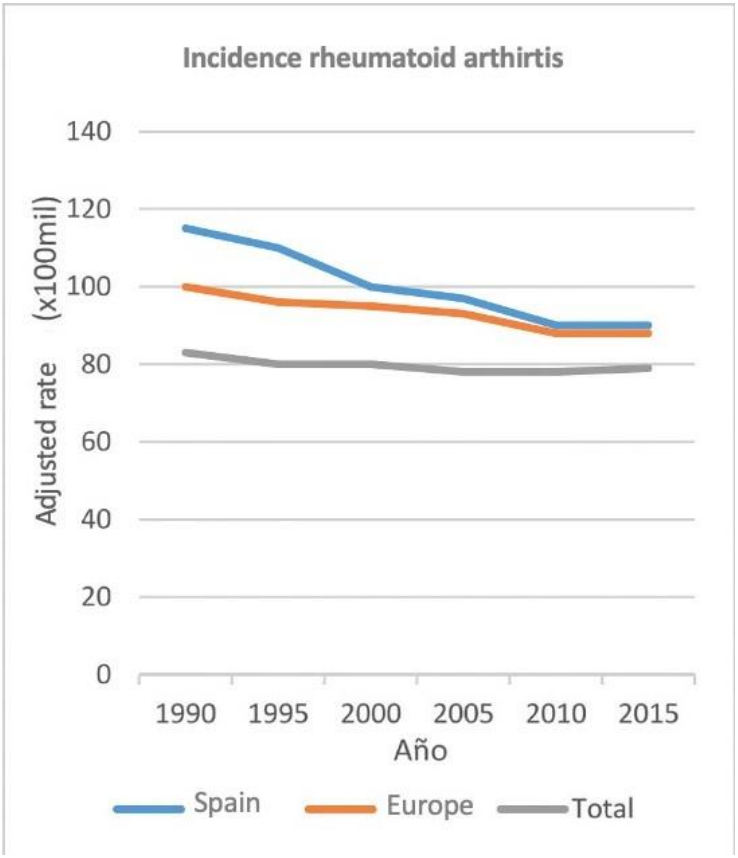


Figure 1 The list of RA cases diagnosed in Spain, Europe, and the rest of the World.
Data obtained from the Clinical Practice Guide for the management of patients with RA 2019. (https://www.ser.es/wp-content/uploads/2019/03/Guia-de-Practica-Clinica-para-el-Manejo-de-Pacientes-con-Artritis-Reumatoide.pdf) Autorización de la SER

Therapeutic changes and new strategies have resulted in a decrease in disease activity, because of a possible increase in the quality of life of patients, but to the detriment the care burden has

increased due to the cost of the new pharmaceuticals and increased visits to the health care professionals for improved control of treatment and adverse effects (37,38).

The impact on the care burden of RA in Spain in 2019 is higher than estimated, being 0.6% of the total, 0.5% in Europe and 0.2% in the rest of the world. In turn, one of the rheumatic diseases creates the highest healthcare and economic burden with 5% despite the seen decrease in incidence (34,36,37,39).

Life expectancy in patients with RA has been observed to be maintained in recent decades, no increased or decreased RA-related mortality, but the difference in life expectancy compared to the average population has increased. It is estimated that 50% of patients with RA have a life reduction of 3 to 10 years with respect to the mean (40–43).

The cause of higher mortality associated with RA is cardiovascular complications. An increased risk of mortality of 50 to 60 percent has been observed with no apparent improvement over time. The mortality related to greater knowledge of the disease process, or the introduction of new pharmaceuticals has not decreased, and perhaps it is still premature to show whether the advances made will reduce mortality (34,40,43).

The pathologies associated with the increase in comorbidity and mortality include cardiovascular pathologies, respiratory diseases, malignant tumours, disorders of the gastrointestinal system, and serious infections with the introduction of biological treatments (40,42,43).

1.2.3 Rheumatoid Arthritis Physiology

Despite the multiple advances in RA, the pathogenesis of the disease has not yet been described. The accumulated advances have been more significant in the disease process that is mediated by an exacerbated autoimmune response, accompanied by microvascular alteration and synovial hyperplasia in joint level. The process can be summarized as a proliferation of macrophages and lymphocytes in the membrane and synovial fluid. This cell proliferation is caused by a cascade of uncontrolled release of pro-inflammatory cytokines, which in turn will be fed back by the different stimulated cells (44,45).

Th1 lymphocytes were considered to be responsible for the autoimmune response of RA. The studies regarding Th1 lymphocytes action in the inflammatory process have been essential in understanding and treating the disease, but this approach was still very simplistic.

Currently a more comprehensive vision is presented, where different types of cells of the immune system are important and collaborating with the specific cells of the affected tissues in the inflammation process, and destruction of joint tissues (46,47).

The cells of the synovial membrane, synoviocytes (type A), have a crucial role in the process. Synoviocytes (type A) or also known as membrane resident macrophages, have the ability to present antigens and release cytokines. When they are activated, they will release TNF-α that will produce microvascular vasodilation, and in turn will induce the release of other inflammatory cytokines, which lead to angiogenesis, fibroblast proliferation and release of growth factors (44,45).

Fibroblasts (type B synoviocytes) with differentiated functions such as: anchoring independence4, loss of contact inhibition5 and the ability to secrete cytokines involved in the RA process, directly lead to the destruction of cartilage, promote the chronicity of synovial inflammation, and generate favourable conditions for the permanence of T and B lymphocytes. Currently it is not yet clarified whether the feedback produced by fibroblasts to maintain inflammation is sufficient to chronify synovitis (47,48).

Specific antigens such as type II collagen, proteoglycans, cartilage binding proteins, among others, have been identified and are considered to be involved in the process and the creation of antibodies to the antigens typical of joint structures (28,47,49).

The immune system identifies these specific antigens in the synovial capsule and cartilage, and considers them invasive tissue, and will feed back into synovitis, triggering osteoclastogenesis and in turn continues the cytokine release cascade initiated by macrophages (28,30,49).

At the same time, the antigen presenting cells (APC) will migrate towards the central lymphoid organs, where they will present them to the T lymphocytes, which will activate the B lymphocytes, which migrate to the synovial membranes (28,50).

Once activated at the plasma level, B lymphocytes are responsible for the generation of antibodies. B lymphocytes can be differentiated into two groups (51,52).

• B1 lymphocytes do not require antigen to be activated and they are able to release antibodies (IgM) to the intercellular space, are associated with a protective function, are involved in the removal of aging cells, in immunomodulation6, and resistance to infections. In RA, B1 lymphocytes actively participate in the creation of autoantibodies and in turn act as antigen-presenting cells.

• B2 lymphocytes are responsible for the immune response in the presence of antigen, which is a very precise response to the collaboration of T lymphocytes. It is a relatively slow process because it requires their plasma differentiation to release antibodies (IgG).

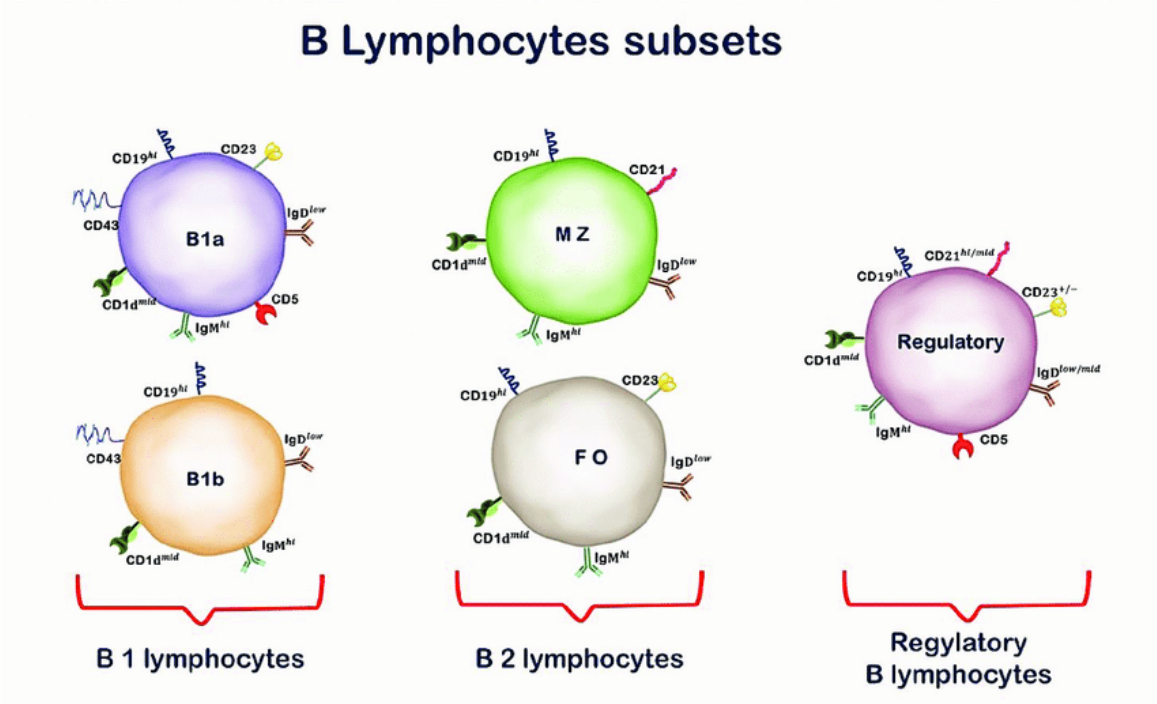


Figure 2 Immunophenotype of mature B-cell subpopulations. The B2-cell population constitutes the majority of spleen B cells formed by follicular cells (FZ) and marginal zone B cells (MZ). B1-a and B1-b cells are smaller populations in terms of frequency in the spleen; they can be distinguished based on CD5 expression: B1-a (CD5+) cells and B1-b (CD5−) cells. The regulatory B cells have phenotypic markers of B1 and B2 cells. (https://www.intechopen.com/books/lymphocyte-updates-cancer-autoimmunity-and-infection/b-lymphocyte-as-a-target-of-bacterial-infections) Free copyright

The antibodies generated by B lymphocytes are associated with the ACPA, FR and many other markers whose clinical importance in the disease is still unknown (51,52).

Th17 lymphocytes migrate to inflamed areas in response to pro-inflammatory cytokines released by macrophages and fibroblasts and increase the inflammatory response by recruiting other helper cells through the release of other cytokines such as IL-17 that will activate Th1 lymphocytes (53,54).

The other recruited cells are neutrophils which occur at the joint level and act in the autoimmune process through the release of proteolytic enzymes that destruct the articular cartilage. In structural studies of cartilage in joints affected with RA, immune complexes are observed embedded in the superficial layers, providing a surface that facilitates the adherence and activation of neutrophils (47).

The immunological process is initiated by the resident macrophages. As the different types of cells that are activated and presented intervene by the identification of antigens and the creation of antibodies, a parallel process occurs and triggers joint erosion at the bone level. The process is called osteoclastogenesis and consists of the activation and maturation of osteoclasts. It is related to the increase of a cytokine secreted by activated T lymphocytes, macrophages, and fibroblasts. It is the receptor ligand associated with nuclear factor kappa beta (RANKL) that will stimulate the nuclear receptor kappa-beta (RANK) on the membrane of osteoclast precursor cells. This cytokine is amplified by the action of TNF-α, IL-1, IL6 (55–57).

Cytokines are the means of intercellular communication and are essential in inflammatory processes. Different pro-inflammatory cytokines present in the joints of patients affected by RA have been identified. Each cytokine has an important role in the total process by triggering, maintaining inflammation and inducing joint destruction (45,58,59).

The analysis of cytokines that are present in fluid and synovial membrane confirmed that the cytokines IL-2 and IFN (related to Th1 lymphocyte) were in negligible concentrations. However, the concentrations of cytokines related to macrophages and fibroblasts (IL1, IL6, TNF-α) were very high, which led to a rethinking of the immunological process and better knowledge of cellular interactions and the participation of interleukins (47,58).

With the introduction of TNF-α blocking pharmaceuticals, the importance of this cytokine in the autoimmune response has been confirmed. The TNF-α blocking slows down the inflammatory process and joint erosion. It is not yet clarified whether TNF-α generates the imbalance of the immune system or a cascade reaction of the rest of cytokines (45,59).

1.2.4 Serological markers.

The most characteristic expression of the autoimmune response is the presence of autoantibodies such as RF and ACPA, regardless of the phase of the disease. One of autoantibodies can be found in up to 75% of patients with RA, and both in 80 % of those who present one (49,50,60–63).

These markers, with a higher frequency RF than ACPA, also appear in other diseases but usually less frequently (49,61,64).

• Rheumatic: systemic lupus erythematosus, Sjögrens syndrome, mixed connective tissue disease, psoriatic arthritis.

• Bacterial infections: Klebsiella pneumoniae, tuberculosis, syphilis.

• Viral infections: hepatitis A, B, C, herpes, HIV.

• Parasitosis: toxoplasma, malaria.

• Healthy population.

The term rheumatoid factor (RF) is called an antibody directed against the Fc fragment of IgMs created by B1 lymphocytes, specifically the union of CH2 and CH3 domains of the heavy chain (Figure 3). Normally IgM isotype is discussed, but other isotypes including IgG, IgA, IgE and IgD have also been identified although they are not used in the clinical analysis (49,64).

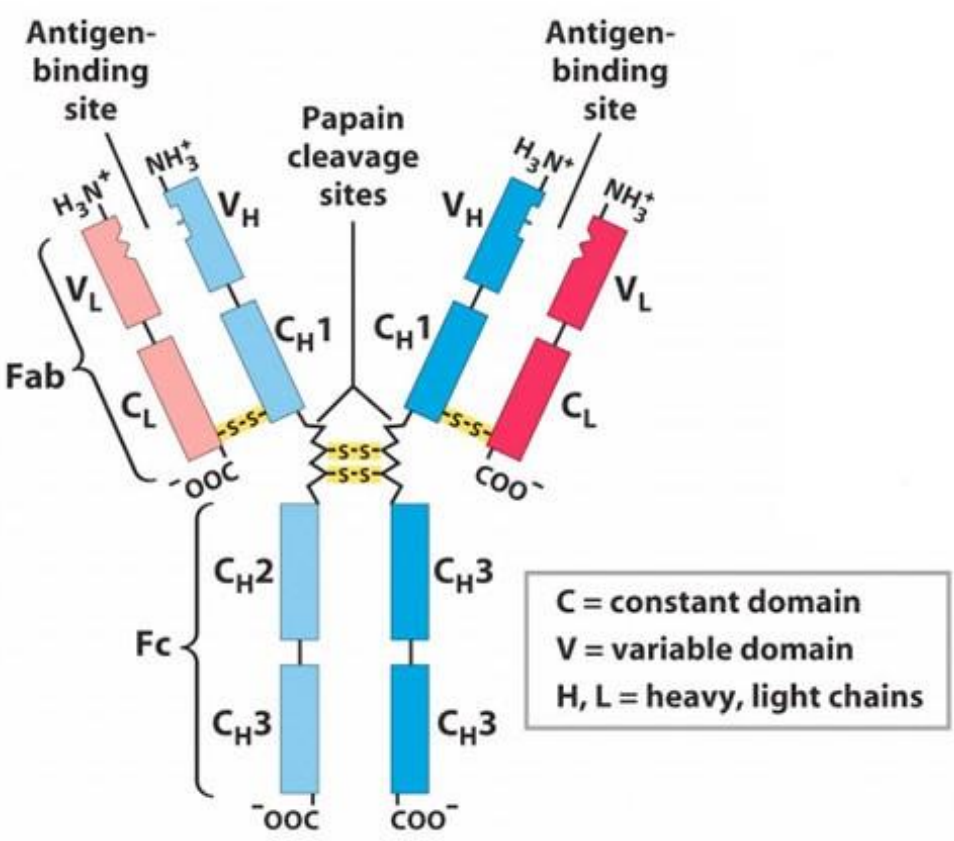


Figure 3 Different functions of different parts of the antibody https://www.news-medical.net/health/Antibody-Function.aspx (permission of the author)

The ACPA marker targets "antigens" with the amino acid citrulline (rare amino acid), for example cimetidine, fibronectin, fibrinogen, and type II collagen. These proteins, citrullinates, are frequently in joints affected in RA, hence this marker is important in RA (60,61,63).

Plasma RF levels have been reported to vary significantly in response to different therapies, but ACPA levels do not behave in this way (50,61).

Both RF and ACPA are the markers used to guide the diagnosis of RA. They are serological markers with similar sensitivities (FR 69% and ACPA 67%) and high specificity.

(RF 85% and ACPA 95%), being useful as predictive markers for the diagnosis of the disease (50,61,62,65,66).

In a prospective cohort study initiated in 1993 by Rooy et al. analysed the evolution of the disease related to the presence of ACPA+ and FR + markers. In ACPA+ patients, greater articular erosion was observed 2.4 times greater than in ACPA-. Patients with high RF + levels in acute phases are associated with greater severity of the disease (67). In a study by Van Nies et al. (2015) analysing the remission time in patients without disease-modifying treatment, it was observed that patients with ACPA- had longer periods of remission than patients with ACPA+ (68).

In a multicentre observational study with 2018 patients, conducted by Aletaha D. et al. (2015), a marker that provides information about activity was searched, with the aim of preventing disease progression (Table 3) (50).

Mark	Activity level	Points
FR– ACPA–	Slow	Disease activity was significantly higher than with ACPA +, but without significant values.
FR+ ACPA–	High	The activity is indifferent to the serological levels of FR +. The value does not indicate activity level.
FR– ACPA+	Slow regarding rest of the groups	It is observed that the activity levels are lower than in the group with ACPA.
FR+ ACPA+	Similar activity	The difference with the FR + and ACPA- group is not the activity, but rather higher FR + levels were identified in these patients.

Table 3 Subgroups of the study sample in relation to RF and ACPA serological markers with disease activity. The different validated methods (DAS28, SDAI, CDAI) to estimate AR activity.

1.2.5 Etiology

The etiology of RA is unknown, but it is postulated that RA is triggered in individuals with a genetic predisposition after repeated exposure to certain environmental agents (69,70).

-*Genetics*: Some studies carried out in twins indicate that the genetic factor counts as 50% in the susceptibility of having RA. An association between HLA and severe RA is demonstrated (71).

The most important genetic risk factor for the appearance of RA is associated with the major histocompatibility complex (HCM), especially with the "Human Leukocyte Antigen" (HLA), to which between 30% and 50% of the risk is attributed total genetics (72).

-*Age*: The maximum incidence point in women is at age 55-64 and in men at age 65-75. The increased age makes them more susceptible to develop RA. In the same way, there is greater severity of RA with the increased age RA appears (71).

-*Hormonal:* In women, RA develops frequently during the time periods when steroid hormones fluctuate a lot, such as postpartum and perimenopause (73).

-*Environmental:* There are certain infections that can cause RA, such as parvovirus and rubella infections. These can activate RA in certain individuals, but it is a small proportion of the prevalence (74). There also appears to be a high risk of disease in individuals following a blood transfusion (75).

-*Tobacco and life habits*: There appears to be an association between tobacco and with the increase in the level of estrogens and androgens that negatively influence immunity (76). Being overweight seems to be associated with RA in women (75).

The risk has been estimated to be approximately twice as high in smokers as in non-smokers, especially in men who smoke heavily and are rheumatoid factor (RF) positive (77).

1.3 Rheumatoid Arthritis Clinic

The different preclinical variables that would predispose a patient to developing the autoimmune disease RA have been described: the factors associated with the disease, the immunological process that occurs, the initiation and establishment of symptoms. We would lack the diagnosis, evolution of the prognosis, and treatment of the disease in the following sections.

Joint manifestation.

RA is the most common autoimmune rheumatic disease with joint involvement as its main clinical manifestation is persistent synovitis. Chronic inflammation occurs causing short-term pain, joint swelling, and long-term progressive joint destruction. The anatomical deformation is parallel to the evolution of the disease. All these causes lead to a deterioration of the functional capacity of the locomotor system (28,29,31).

The usual symptoms consist of the following signs and symptoms: asthenia, general malaise, myalgia, fever, anorexia, weight loss, joint pain, morning joint stiffness (at least one hour before improvement) and joint inflammation. Altered laboratory tests with elevated CRP and ESR are present. This symptomatology is not exclusive to the disease, which is problematic (31,36).

The most frequent clinical presentation of RA is gradual onset of inflammatory polyarthralgia with erosive joint degeneration, with symmetrical, intermittent, and migratory involvement, especially in the hands and feet. The evolution of the disease is very heterogeneous with the synovial joints being affected regardless of type and size (28,29,65,78).

Extra-articular manifestations

RA is a systemic disease that can affect other tissues, structures of the musculoskeletal system (tendons, ligaments, and fascia) and organs outside the musculoskeletal system. The incidence is that 40% of patients diagnosed with RA have these clinical manifestations (31,79).

These manifestations can occur at any time in the disease process, regardless of age and time of disease evolution. A higher incidence is observed in severely affected patients and is directly proportional to higher mortality. The seropositivity in RF and markers of the HLA-DRB1 gene increase the probability of extra-articular presentation (31,79,80).

These manifestations are to be considered of a serious nature. Patients who present them must undergo a more exhaustive follow-up since these clinical manifestations indicate a greater severity of the disease state and increased morbidity (80).

Tendon Sheath Level.

Tenosynovitis in flexor and extensor tendons of the fingers can be one of the first signs of RA with progressive development of months. Acute involvement has also been described with signs of swelling and impaired movement. This clinical sign is usually accompanied by neuropathies, as in feet in tarsal tunnel syndrome due to compression of nerves adjacent to the involved tendon (31).

In advanced stages of the disease, weakening and partial or complete rupture of a tendon already affected by tenosynovitis is frequent. This potential complication generates increased joint instability, severe joint dislocation, and increased deformity. One of the most affected tendons in the foot is the posterior tibial tendon (31).

Synovial bag or bursa level.

Periarticular pain can be directly associated with abnormal bursa alterations such as inflammation (bursitis) and communications with adjacent joints, which can be frequent in early RA (31).

Muscle level.

Muscle weakness and / or atrophy, which usually occurs in patients with RA, is associated with joint limitation of movement, impingement of motor nerves, and corticosteroid treatment with adverse effects such as myositis, focal necrosis, chronic myopathy, among others (31).

Tendon involvement, due to sheath thickening or loss of continuity, directly leads to muscle weakness, the affected tendon, overloading of muscles, associated with the movement of the affected muscle (31).

Dermatological level.

Rheumatoid nodules, with appearance in approximately 7% of the patients in early stages and in 30% of long-standing patients, are the most frequent extra-articular manifestation and approximately 20% of patients present them. Its appearance in early stages increases the possibility of presenting more serious manifestations (28,79,80).

Rheumatoid nodules are associated with a subcutaneous origin, although they can be found at other levels of the tissue. Their sizes vary depending on the affected region and are frequent in regions associated with pressure, bony prominences, tendon areas, and flexor muscles. Histologically, focal fibrinoid necrosis is present with surrounding fibroblasts (28,79).

It is important to consider that MTX (Methotrexate) has the induction of "Nodulosis, lesions similar and indistinguishable from rheumatoid nodules (30)." Neutrophilic dermatitis presents infiltrated erythematous plaques, characteristic of the presence of neutrophils without symptoms of infection (28).

Vascular level.

Manifestations at the vascular level range from isolated digital infarcts to systemic vasculitis (81). Patients with long-standing RA may present with rheumatoid vasculitis of small vessels with clinical representation on the skin and nails, known as splinter hemorrhages (28). Pyoderma gangrenosum is a rare disease characterized by chronic recurrent ulcerations of non-infectious origin. The ulcerations originate from necrotizing vasculitis and are usually found in the lower limbs, although they have been described in other regions of the body. Pyoderma gangrenosum etiology is unknown but it is closely associated with RA in seropositive RF patients (28,79,81).

Neurological level.

The most frequent neurological alterations observed in patients with RA occur due to entrapment of peripheral nerves such as the posterior tibial and median nerve. They are associated with sustained synovitis, generating carpal or tarsal tunnel syndrome. The neurological symptoms can be present even in the early stage of the RA (28).

Patients with a long evolution of the disease can present other rare neuropathies: ischemic neuropathies and demyelination, or cervical myelopathy due to pannus formation or vertebral subluxation (79).

1.4 Rheumatoid Arthritis in the Foot and Ankle.

Foot health was defined by Helfand et al. (1998) as " a stable foot condition, relatively free from diseases and disorders, comfortable for the individual and allowing for ambulation and mobility for the most part without restriction and pain " (82).

The foot is a human structure of great anatomical complexity, composed of 28 bones, 33 joints, 112 ligaments and controlled by 13 extrinsic and 21 intrinsic muscles. It is considered the support base of the locomotor system, supporting the weight of the body on a small surface and has the ability, due to its distinctive biomechanics, to become a flexible or rigid structure depending on the needs of compensation and adaptation to irregularities from the ground (83–86).

Foot involvement is very significant in RA. Upon diagnosis, approximately 20% of patients report some type of foot problem and as the disease progresses, its prevalence increases to 90% (see Table 4). The first manifestations are usually in the forefoot, followed by the hindfoot and midfoot, although the order may vary. The clinical evolution tends to be rapid, with significant structural changes described after 6 months (87–89). In early stages of the disease, foot symptoms sometimes go unnoticed on clinical examinations. The patient usually refers to pain of unknown origin, local inflammation with difficult association with the affected structure, so it is important to use X-ray exploratory methods on the foot (87,90,91).

The first affected joints in RA are the small synovial joints, the foot being one of the body regions with the highest incidence. Destruction of hyaline cartilage, pannus formation, erosion of joint facets, and sustained synovitis lead to capsule distention, increased laxity of associated ligaments, and muscle-tendon dysfunction. All these alterations lead to joint deviations (87,91,92).

Joint deviations are also influenced by the forces generated by the foot, by the anatomical structures linked to it and by the external elements used by the patient. Joint deviations can be caused by (91,92):

• Alteration of ligaments

• Alteration of tendons and muscles, both intrinsic and extrinsic of the foot

• Distribution of loads

• Gait pattern of the patient prior to the disease

• Antalgic gait changes caused by the symptoms of the disease

• Type of footwear commonly used

Significant changes in adjacent tissues or structures related to the affected joint have also been identified, such as local edema, displacement of the adipose panicle, bursitis, fasciitis, and neuritis (83,88). All these morphological changes in the foot will negatively condition the quality of life, with an increase in disability and pain, and hindering the usual tasks that require standing, bearing weight, or traveling long distances (88,91,93).

1.4.1 Prevalence of rheumatoid arthritis in the foot.

Deformation of the foot and ankle has been described by subdividing the foot by regions. In approximately 90% of patients, deformations are identified in the forefoot, 40-60% in the midfoot and 30-60% in the hindfoot and ankle. (See table 4) (91,94–97).

Vainio *et al.* 1956	The prevalence of RA in the foot in a study with a population of 1000 RA patients: • 16% had clinical symptoms in the foot and ankle when they were diagnosed with RA. • With a prevalence of 91% in women and 85% in men. • In the forefoot, 59% of women and 42% of men. • Flat feet are worth 40% in women and 19% in men. • It was described that patients with less than 5 years of evolution had lax valgus flat foot, and in patients with more than 10 years of evolution had rigid valgus flat foot.
Thould *et al.* 1966	The evidence of bone changes in the joints of the foot and hand: • 75% of the patients analysed had alterations in the hands and feet. • 16% more only in feet (91%). The 3-year follow-up: • Describes further deterioration in the joints of the foot. • Associates joint damage with the evolution of the disease. • The joints studied are in forefoot, midfoot or rearfoot are not referred to.
Jacoby *et al.* 1973	The analysed patients when diagnosed with RA: • 21% have foot symptoms.
Minaker *et al.* 1973	The prevalence in standing in patients with RA: • 86% with clinical symptoms in the foot. • 92% with radiological alterations in feet.
Vidigal *et al.* 1975	The patients diagnosed with RA: • 70% joint involvement in the forefoot. • 62% involvement in the midfoot. • 32% in ASA. • 9% in ATPA.
Fleming *et al.* 1976	In the first three months of disease evolution since its diagnosis: • 19% had clinical symptoms in the foot (13%) and ankle (6%).
Kirkup *et al.* 1977	The deformation of the first radius with a population of 200 RA patients: • 59% had HAV deformation. • 28% deformation of hallux rigidus2 • 13% other deformations of hallux flexus3, hallux malleus4, hallux varus5, hallux extensus6. • Not always symmetrical deformations.
Spiegel *et al.* 1982	The patients with 10 years of evolution: • 75% presented synovitis in FMA • The deformation is proportional to the years of evolution of the disease.
Van der Heijde *et al.* 1992	The patients with early RA: • 15% affected the first AMTF in the first year of evolution. • 28% in the third year.
Kerry *et al.* 1994	At the beginning of the RA: • 47% of the patients had clinical symptoms in the foot. • In long-standing patients, it increases to 79%. • The prevalence of HAV1 was 67%.

Michelson *et al.* 1994	The prevalence study in the foot and ankle: • All patients report pain at some point in the evolution of the disease. • 42% indicated in the ankle. • 28% in the forefoot. • 14% in both. Forefoot deformation: • 36% have moderate or severe HAV. • 58% fingers (2nd-5th) without changes of interest. • 17% flexible claw fingers. • 25% rigid claw toes. Hindfoot valgus deformity • 64% had flat feet, of which 11% had posterior tibial involvement.
Haas *et al.* 1999	The 5-year follow-up in patients diagnosed with RA with a mean evolution time of 19 years: • 90% of patients with radiographic alterations. • 87% had forefoot alterations. • 60% had HAV. • In the 5 years of study, 83% presented changes in the forefoot, 72% in the midfoot and 59% in the hindfoot.
Hulsmans *et al.* 2000	The observational study of the first 6 years of evolution with a study population of 32 patients with RA using the van der Heijde method: • The first year, prevalence in the forefoot of 16%. • In the sixth year of the study, prevalence of 95% of patients, with joint erosion in 79% and / or joint space narrowing in 69%.
Matricali *et al.* 2006	The impact on the forefoot of 285 RA patients treated with DMARDs: • 36% present pain in the forefoot, of which 22% is in AMTF and 14% in other forefoot structures. • 7% in hindfoot and ankle. • The pain in the foot divided into: 6% disabling, 28% accentuated, 47% moderate, 19% mild.
Grondal *et al.* 2008	In a study population of 1000 patients with RA, at the onset of the disease reported pain in: • 45% in forefoot joints. • 17% in hindfoot joints. In the same study current clinical status was observed: • 86% have forefoot problems. • 52% in rearfoot. • 45% in both.
Marike *et al.* 2008	In an 8-year observational study in newly diagnosed patients, the prevalence of pain and bone erosion in the forefoot joints was analysed: • Prevalence of pain: at the beginning of the study, it was 70% which progressively decreased to 40-50%. • Prevalence of joint erosion: at the beginning of the study, it was 19% and at 8 years it increased to 60%.
Rome *et al.* 2009	In a study with 100 participants analysing foot involvement and the care received: • 89% of patients have a foot problem. • 64% HAV. • 86% minor finger deformations. • 27% had received foot surgery prior to the study.
Otter *et al.* 2010	In a study carried out with 585 patients, the prevalence of foot pain was presented: • 93.5% referred pain in the foot. • 68% rated it as moderate or severe foot pain daily. • Pain was most frequently identified in the forefoot and / or ankle. • 35% indicated the foot as the first affected place.
Broman *et al.* 2012	In a study carried out with 100 patients with RA, the prevalence of deformation and pain in the foot was presented: • 89% described foot problems: ankle 36%, forefoot 35%, hindfoot 34%, midfoot 12%. • 14% reported it at the beginning of the disease. • Pain according to region: 30% forefoot, 7% midfoot, 17% hindfoot, 36% ankle. • Other manifestations observed: 68% swollen feet, 51% numbness, 24% skin changes, 14% bunions, 11% flat feet.
Stolt M. *et al.* 2017	In a systematic review of the prevalence of the foot joints in patients with RA: • Forefoot pain is the most frequent type of pain, 30-94.1%. • Rearfoot pain between 17-61%. • Ankle pain ranges between 6.8-58.8% • Pain in the midfoot seems to be less when it is between 5-10%.
Yano *et al.* 2018	The population of 5479 patients with RA was studied and divided into two groups according to whether foot was altered or not at diagnosis: • 44% refer some alteration in the foot or ankle to the diagnosis of RA. • 66% had no foot or ankle symptoms at diagnosis. When conducting the study:

	• 71.3% of the patients with foot and ankle debut had pain or alteration in the foot, 28.7% in the ankle. • 37.3% of the patients without debut in the foot presented alteration in foot. The foot-onset patients recorded: • Greater activity (DAS28). • Higher percentage of seropositivity (FR and ACPA). • Major disability (HAQ). • Greater consumption of NSAIDs. • They found no significant differences associated with treatment with DMARDs or DMARDb.
Sung W.L. *et al.* 2019	The cross-sectional study with a sample of 2,046 patients, an average of 8 years of evolution: • 29.2% presented alterations in the foot or ankle. Among patients with foot and ankle impairment: • 71.4% presented pain in the ankle. • 59.5% inflammation in the ankle. • With forefoot pain / swelling in order from highest to lowest: 3rd AMTF: 30.9% / 22.4%, 2nd AMTF: 29.6% / 21.4%, 4th AMTF: 27.6% / 18.4%, 1st AMTF: 26.3% / 14.9% and 5th AMTF: 18.9% / 10.5%. • Total patients in remission according to evaluation method: DAS28-ESR 8.6%, DAS28-CRP 17%, SDAI 5.9%, CDAI 3.5%, RAPID-3 6.9%. • Patients with foot / ankle alteration are in remission according to: DAS28-ESR 3.5%, DAS28-CRP 6.4%, SDAI 1%, CDAI 0.5%, RAPID-3 2%. Results of radiographic alterations: • 36.7% had only erosions on the foot. • 34.8% only hand erosions. • 40% erosions in hands and feet.
1. HAV: hallux abductus valgus deviation of the first metatarsal towards the medial and first phalanx towards the side, valgus deviation of the first AMTF. 2. Hallux rigidus: dorsiflexion restriction due to joint block of the first FMA 3. Hallux flexus: dorsal flexion restriction due to involvement of flexor muscles of the first radius. 4. Hallux malleus: hammer-shaped deformation of the first toe. 5. Hallux varus: deformation of the first finger medially. 6. Hallux extensus deformation with sustained extension of the first toe.	

Table 4 Prevalence of symptoms and joint erosion in the foot and ankle in different specific studies in patients with RA.

In studies prior to 2010, it must be considered that the ACR 1987 diagnostic criteria were used to confirm the diagnosis of advanced RA, where joint erosions could have already developed, and the diagnosis was usually late. With the change of the ACR and EULAR 2010 criteria, the aim is to carry out an early detection and start treatment in the "window of opportunity" period and it may or may not influence the prevalence. It remains an assumption as there is not enough evidence-based literature on it (98).

1.4.2. Structural deformation of the foot.

The influence on the foot in general is proportional to the years of evolution of the disease and entails an increase in disability. The progression of the disease in the feet is as unpredictable as in other regions of the body, due to the heterogeneity of the disease and the characteristics of the patient (83,88,99).

Factors associated with deformity, pain, disability, functional alteration, and instability have been studied, but there are no relevant conclusions regarding the relationship between them (88,100).

In the lower limbs in patients with RA, it has been described: muscular atrophy (loss of strength), elongation / rupture of tendons and ligaments, decreased range of joint motion, joint instability, joint deviation, stiffness, pain, gait alteration, paresthesias, and intolerance to activities of daily living and exercise (101,102).

The involvement of RA in the foot is normally studied by dividing it into forefoot, midfoot, and hindfoot involvements as being independent deformations, although they are strongly associated. A modification or alteration in one of these regions will have an impact on the other two (103,104).

Forefoot

In the first three years of the evolution of the disease, 65% of patients have an alteration in at least one of the FMA, the presence of synovitis in these joints is considered an early sign of RA. Other identifiable signs in the early stages of the disease are radiological erosions and periarticular decalcification. The general symptomatology of AMTF is painful and disabling (92,105).

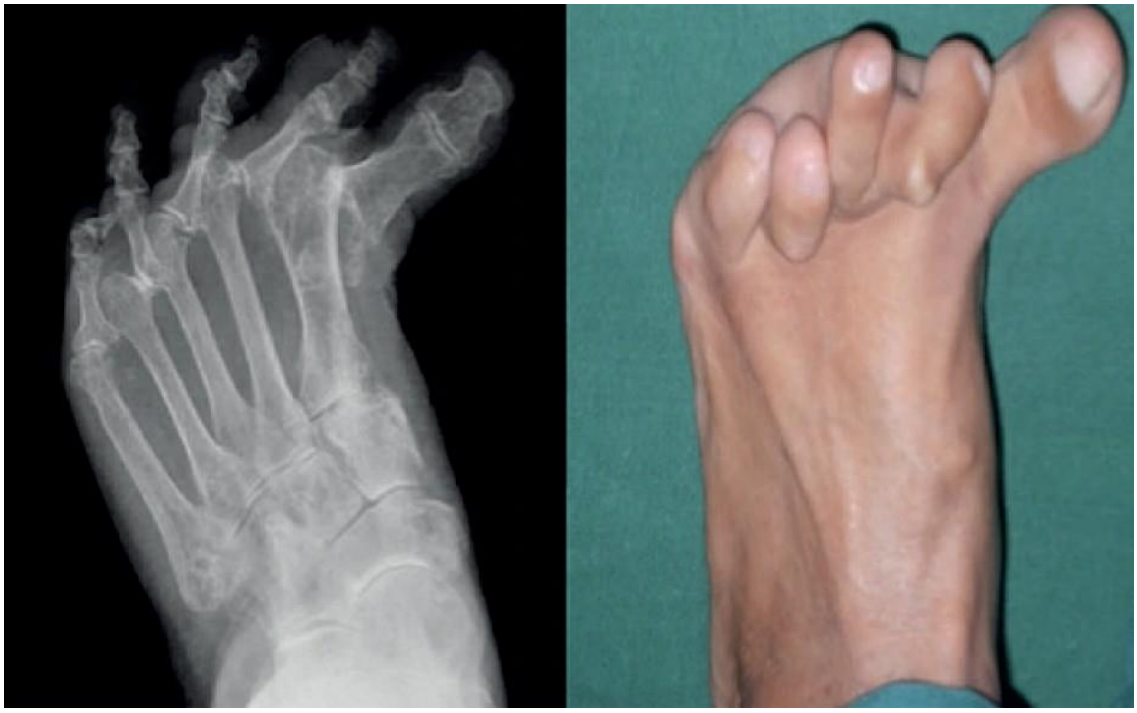


Figure 4 Forefoot deformities (toes and metatarsal joints) Free copyright

The affected FMAs present their deformation in the planes: frontal (flexion-extension) and sagittal (abduction-adduction). The most frequent deformation described and studied of hallux, with a prevalence between 23-91%, is HAV. Hallux varus, hallux rigidus and metatarsus primus varus are also described with a higher frequency than in the healthy population. In the minor

radii, with values between 6.3-94%, the deformations (reducible or rigid) with dislocation or dorsal subluxation, abduction or adduction of the lesser fingers, deformations of hammer toe, claw toe, tailor's bunion are presented. The set of alterations of the different MTPAs causes a widening of the forefoot in 40-86% of patients (89,94,96,106–109).

Chronic synovitis and progressive joint erosion indirectly generate alterations of the structures adjacent to the FMA: the plantar plate or flexor plate is stretched distally and dorsally and may even partially or totally rupture. The aponeurosis or plantar fascia in its distal insertion moves dorsally and distally, surrounding the metatarsal head, the joint capsule may even herniate. Finally, a distal displacement of the adipose pad leaves the metatarsal heads without cushioning and exposed plantarily (92,107–110).

The development of HAV in patients with RA occurs in less time than in patients healthy associated with the following structural alterations of the foot (91,97,107,108):

• Maintained hindfoot valgus deviation, ASA eversion in all phases of gait.

• Increased medial forefoot load.

• Synovitis maintained in the first AMTF causes increased laxity of the joint capsule, increasing its instability.

• Articular erosion tends toward deviation in the transverse plane of the first FMA.

• Elongation or increased laxity of the Lisfranc ligament increases the intermetatarsal angle 1-2 and tends toward the instability of the internal arch.

• Elongation, partial or total rupture of the posterior tibial tendon.

The clinical presence described as a typical deformation of the rheumatic foot is: “descent of the internal longitudinal arch, hindfoot in valgus, widening of the forefoot, HAV and minor claw toes with subluxation or dorsal dislocation and presence of 5th varus finger”. Dave Malhar et al. associate this deviation with the use of footwear. This conclusion was reached by studying two populations with RA, one in the United Kingdom with footwear and another in India without footwear, obtaining the following results (Table 5, 108):

UK study population with regular shoe wear (101 feet)		Study population of India without regular shoe wear (25 feet)	
Hallux valgus deformation			
• Prevalence	91%	• Prevalence	24%
Hallux varus deformation			
• Prevalence	1%	• Prevalence	76%
Angles related to first metatarsal joint deformation.			
• Angle metatarsal joint 1-2	2º a 27º	• Angle metatarsal joint 1-2:	2º a 12º.
• Angle hallux	-7º a 65º	• Angle hallux:	-85º a 63º.
• Angle hallux mean	34º	• Angle hallux mean	20.72º
More frequent deformation of toes			
• Sublux.[2] dorsal 2º-5º metatarsal joint[3]	7.7%.	• Deviation medial 2º-5º mtt	24%
• Sublux. dorsal 2º-4º metatarsal joint medial 5º	44.5%	• Deviation medial2º lateral 3º-5º	12%
• Lux.[4] dorsolateral 2º-4º metatarsal joint medial 5º	35.4%	• Sublux. dorsomedial 2º-5º	56%

Table 5 Comparative analysis of forefoot deformity between patients with habitual shoe use (UK population) and patients who do not wear shoes (Indian population)

In a study by Fukushi et al. (2016) it was suggested that in patients in remission or low disease activity, forefoot pain is related to deformations caused by accumulated erosion and chronic synovitis (107).

Marike et al. 2007 presented a study population of 848 patients at the onset of the disease, of whom 727 ended the follow-up at 8 years (7). It was observed that at the beginning of the symptoms a high percentage of patients referred to pain in the forefoot, which decreased with the evolution of the disease, especially, a significant decrease after 2 years of treatment was highlighted. On the other hand, they observed a noticeable increase, three times higher than at the beginning, in the percentage of patients who presented joint erosion at the end of the study. They concluded that even after controlling the symptoms with treatment, the disease activity in the forefoot joints continues as joint erosion (see table 4) (111)

Midfoot

Despite the high prevalence of valgus flatfoot has been described, no specific articles on the involvement of the midfoot joints have been found. It has been extensively studied that alterations in the forefoot and hindfoot have an impact on the midfoot with increased instability, causing a collapse of the internal longitudinal arch (ALI). The most frequent deformations (46-81%) in the midfoot are flattening of the ALI and a marked abduction of the forefoot, and an increase in midfoot width (87,89,109,112–114).

The joints most affected by synovitis and joint erosion in the midfoot are AAE, in 39% of patients and ACCu joint, in 29% of the patients. These two joints form the Chopart joint and have a major impact on midfoot valgus deviation. The rest of the are seen to be altered with MRI or CT, as has already been seen in radiological methods. They are not evaluated as they are small joints with little mobility (115).

The cross-sectional study conducted by Matsumoto et al. (2016) analysed the impact of the degree of deformation of the HAV would have on the midfoot. The conclusion was that when the FMA was deformed, the ability of the first radius to invert the hindfoot (the subtalar joint) was lost, as described by the Windlass mechanism, leading to the flattening of the ALI and the deformation of the flexible valgus flatfoot (116).

In another study by Matsumoto et al. (2014) with a study population of 274 patients with RA, of whom 212 were radiographically evaluated, the criteria of the Larsen radiological evaluation method were used and applied to the forefoot, midfoot and hindfoot joints. It was observed that in the first years of the disease, the midfoot joints were not affected as the forefoot joints were affected, but in the period of disease of 5 to 10 years of evolution, joint erosion increased in both midfoot and hindfoot causing synovitis, distension of the joint capsule and associated ligaments. All these alterations lead to midfoot collapse and increased stiffness (117).

Rearfoot

Rearfoot involvement has a prevalence of approximately 30%. ASA pain can be identified in the posterolateral region. Both AAE and ASA are considered the primary joints with foot symptoms at the onset of the disease. In the medium term, this deformation is directly associated with valgus flatfoot (109,112,113,118).

In a high percentage of patients, even in remission, severe hindfoot joint destruction has been observed.

. This leads to an alteration in joint alignment, reduction of mobility, and a change in

pressure distribution towards the medial. These changes lead to midfoot valgus deviation and flattening of the ALI (89,96).

The deformation of the valgus foot is accompanied by an increase in the laxity of the ligaments of the ATPA, ASA, AAE joints. These, when affected directly or indirectly by the inflammatory process, stop stabilizing the joint, allowing medial displacement of the talus and valgus deviation of the calcaneus (118,119).

A radiological study by Seltzer et al. (1985) identifies alterations in the ASA such as: soft tissue inflammation, joint space narrowing, cartilage loss, erosions of bone, and structural changes with calcaneal valgus deviation, flattening of the sustentaculum tali, and medial glide of the talus (120).

In a study where Wang B. et al. (2015) analysed 380 patients with various pathologies and involvement in ATPA and ASA with radiological tests, it was found that 7% of the patients studied had RA. This population was the 4th with the prevalence of different types of traumatic injuries involving the foot and ankle (121).

1.4.3 Extra-articular lesions identified in the foot in patients with RA

Different clinical manifestations of the disease have been described in soft tissues, such as bursitis, tendonitis, fasciitis, neuritis, and vasculitis (119,122).

Tendinopathies are relatively frequent pathologies associated with the deformation of the foot in RA. The most studied tendon is the tibialis posterior (TP). The rest of the tendons have a lower dysfunction and rupture rate. For example, the rupture of the Achilles tendon is extremely rare in RA, but enthesopathies and bursitis associated with it have been described extensively (87,118,119,122,123).

The tibialis posterior muscle is the main muscle that intervenes in the inversion of the foot, assists in plantar flexion and is a dynamic stabilizer of the ALI. In a normal gait, it will lock the midfoot bones, forming a semi-rigid ALI. Tibialis posterior dysfunction has been described in 64% of patients with RA and partial or even total rupture in 11% of patients with acquired valgus flatfoot. It is not clearly shown if the tendon, when affected, leads to the collapse of the ALI or if joint laxity creates an imbalance and causes partial or total rupture of the tendon (87,124,125).
In a study by Gutiérrez et al. (2016) with a study sample of 214 RA patients and a control sample of 200 healthy people, the subclinical involvement of the foot and ankle was analysed with ultrasound. It was described that 87% of the study sample showed alterations in some of the analysed structures compared with 28% of the control sample, even in different structures

and different frequencies. Similar results have been obtained in studies with magnetic resonance imaging. Breaking down the prevalence according to structures (124,126):

• 32% tenosynovitis in the posterior tibial tendon (TP)

• 27% tenosynovitis in the long lateral peroneal tendon (PLL)

• 25% synovitis in the tibiofibular joint (ATPA)

• 24% tenosynovitis in the short lateral peroneal tendon (PLC)

• 24% tenosynovitis in the anterior tibial tendon (TA)

• 19% enthesitis and 10% bursitis in the Achilles tendon (AT)

• 12% tenosynovitis in extensor hallux tendon (EH)

• The rest, common extensor tendons (EC), common flexor tendon (FC), flexor hallucis tendon (FH), peroneus brevis tendon (PC), and plantar fascia (FP), presented prevalence of less than 10%

In a study by Bilde et al. (2019) it was confirmed that when the TP is weakened, the flexor muscles and collaborators in the inversion, common flexor longus and long flexor of the first toes, increase their activity trying to compensate it. This increased activity can promote claw deformation of the 2nd to 5th toes and lateral deviation of the hallux (125).

In a study by Keenan et al. (1995) where the electromyographic activity of the TP muscle was analysed and in another by Barn et al. (2013) a greater activity was reported in the posterior tibial muscle of patients with RA and valgus flatfoot deformation. It was associated with a greater effort of the muscle to try to maintain the ALI and reduce the valgus deformity, but this increase in activity was not enough to keep the ALI stable during walking (112,127).

Rheumatoid nodules in the foot are associated with higher pressure surfaces, bony prominences such as malleoli (tibial and peroneal) and articular deviations in the forefoot, such as HAV and stress areas of the skin and subcutaneous tissue (122).

The most common neuropathies in RA are tarsal tunnel syndrome (tibial or peroneal) or interdigital neuropathy. Baylan et al. (1981) found neuropathies in 25% of RA patients. Neuromas have been described in the prevalence study by Vainio (2004) et al., 52% patients with resection of interdigital neuromas were reported. Normally its etiology is secondary (80%)

to the deformation and inflammation of connective tissues of the flexor retinaculum (122,128–130).

In an electrophysiology study conducted by Ibrahim et al. (2013), in patients with RA a decrease in nerve conduction velocity (medial plantar, lateral plantar and sural nerve) was observed and associated it with pain and paresthesia in the foot. This should be considered an option to be evaluated in patients who report difficulties with pain control with pharmacological treatment (129).

Intermetatarsal bursitis is described as the intermetatarsal bursa undergoing an inflammatory process and due to its increase in size it causes neurovascular compromise (131).

Adventitial bursitis are collections of fluid in soft tissues without synovial capsule, which appear due to tension in tissues. The usual location is in the plantar fat pad of the forefoot (131,132).

1.5 Methods used in the evaluation of rheumatoid arthritis in the foot.

In medicine, the outcomes of a disease or a healthcare process are interpreted with objective data, but not everything is measurable. Subjective information such as quality of life, pain, functionality requires evaluation methods that quantify and are close to reality.

With these methods, we can assess health dimensions that were not quantifiable and thus compare them between different study populations or over time (133).

The standardized and validated methods for the analysis of RA in general do not usually include the foot. In some radiological methods, only the metatarsophalangeal and some interphalangeal joints are evaluated, knowing the impact they have on the foot (133,134).

The morphological changes occurring in the foot that are associated in RA are increased pain, dysfunction, and loss of quality of life. The impact they generate is very negative and therefore it is important to be able to quantify these parameters. In the area of foot, we do not currently have a specific method such as those already referenced DAS28, SDAI, CDAI, among others (135).

In many methods, the usefulness to evaluate RA is not clear, which raises the question of whether the methods are reliable. All the methods do not have a cross-cultural validation with scientific rigor.

Most of the measures mentioned above have deficiencies in the construct of validity, responsiveness, and interpretability. These deficiencies may have an impact on the clinical setting (134).

The DAS 28 is the method considered the gold standard for RA and is used in many studies, but the foot is not included. In a study by Bakker et al. (2012) comparing the activity of the disease with the evolution of joint damage in the feet, it was confirmed that the DAS28 is not reliable to assess the level of activity in the feet with the following results (136):

• Analysis of the study population in general: linear correlation between DAS28 and joint erosion.

• A group with predominant activity in the hands, there is a linear correlation between the two.

A group with predominant activity in feet, there is no correlation between the study variables. In a study by Yano et al. (2018) (table 5) the prevalence in the foot and the activity analysed with DAS28 were evaluated It was observed that the patients with the highest activity index had higher percentage of alterations in the foot with poorer quality of life and functionality,

regardless of treatment with DMARDs or DMARDb (137).

Both studies drew similar conclusions and recommended that the evaluation of the feet in the routine consultation was essential. By omitting its impact on disease activity is being underestimated, and, in turn the concept of remission should be re-established (136,137).

1.6. Justification

Rheumatoid arthritis is a disease that primarily affects the feet and hands, affecting more than 90% of the patients with more than ten years of evolution of the disease (138). For podiatrists, foot care is one of the main objectives, although the field of rheumatology is insufficiently studied by this group to provide evidence of effects and structural alterations.

The appearance of hallux valgus (139), claw toes (140) or gait abnormalities such as pronation and supination (141) are highly recurrent themes in the scientific literature in the field of podiatry. But to date is the first study that determines from the point of view of the evolution of the patient, the deformities that can be found within the patient with RA.

The treatments are adapted to address these pathologies to prevent degeneration and to help the patient with RA to improve their quality of life. The patients have already experienced deterioration by their disease (142). The foot is one of the most vulnerable points, as has already been determined in other publications of this research group (143). This work can serve as a starting point for future research. From a pharmacological (144) and non-pharmacological point of view (145), it will improve podiatrists' understanding of the feet of patients with RA and their symptoms, associating them with general, classic pathologies within podiatry, such as the pronated foot or claw toes, in the context of an inflammatory disease such as RA. These pathologies generate disability, decrease quality of life, and may cause depression.

Therefore, this work is included in the research line of the PODUMA Group of the University of Malaga, where the purpose of the research is to help patients who attend podiatry consultations and generate specific knowledge in the field of rheumatology and the foot.

Chapter IV

Objectives

2. Objectives

2.1. The main objective

The aim of this study is to evaluate and classify the feet types and frequency of foot deformities in patients with RA.

2.2. Secondary objectives

To determine the relationship of the posture of the foot with the years of evolution of the disease

To determine the relationship of the deviations of the Hallux valgus with the evolution of the disease

To determine the relationship of the deviations of the minor radii with the evolution of the disease

Chapter V

Method

3. Materials and Methods

3.1 Ethical approval

Institutional review board that approved the protocol for the study: Medical Research Ethics Committee of University of Malaga (CEUMA-91-2015-H) and PEIBA Andalucía (ARC0001), Spain.

3.2 Design

A cross-sectional study

3.3 Participants

A convenience sample was obtained of 237 patients with foot pain and RA classification criteria (approved by the American College of Rheumatology and the European League Against Rheumatism in 2010) (11), of whom seventeen subsequently declined to participate, citing lack of time (the study questionnaire required 30 minutes to complete).

The patients were enrolled at the hospital outpatient clinics from January to December 2018. All the included participants in the study were:

- Adults (over 18 years old) who had a history of subtalar and/or ankle and/or talonavicular or hindfoot pain
- did not use of walking aids daily
- were able to achieve the normal range of motions in the ankle, subtalar and midtarsal joints (Even if maximum dorsiflexion, pronation, or supination in these joints could not be produced, a sufficient range of motion was achieved by adjusting the dynamics, for example by reducing stride length) (12).

The exclusion criteria applied were:

- concomitant musculoskeletal disease
- central or peripheral nervous system disease
- endocrine disorders (especially diabetes mellitus).

Patients who met the criteria for inclusion were approached by members of the rheumatology service at the Virgen de la Nieves Hospital (Granada, Spain), given an information sheet and invited to participate. Those participants who agreed were interviewed and given further details of the study. All participants provided written consent prior to starting the interviews.

3.4 Data collection

Demographic and clinical characteristics

The demographic characteristics recorded included the patient's age, gender, disease duration and current therapy. The clinical data were recorded to assess the patient's disease status utilizing the following methods. The visual analogue scale for pain (VAS pain) (13) is a validated, subjective measure for acute and chronic pain. Scores are recorded by making a handwritten mark on a 10-cm line that represents a continuum between "no pain" and "worst pain" (Figure 5).

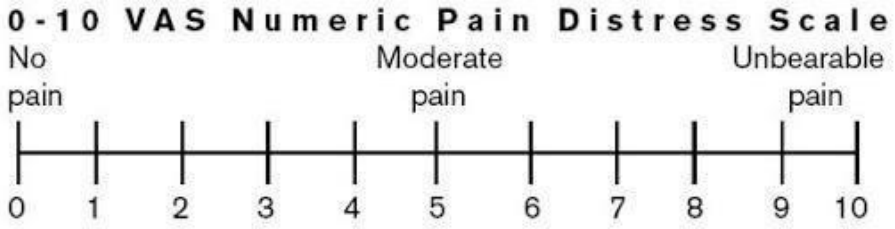


Figure 5 The visual analog scale (VAS) http://www.trialdatasolutions.com/tds/howto/vas.jsp

Disease Activity Score-28 (DAS28) (14), including 28-joint count, can discriminate between high and low disease activity as well as Disease Activity Scores with more comprehensive joint counts (Table 5) and in the hands, the joints that are evaluated include the first through fifth metacarpophalangeal joint, the interphalangeal joint of the thumb, and the second through fifth proximal interphalangeal joint. The GH or Global Health parameter represents the patient's self-assessment of disease activity on a 0-100 scale where 100 means maximal activity. DAS-28 reduction by 0.6 represents a moderate improvement. A reduction more than 1.2 represents a major improvement (146). The equation to obtain the score is DAS28 = (0.56 * sqr(TJC)) + (0.28 * sqr(SJC)) + (0.7 * ln(ESR)) + (0.014 * GH). (147).

DAS28 < 2.6: Remission
DAS28 >= 2.6 and <= 3.2: Low Disease Activity
DAS28 > 3.2 and <= 5.1: Moderate Disease Activity
DAS28 > 5.1: High Disease Activity

Table 5 Disease Activity Scores DAS28

The Simplified Disease Activity Index for Rheumatoid Arthritis (SDAI) is a scoring system that has been validated in both research and clinical settings. Remission is defined as an SDAI of <3.3, low disease activity as ≤11, moderate disease activity as ≤26 and high disease activity as >26 (15). The SDAI is the numerical sum of five outcome parameters: tender and swollen joint count (based on a 28-joint assessment), patient and physician global assessment of disease activity [visual analogue scale (VAS) 0-10 cm] and level of C-reactive protein (mg/dl, normal <1 mg/dl). The formula of the SDAI is as follows:

$$SDAI = TJC + SJC + PGA + MDGA + CRP$$

A series of outcomes were assessed to measure the morphological characteristics of the feet. The Foot Posture Index (FPI) is a reliable instrument for this purpose (16). Furthermore, the Manchester Scale of Hallux Valgus (148) and the Nijmegen classification of forefoot disorders (9) were assessed.

3.5 Procedure

Two researchers (ARC and GGN) independently interviewed the patients to obtain the study data. The clinical interview was conducted in one room, where the patients were asked to complete demographic characteristics. In a separate room, the foot posture of each patient was measured. For that purpose, The Foot Posture Index (FPI) is an observational measurement instrument that considers the three-dimensional nature of foot posture and has been shown to achieve good reliability in adults (18,149) and in children (20,149–151). It has also been considered an appropriate measure for subjects who are not in good health (152–155). Reference FPI values have been established for the adult population (18) the FPI was assessed (intraclass correlation coefficient (ICC) for the clinician, 0.94-0.96).

Each criterion was scored as −2, −1, 0, +1 or +2. The following FPI cut-off points, defining foot type category were used: a) highly supinated from −12 to −4, b) supinated from −3 to 0, c) neutral from 1 to 6, d) pronated from 6 to 10 and e) highly pronated from 11 to 12 (18). Items included: talar head palpation, curves above and below the lateral malleoli, calcaneal angle, talonavicular bulge, medial longitudinal arch, and forefoot to rearfoot alignment (Figure 6).

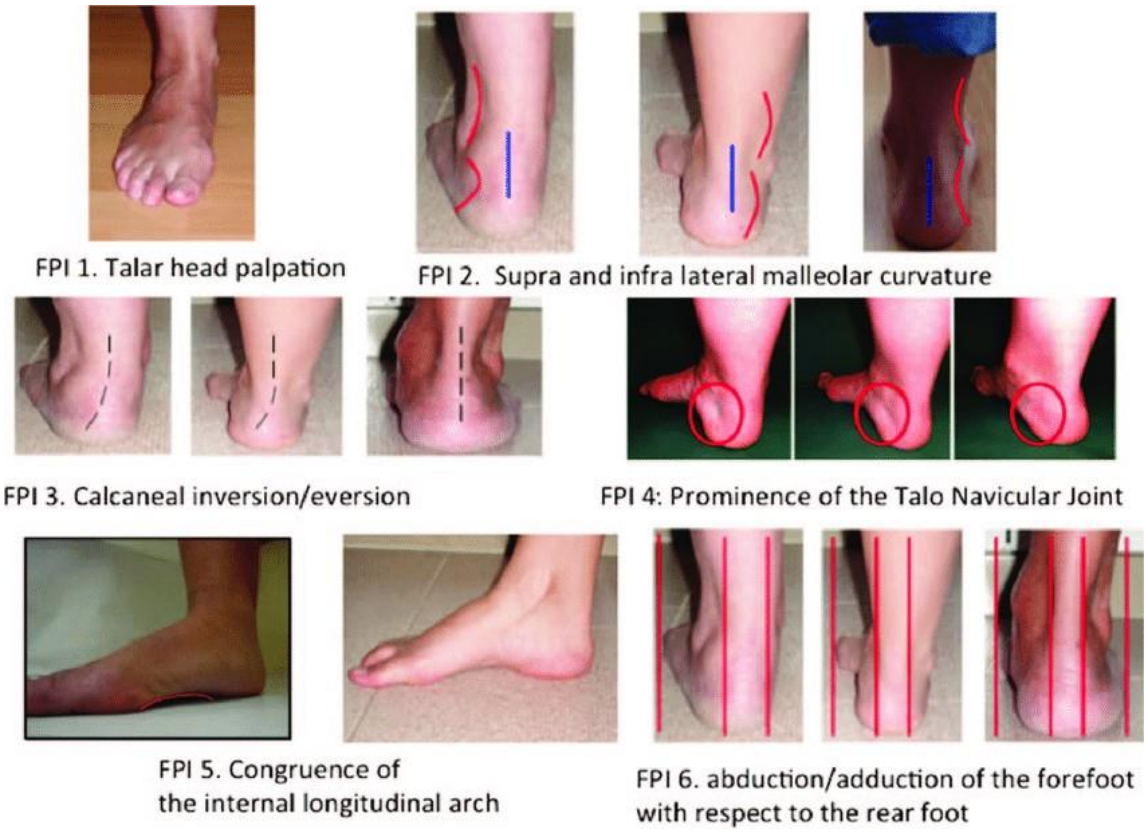


Figure 6 Foot Posture Index items (Free copyright)

The presence/absence of hallux valgus was determined according to the Manchester Scale of Hallux Valgus (ICC for the instrument, 0.93-0.97). It is a clinical tool consisting of photographs of feet with four levels of hallux valgus: none, mild, moderate, and severe (148, Figure 7).

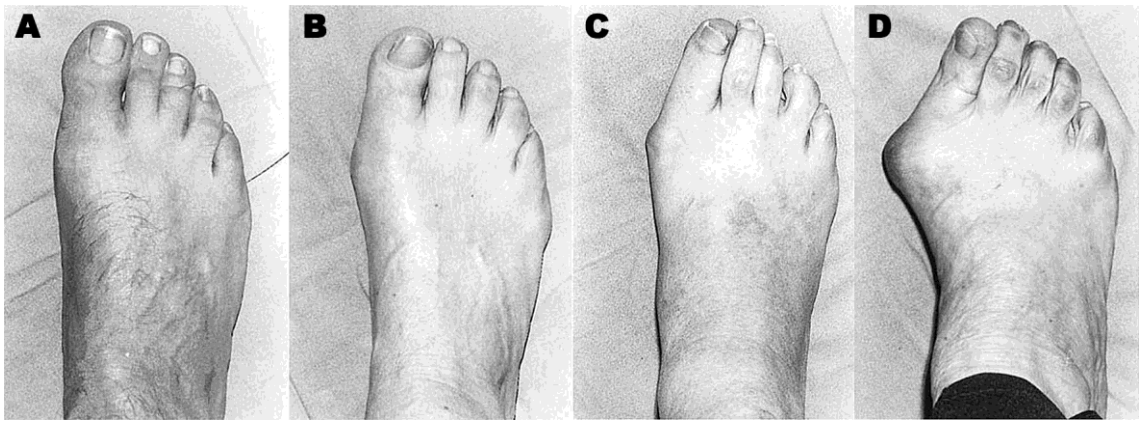


Figure 7 Graphic representation of the Manchester Hallux Abductus Valgus scale.(Author permission)

A) no deformation, B) mild deformation, C) moderate deformation, D) severe deformation. Illustration obtained from the article "The rating of the Hallux Valgus, The Manchester Scale" Garrow et al. (2001).

The Nijmegen classification of forefoot disorders is a classification system which can be used to grade the severity of the forefoot deformity. It presents four different levels to assess the deformity (Figure 8): Grade 0. No clinical changes in the metatarsophalangeal (MTP) joints, none or mild radiographic changes; Grade 1. Decreased mobility of one or more of the joints, particularly of plantarflexion, with the ability to reduce the plantar soft tissues under the metatarsal heads, and with adequate quality of the plantar soft tissues and/or radiographic erosive changes (Larsen 2-5) or evident intra-articular changes; Grade 2. Loss of plantar flexion in one or more of the MTP joints (up to 00), and loss of the ability to reduce the plantar soft tissues under the metatarsal heads, and/or with inadequate quality of the plantar soft tissues A. with a hallux valgus of more than 20º. B. without a hallux valgus of more than 20º; Grade 3. Deep contracture in one or more MTP joints, with or without radiographic subluxation or dislocation A. with a hallux valgus of more than 20º. B. without a hallux valgus of more than 20º (9) (ICC for the clinician, 0.83-0.87).

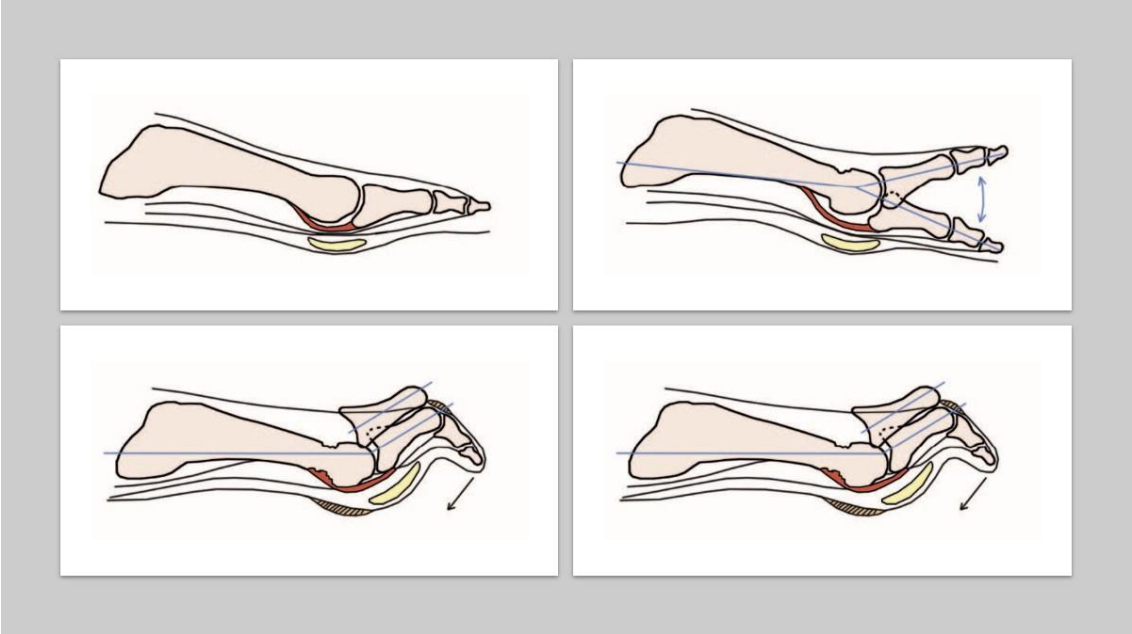


Figure 8 obtained from the article "A clinical classification system for rheumatoid forefoot deformity" Doorn et al. 2011(Author permission)

3.6 Statistical analysis

The results obtained are reported as the median and interquartile range, the non-normal distribution of the variables, and as the mean and standard deviation (SD) due to the normal distribution. The normality of the distributions was examined by the Kolmogorov-Smirnov test. The intra-rater reliability of the measurement instruments was calculated by a two-way mixed-consistency ICC model. The bivariate analysis was performed with Student's t test and the non-parametric Wilcoxon test; for the association of qualitative variables, the chi-square test was used for the comparison of proportions. The significance level was set at $p<0.05$. All statistical analyses were conducted using SPSS v. 24.0 statistical software (SPSS Inc., Chicago, IL, USA).

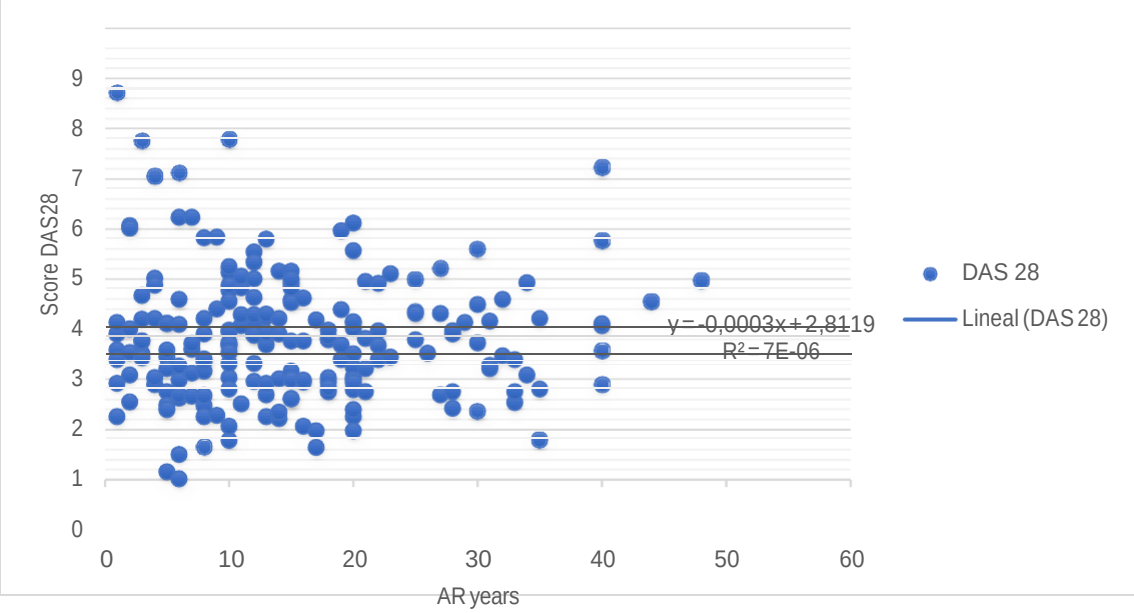
Chapter VI

Results

4. Results

This PhD thesis is available with the paper *Reinoso-Cobo A, Anttila P, Ortega-Avila AB, Cervera-Garvi P, Lopezosa-Reca E, Marchena-Rodriguez A, Ramos-Petersen L, Gijon-Nogueron G. Morpho-structural characteristics of feet in patients with rheumatoid arthritis: A cross sectional study. Int J Med Sci. 2021 Mar 30;18(11):2269-2275. doi: 10.7150/ijms.56935.*

In total, 220 patients with RA were analysed, (average duration of RA in years, 15.44, SD 10.54 years), 173 patients were female. The values for median age and interquartile range (IR) were 59 and 16 years for the patients with RA. The median values for height and weight were 162 cm (IR: 10) and 65 kg (IR: 15). The patients with RA were treated with biological disease-modifying antirheumatic pharmaceuticals (bDMARDs) (42%), methotrexate (35%) or nonsteroidal anti-inflammatory drugs (NSAIDs) / corticosteroids (20%). The mean scores were, of DAS 28 2.77(SD 1.27) and SDAI 10.10(SD 7.88) , and distribution of DAS28 score and SDAI score in relation with years of disease were inverse(Figure 9 and 10).



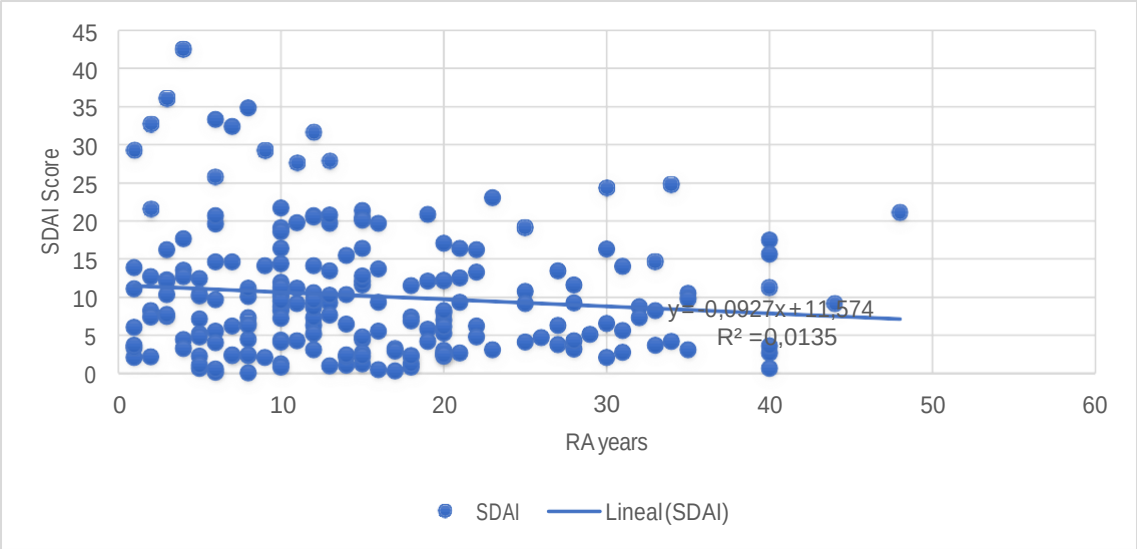


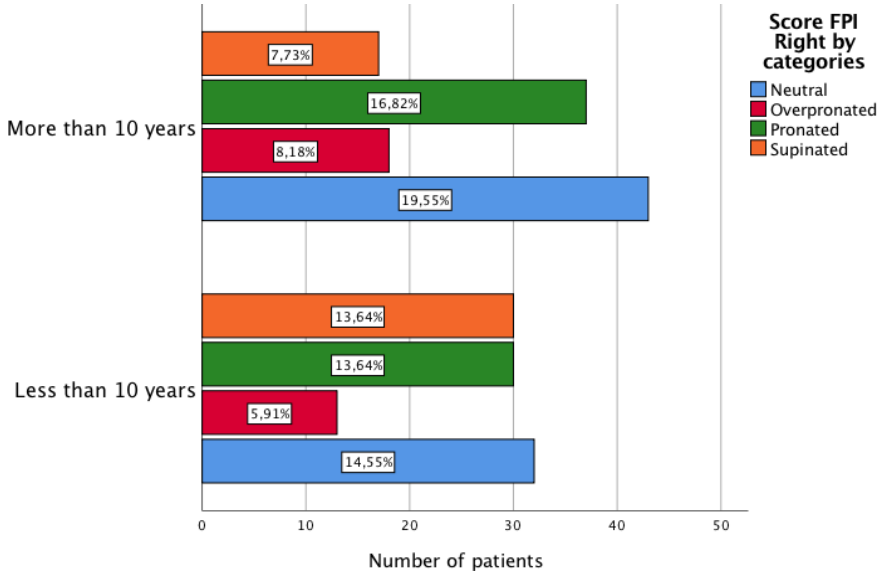
Figure 9 and 10 Distribution of DAS28 score and SDAI score in relation with years of disease

The most common foot posture according to the FPI assessment are the pronated position in the left foot (32.7% of participants) and the neutral position in the right foot (34.1% of participants) (Table 6).

N(220)			Frequency (number)	Percentage (%)
Foot Posture Index	Left	Supinated	46	20.9
		Neutral	57	25.9
		Pronated	72	32.7
		Overpronated	45	20.5
	Right	Supinated	47	21.4
		Neutral	75	34.1
		Pronated	67	30.5
		Overpronated	31	14.1
The Nijmegen classification	Left	Grade 0	34	15.5
		Grade 1	53	24.1
		Grade 2A	12	5.5
		Grade 2B	70	31.8
		Grade 3 A	22	10
		Grade 3B	29	13.2
	Right	Grade 0	36	16.4
		Grade 1	68	30,9
		Grade 2A	12	5.5
		Grade 2B	55	25
		Grade 3 A	18	8.2
		Grade 3B	31	14.1
Manchester Scale of Hallux Valgus	Left	None	105	47.7
		Mild	74	33.6
		Moderate	30	13.6
		Severe	11	5
	Right	None	111	50.5
		Mild	73	33.2
		Moderate	23	10.5
		Severe	13	5.9

Table 6 Characteristics of the sample in relation with the morphological foot in patients with RA

In patients who were diagnosed with RA less than 10 years ago, the right feet show a supinated position (13.64% of participants). On the other hand, in patients after 10 years of RA evolution, the right foot's neutral position is the most common (19.55% of participants). In the left feet different results are shown. In patients after 10 years of RA evolution, the left feet have a pronated position (19.55% of participants) (Figure 11A/B). Non- statistically significant differences were found using the chi-square test in both feet (p=0.098 and p=0.257).



.

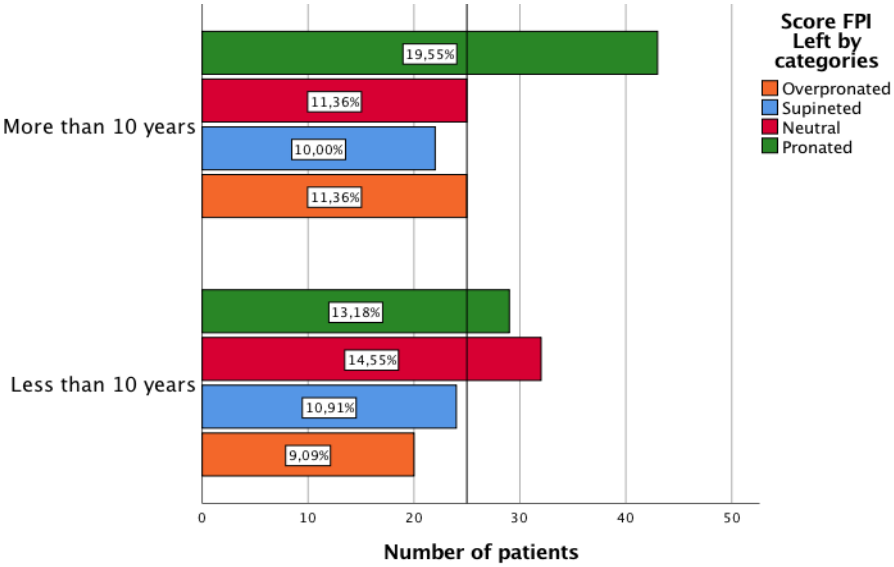
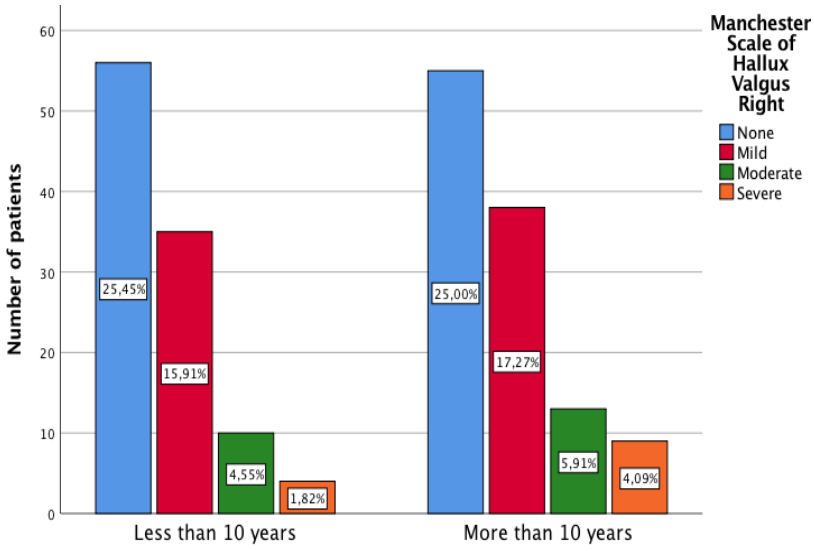


Figure 11A y B Score of FPI differentiating according to years of disease evolution

The hallux valgus progression of deformity overall is exacerbated. 1.82% of patients present a severe level of hallux valgus in patients before 10 years of RA evolution, whereas 4.09% of patients present a severe level of hallux valgus in patients after 10 years of RA evolution. Statistically significant differences were not found using the chi-square test in the right foot (p=0.573), however, statistically significant differences were found in the left foot (p=0.024) (Figure 12A/B).



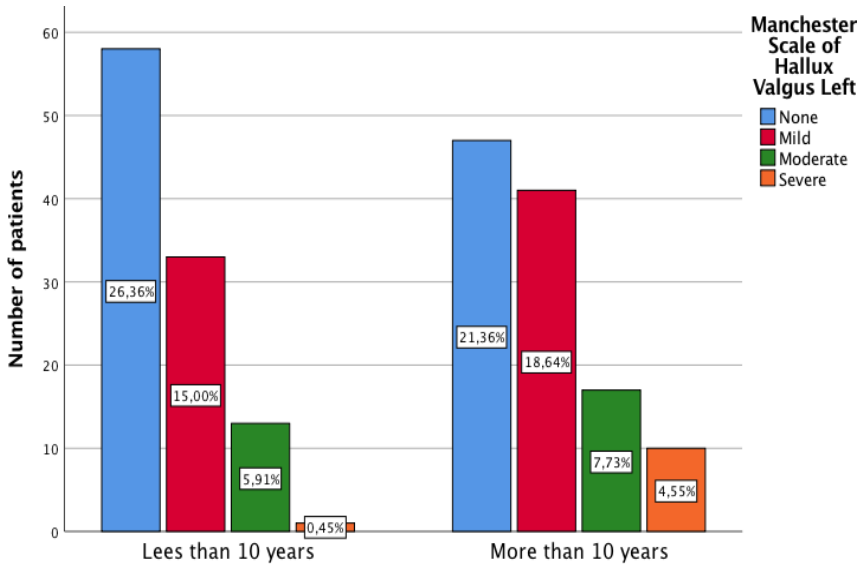
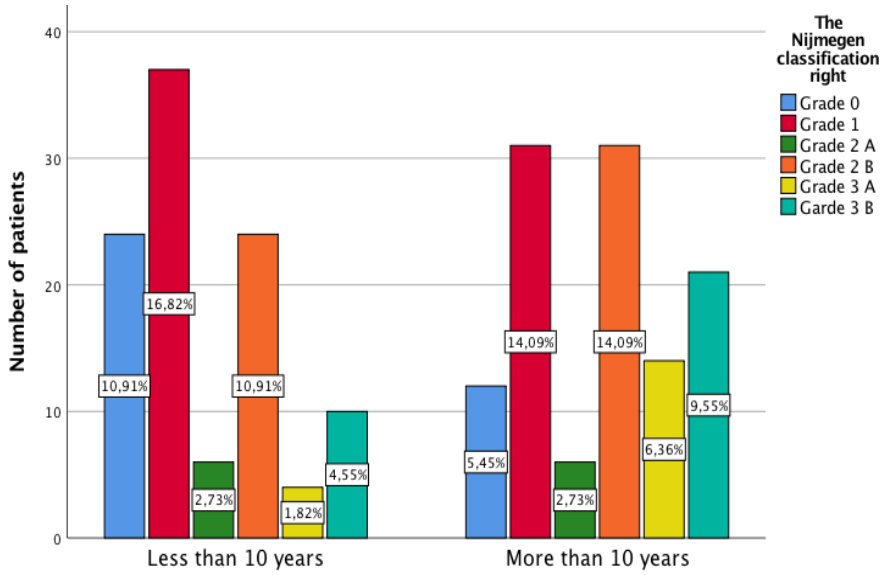


Figure 12 A and B Severity of Hallux Valgus by categories of Manchester Scale of HV differentiating according to years of disease evolution

In terms of lesser metatarsophalangeal deformities, statistically significant differences are presented in both feet (p=0,013 and p=0,007). The Grade 3 increases its percentage in both feet in patients with more than 10 years of RA evolution (Figure 13A and B).



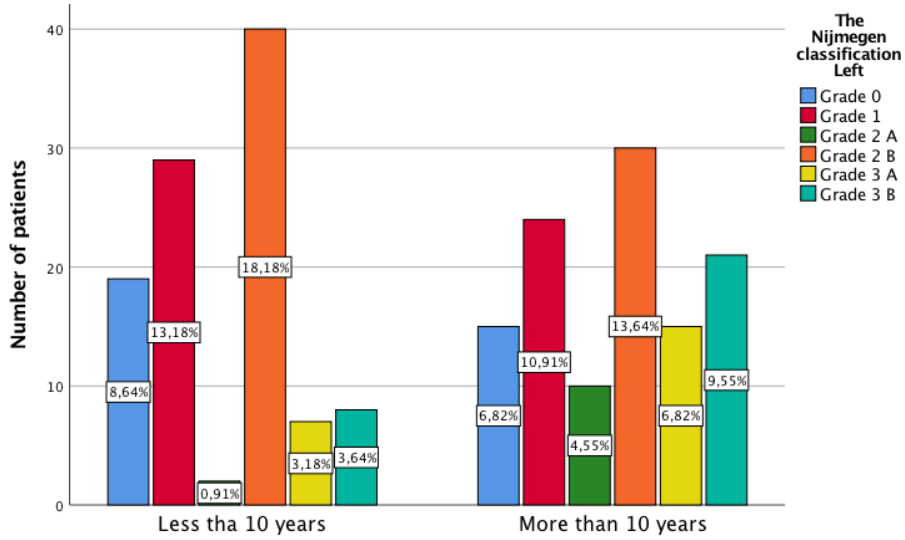


Figure 13 A and B Severity of metatarsophalangeal by categories of Nijmegen classification differentiating according to years of disease evolution

Chapter VII

Discussion

5. Discussion

The aim of this cross-sectional study was to evaluate and classify the types and frequency of foot deformities in patients with RA. For this study, the foot type defined by FPI, the Manchester Scale of Hallux Valgus (17) and the Nijmegen classification of forefoot disorders were assessed in patients with RA. As a result, the prevalence of HAV, forefoot deformities and foot type were described.

Currently, in healthcare practice the foot and ankle examination of RA patients tends to be omitted. Souza et al. reported in their study that 54% of the physicians did not examine the feet routinely as it is not included in the joint count (DAS28, TJC28 and SJC28) or have an interest in the validated methods used to quantify radiologically joint deterioration. Yano et al. reported that professionals prefer to examine hands rather than feet and ankles in the routine consultation due to time constraints. In their study Otter et al. concluded that in the respondents the most recent reference of the foot was 16.5 months ago and the hand only 6.2 months ago. Considering the available data, validated and useful methods for general clinical practice to evaluate a fundamental structure, of feet, are required, because the deterioration of this structure affects the disability and quality of life and of the patient (137,142,156).

Foot involvement in RA is underestimated and has presented limited clinical interest. Assessing the impact of RA on the different affected areas of the foot is usually omitted due to the time constraints, unless the surgery is required, in which case radiological methods are used. During the period from diagnosis to surgery, a detailed evaluation and orthopaedic treatments that can improve the quality of life of the patient.

Clinical practice guidelines are important for routine treatment and care protocol changes. Recommendations should be based on collected updated scientific evidence. In a 2016 review by Hennessy et al. the recommendations that regarded foot and ankle care and recommendations were searched, 24 met the search criteria, 5 had guidelines referring to foot and ankle care, 12 only collected recommendations, and the rest did not make a reference (157).

The previous studies that mentioned different structural deformations in the foot, the quantitative method to demonstrate these structural changes were not described (19,20). In this study objective, validated foot outcomes have been included, except the Nijmegen classification. The results of this study are comparable to the results of Biscontini at al. in 2009 study (21), which concluded that patients with RA frequently present with hallux valgus and pronated foot based on the FPI and the Manchester Hallux Valgus.

Both studies concede that feet of patients with RA present valgus pathology and forefoot deformity. However, several studies have demonstrated that some musculoskeletal alterations appear in the upper limbs, such as muscle atrophy, severed tendons, decreased joint range of motion, join instability, stiffness, pain, and biomechanical impairment., which are not all associated with the osteoarticular deformation of the foot (22,23). In addition, this study provides process evolution data with the differentiation between patients that present RA before and after 10 years. As in comparison to previous studies, such as Lee et al. (2019), which analysed the incidence of the foot and ankle effects in patients with a mean RA disease evolution of only 8 years, quantifying the number of affected joints with pain, inflammation and radiological alterations in the foot and ankle (20).

As it has been described in this study, many patients, especially female, with RA suffer from hallux valgus and lesser toe deformities, such as decreased mobility of one or more of the MTP joints, a reduction of soft tissues under MTP joints and/or radiographic erosive changes. It has been discussed in previous studies that foot symptoms are common among patients with RA and are frequently severe, despite the significant progress in RA treatments (2).

Yano et al. (2019) only analysed the incidents in which patients presented alterations in the foot at the time of the diagnosis, not reporting the prevalence of foot deformities (19). The first foot manifestations are usually in the forefoot and get worse over time (2). This is comparable to the results of this study that shows patients with RA presenting a more severe Hallux Valgus in patients after 10 years of RA evolution than before 10 years of evolution. The development of HAV in patients with RA occurs in a shorter period than in the general population due to the following structural alterations of the foot: increased medial pressure on the forefoot, synovitis in the first MTP joint causing joint capsule laxity and instability, joint erosion leading to deviation in the transverse plane of the first MTP joint, and increased laxity of the Lisfranc ligament increasing the intermetatarsal angle (24,25).

The FPI results showed that patients with RA present a wide variety of foot types, including neutral, pronated, overpronated and supinated foot posture. The most common foot posture was the neutral and pronated position, showing a tendency to higher values in the FPI after 10 years of disease evolution, which means pronated foot posture. These results concur with previous studies, which concluded that the hindfoot is frequently found in a valgus position in patients with RA. An alteration in joint alignment, a reduction in mobility and a change in pressure distribution to the medial aspect of foot progress are present in a valgus deformation (24–26).

The foot is a complex anatomical structure of the locomotor system, formed by bones with different functions that are joined by the types of synovial joint, due to their characteristics, that will be affected as previously mentioned.

Based on the literature review, it is shown that all the joints of the foot have not been given the same importance or have been included in many investigations. The main joints referenced are the metatarsophalangeal, subtalar, talonavicular, and tibiofibular-talar joints, which are directly involved in the most referenced and accepted type deformation of the foot.

These joints have greater mobility which possibly leads them to deviate in the same plane of movement (MTJ dorsiflexion) or even in a different plane from their usual movement (MTJ abduction) due to the influence of associated structures that can be flexors and extensors.

The impact of morphostructural and functional alterations have on the foot are significant causing reduction of dorsal and plantar flexion of ATPA, increased hindfoot valgus, deformation of the hallux, claw toes, and minor toe deviation. These alterations influence the biomechanics of walking by reducing speed, increasing instability, and making it difficult to adapt to the terrain (100,158).

The rest of the joints, talocuboid, cuneocuboid, navicular-cuboid, scapho-cuneal, intercuneal, cuneometatarsal, cuboid-metatarsal, intermetatarsal, interphalangeal (proximal, medial, and distal), the impact on the foot, at the level of joint alteration, has not been studied for pain and functionality. These joints, except the interphalangeal joints, belong to the midfoot. They provide stability and allow the transmission of the step from hindfoot to forefoot. These joints have little mobility in a single plane, except for calcaneocuboid joint.

The radiological methods have shown the impact of RA in the joints of the hand, but not usually in joints of the foot. The importance of the joints of the foot and the impact of RA may not have been considered enough since there is lack of evidence and evaluation methods. Matsumoto et al. reached the same conclusion when applying the criteria of the Sharp / van der Heijde method in midfoot joints (117).

Unlike the studies carried out on the hands analysing the deformity and alteration of functions, the involvement of the foot has received interest until recently. Most of the studies analyse pain, quality of life and disability according to the time of evolution of the disease, apart from the mentioned variables. Other symptoms are identified such as stiffness, swelling, and limitation of the joint range of motion.

Strengths and weaknesses of the study:

The strengths of this study include validated and reliable outcome measures and questionnaires used to assess foot types and frequency of foot deformities in patients with RA. All the participants presented a duration of the disease of more than 10 years, which was useful to establish a classification before and after 10 years of evolution. Also, a protocol was followed with each patient.

Chapter VIII

Limitations and future research

6. Limitations and future research

Future research:

In further studies, analysing more homogeneous sample sizes are needed, as a non-homogeneous sample size may influence the results. Furthermore, studies with outcomes that allow making a relationship between pain, loss of functionality and/or quality of life, and feet deformity are required.

The increase of knowledge about the impact of RA in feet and development of podiatry treatments that consider the years of evolution of disease is needed. Additionally, the development of a system that follows up patients every 6 months about their disease and the changes produced in their feet would assist in determining more effectively the procedure for pharmacological and non-pharmacological treatments.

Limitations:

The limitations associated with this study must be acknowledged when interpreting the results. First, all the participants were mainly women, which correlated with the information that RA is most common in females in Europe. Secondly, the influence of biologics treatment should have been assessed to differentiate the effects of the treatments on soft tissues (ligaments and muscles). Biologics treatment may influence soft tissues depending on how long the treatment has been used. As a result, biologic treatment may influence the appearance of pronated foot types.

Chapter VIII

Conclusions

Conclusions

1. The most frequently found foot type in patients with RA is the pronated foot, with deformities in the MTP joints without Hallux Valgus. However, a percentage of patients with RA present with a supinated foot.

2. The evolution of the disease shows some morphological changes in terms of the patient's feet. An evolution of more severe stages of foot deformities are presented, such as Hallux Valgus or Grade 3 of MTP joints in the Nijmegen classification scale.

3. The feet of patients with RA and more than 10 years of evolution increase their degree of pronation according to the Foot Posture Index.

4. The degree of severity of hallux deformity is increased according to the Manchester scale in patients with RA of more than 10 years of evolution.

5. The degree of severity of metatarsophalangeal joint deformity by categories of Nijmegen classification increases in patients with more than 10 years of evolution

Chapter VIII

References

References

1. Hennessy K, Woodburn J, Steultjens M. Clinical practice guidelines for the foot and ankle in rheumatoid arthritis: A critical appraisal. J Foot Ankle Res [Internet]. 2016 Aug 19 [cited 2021 Apr 25];9(1). Available from: https://pubmed.ncbi.nlm.nih.gov/27547242/
2. Stolt M, Suhonen R, Leino-Kilpi H. Foot health in patients with rheumatoid arthritis—a scoping review [Internet]. Vol. 37, Rheumatology International. Springer Verlag; 2017 [cited 2021 Apr 25]. p. 1413–22. Available from: https://pubmed.ncbi.nlm.nih.gov/28324133/
3. Laroche D, Pozzo T, Ornetti P, Tavernier C, Maillefert JF. Effects of loss of metatarsophalangeal joint mobility on gait in rheumatoid arthritis patients. Rheumatology [Internet]. 2006 Apr [cited 2021 Apr 25];45(4):435–40. Available from: https://pubmed.ncbi.nlm.nih.gov/16249238/
4. Westhoff G, Listing J, Zink A. Loss of physical independence in rheumatoid arthritis: Interview data from a representative sample of patients in rheumatologic care. Arthritis Care Res. 2000;13(1):11–22.
5. Katz P, Margaretten M, Gregorich S, Trupin L. Physical Activity to Reduce Fatigue in Rheumatoid Arthritis: A Randomized Controlled Trial. Arthritis Care Res [Internet]. 2018 Jan 1 [cited 2021 Apr 25];70(1):1–10. Available from: https://pubmed.ncbi.nlm.nih.gov/28378441/
6. Verma C, Parikh R, Nadkar M, Mehta A. Correlation of functional ability of the hand with upper limb function and quality of life in patients with rheumatoid arthritis. J Assoc Physicians India [Internet]. 2017 Mar 1 [cited 2021 Apr 25];65(MARCH):20–4. Available from: https://europepmc.org/article/med/28462539
7. van der Leeden M, Steultjens MP, Dekker JHM, Prins APA, Dekker J. The relationship of disease duration to foot function, pain and disability in rheumatoid arthritis patients with foot complaints. Clin Exp Rheumatol [Internet]. 2007 Mar 1 [cited 2021 Apr 25];25(2):275–80. Available from: https://europepmc.org/article/med/17543153
8. Hulsmans HMJ, Jacobs JWG, Van Der Heijde DMFM, Van Albada-Kuipers GA, Schenk Y, Bijlsma JWJ. The course of radiologic damage during the first six years of rheumatoid arthritis. Arthritis Rheum [Internet]. 2000 [cited 2021 Apr 25];43(9):1927–40. Available from: https://pubmed.ncbi.nlm.nih.gov/11014342/
9. Doorn PF, Keijsers NLW, van Limbeek J, Anderson PG, Laan RFJM, Bosch P van t. P, et al. A clinical classification system for rheumatoid forefoot deformity. Foot Ankle Surg [Internet]. 2011 Sep [cited 2021 Apr 25];17(3):158–65. Available from: https://pubmed.ncbi.nlm.nih.gov/21783077/

10. Firth J, Hale C, Helliwell P, Hill J, Nelson EA. The prevalence of foot ulceration in patients with rheumatoid arthritis. Arthritis Care Res [Internet]. 2008 Feb 15 [cited 2021 Apr 25];59(2):200–5. Available from: https://pubmed.ncbi.nlm.nih.gov/18240257/
11. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO, et al. 2010 Rheumatoid arthritis classification criteria: An American College of Rheumatology/European League Against Rheumatism collaborative initiative [Internet]. Vol. 62, Arthritis and Rheumatism. John Wiley and Sons Inc.; 2010 [cited 2021 Apr 25]. p. 2569–81. Available from: https://pubmed.ncbi.nlm.nih.gov/20872595/
12. Dubbeldam R, Baan H, Nene A V., Drossaers-Bakker KW, van de Laar MAFJ, Hermens HJ, et al. Foot and Ankle Kinematics in Rheumatoid Arthritis: Influence of Foot and Ankle Joint and Leg Tendon Pathologies. Arthritis Care & Res [Internet]. [cited 2021 Apr 25];65(4):503–11. Available from: https://www.academia.edu/17113321/Foot_and_Ankle_Kinematics_in_Rheumatoid_Arthritis_Influence_of_Foot_and_Ankle_Joint_and_Leg_Tendon_Pathologies
13. Sendlbeck M, Araujo EG, Schett G, Englbrecht M. Psychometric properties of three single-item pain scales in patients with rheumatoid arthritis seen during routine clinical care: A comparative perspective on construct validity, reproducibility and internal responsiveness. RMD Open [Internet]. 2015 Jan 1 [cited 2021 Apr 25];1(1). Available from: https://pubmed.ncbi.nlm.nih.gov/26719815/
14. Van Der Heijde DMFM, Van 't Hof M, Van Riel PLCM, Van De Putte LBA. Development of a disease activity score based on judgement in clinical practice by rheumatologists. In: Journal of Rheumatology [Internet]. 1993 [cited 2021 Apr 25]. p. 579–81. Available from: https://europepmc.org/article/med/8478878
15. Smolen JS, Breedveld FC, Schiff MH, Kalden JR, Emery P, Eberl G, et al. A simplified disease activity index for rheumatoid arthritis for use in clinical practice. Rheumatology [Internet]. 2003 Feb 1 [cited 2021 Apr 25];42(2):244–57. Available from: https://pubmed.ncbi.nlm.nih.gov/12595618/
16. Redmond AC, Crosbie J, Ouvrier RA. Development and validation of a novel rating system for scoring standing foot posture: The Foot Posture Index. Clin Biomech [Internet]. 2006 Jan [cited 2021 Apr 25];21(1):89–98. Available from: https://pubmed.ncbi.nlm.nih.gov/16182419/
17. Garrow AP, Papageorgiou A, Silman AJ, Thomas E, Jayson MIV, Macfarlane GJ. The grading of hallux valgus: The Manchester scale. J Am Podiatr Med Assoc [Internet]. 2001 [cited 2021 Apr 25];91(2):74–8. Available from: https://pubmed.ncbi.nlm.nih.gov/11266481/
18. Redmond AC, Crane YZ, Menz HB. Normative values for the Foot Posture Index. J Foot Ankle Res [Internet]. 2008 Jul 31 [cited 2021 Apr 25];1(1). Available from:

https://pubmed.ncbi.nlm.nih.gov/18822155/

19. Yano K, Ikari K, Inoue E, Sakuma Y, Mochizuki T, Koenuma N, et al. Features of patients with rheumatoid arthritis whose debut joint is a foot or ankle joint: A 5,479-case study from the IORRA cohort. Lin C-Y, editor. PLoS One [Internet]. 2018 Sep 6 [cited 2021 Apr 25];13(9):e0202427. Available from: https://dx.plos.org/10.1371/journal.pone.0202427
20. Lee SW, Kim SY, Chang SH. Prevalence of feet and ankle arthritis and their impact on clinical indices in patients with rheumatoid arthritis: A cross-sectional study. BMC Musculoskelet Disord [Internet]. 2019 Sep 11 [cited 2021 Apr 25];20(1):420. Available from: https://bmcmusculoskeletdisord.biomedcentral.com/articles/10.1186/s12891-019-2773-z
21. Biscontini D, Bartoloni Bocci E, Gerli R. Analysis of foot structural damage in rheumatoid arthritis: clinical evaluation by validated measures and serological correlations. Reumatismo [Internet]. 2011 Jun 24 [cited 2021 Apr 25];61(1). Available from: https://pubmed.ncbi.nlm.nih.gov/19370188/
22. Toprak CŞ, Duruöz MT, Gündüz OH. Static and dynamic balance disorders in patients with rheumatoid arthritis and relationships with lower extremity function and deformities: A prospective controlled study. Arch Rheumatol [Internet]. 2018 Sep 1 [cited 2021 Apr 25];33(3):328–34. Available from: https://pubmed.ncbi.nlm.nih.gov/30632523/
23. Aydoğ E, Bal A, Aydoğ ST, Çakci A. Evaluation of dynamic postural balance using the Biodex Stability System in rheumatoid arthritis patients. Clin Rheumatol [Internet]. 2006 Jul [cited 2021 Apr 25];25(4):462–7. Available from: https://pubmed.ncbi.nlm.nih.gov/16247584/
24. Dave MH, Mason LW, Hariharan K. Forefoot Deformity in Rheumatoid Arthritis: A Comparison of Shod and Unshod Populations. Foot Ankle Spec [Internet]. 2015 Oct 22 [cited 2021 Apr 25];8(5):378–83. Available from: https://pubmed.ncbi.nlm.nih.gov/25941210/
25. Göksel Karatepe A, GüNaydin R, Adibelli ZH, Kaya T, DuruöZ E. Foot deformities in patients with rheumatoid arthritis: The relationship with foot functions. Int J Rheum Dis [Internet]. 2010 [cited 2021 Apr 25];13(2):158–63. Available from: https://pubmed.ncbi.nlm.nih.gov/20536601/
26. Woodburn J, Helliwell PS. Relation between heel position and the distribution of forefoot plantar pressures and skin callosities in rheumatoid arthritis. Ann Rheum Dis [Internet]. 1996 [cited 2021 Apr 25];55(11):806–10. Available from: https://pubmed.ncbi.nlm.nih.gov/8976636/
27. Arnett FC, Edworthy SM, Bloch DA, Mcshane DJ, Fries JF, Cooper NS, et al. The

american rheumatism association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum [Internet]. 1988 Mar 1 [cited 2021 Apr 25];31(3):315–24. Available from: http://doi.wiley.com/10.1002/art.1780310302

28. Turrión Nieves A, Martín Holguera R, Pérez Gómez A, Álvarez de Mon-Soto M. Artritis reumatoide. Med [Internet]. 2017 Mar 1 [cited 2021 Apr 25];12(28):1615–25. Available from: https://www.medicineonline.es/es-artritis-reumatoide-articulo-S0304541217300434
29. Sharif K, Sharif A, Jumah F, Oskouian R, Tubbs RS. Rheumatoid arthritis in review: Clinical, anatomical, cellular and molecular points of view. Clin Anat [Internet]. 2018 Mar 1 [cited 2021 Apr 25];31(2):216–23. Available from: https://pubmed.ncbi.nlm.nih.gov/28833647/
30. Smolen JS, Aletaha D, McInnes IB. Rheumatoid arthritis [Internet]. Vol. 388, The Lancet. Lancet Publishing Group; 2016 [cited 2021 Apr 25]. p. 2023–38. Available from: http://dx.doi.org/10.1016/
31. Grassi W, De Angelis R, Lamanna G, Cervini C. The clinical features of rheumatoid arthritis. In: European Journal of Radiology [Internet]. Elsevier Sci Ireland Ltd; 1998 [cited 2021 Apr 25]. Available from: https://pubmed.ncbi.nlm.nih.gov/9652497/
32. Silman AJ, Pearson JE. Epidemiology and genetics of rheumatoid arthritis [Internet]. Vol. 4, Arthritis research. Arthritis Res; 2002 [cited 2021 Apr 25]. p. S265–72. Available from: https://pubmed.ncbi.nlm.nih.gov/12110146/
33. Carmona L, Villaverde V, Hernández-García C, Ballina J, Gabriel R, Laffon A. The prevalence of rheumatoid arthritis in the general population of Spain. Rheumatology [Internet]. 2002 [cited 2021 Apr 25];41(1):88–95. Available from: https://pubmed.ncbi.nlm.nih.gov/11792885/
34. Cross M, Smith E, Hoy D, Carmona L, Wolfe F, Vos T, et al. The global burden of rheumatoid arthritis: Estimates from the Global Burden of Disease 2010 study. Ann Rheum Dis [Internet]. 2014 [cited 2021 Apr 25];73(7):1316–22. Available from: https://pubmed.ncbi.nlm.nih.gov/24550173/
35. Alamanos Y, Voulgari P V., Drosos AA. Incidence and Prevalence of Rheumatoid Arthritis, Based on the 1987 American College of Rheumatology Criteria: A Systematic Review. Semin Arthritis Rheum [Internet]. 2006 Dec [cited 2021 Apr 25];36(3):182–8. Available from: https://pubmed.ncbi.nlm.nih.gov/17045630/
36. Manejo de Pacientes con Artritis Reumatoide para el.
37. Kiadaliri AA, Kristensen LE, Englund M. Burden of rheumatoid arthritis in the Nordic region, 1990–2015: a comparative analysis using the Global Burden of Disease Study 2015. Scand J Rheumatol [Internet]. 2018 Mar 4 [cited 2021 Apr 25];47(2):1–101. Available from: https://pubmed.ncbi.nlm.nih.gov/28766390/

38. Hamuryudan V, Direskeneli H, Ertenli I, Inanc M, Karaaslan Y, Oksel F, et al. Direct and indirect healthcare costs of rheumatoid arthritis patients in Turkey. Clin Exp Rheumatol [Internet]. 2016 Nov 1 [cited 2021 Apr 25];34(6):1033–7. Available from: https://europepmc.org/article/med/27749224
39. Moradi-Lakeh M, Forouzanfar MH, Vollset SE, El Bcheraoui C, Daoud F, Afshin A, et al. Burden of musculoskeletal disorders in the Eastern Mediterranean Region, 1990-2013: Findings from the Global Burden of Disease Study 2013. Ann Rheum Dis [Internet]. 2017 Aug 1 [cited 2021 Apr 25];76(8):1365–73. Available from: https://pubmed.ncbi.nlm.nih.gov/28209629/
40. Myasoedova E, Davis JM, Crowson CS, Gabriel SE. Epidemiology of rheumatoid arthritis: Rheumatoid arthritis and mortality [Internet]. Vol. 12, Current Rheumatology Reports. Curr Rheumatol Rep; 2010 [cited 2021 Apr 25]. p. 379–85. Available from: https://pubmed.ncbi.nlm.nih.gov/20645137/
41. Radovits BJ, Fransen J, Al Shamma S, Eijsbouts AM, Van Riel PLCM, Laan RFJM. Excess mortality emerges after 10 years in an inception cohort of early rheumatoid arthritis. Arthritis Care Res [Internet]. 2010 Mar [cited 2021 Apr 25];62(3):362–70. Available from: https://pubmed.ncbi.nlm.nih.gov/20391482/
42. Gonzalez A, Kremers HM, Crowson CS, Nicola PJ, Davis JM, Therneau TM, et al. The widening mortality gap between rheumatoid arthritis patients and the general population. Arthritis Rheum [Internet]. 2007 Nov [cited 2021 Apr 25];56(11):3583–7. Available from: https://pubmed.ncbi.nlm.nih.gov/17968923/
43. Buleu F, Sirbu E, Caraba A, Dragan S. Heart involvement in inflammatory rheumatic diseases: A systematic literature review. Med. 2019;55(6):1–13.
44. Gonzalo-Gil E, Galindo-Izquierdo M. Papel del factor de crecimiento transformador-beta (TGF-β) en la fisiopatología de la artritis reumatoide [Internet]. Vol. 10, Reumatologia Clinica. Ediciones Doyma, S.L.; 2014 [cited 2021 Apr 25]. p. 174–9. Available from: http://www.reumatologiaclinica.org/es-papel-del-factor-crecimiento-transformador-beta-articulo-S1699258X14000345
45. Dayer JM. The process of identifying and understanding cytokines: From basic studies to treating rheumatic diseases [Internet]. Vol. 18, Best Practice and Research: Clinical Rheumatology. Bailliere Tindall Ltd; 2004 [cited 2021 Apr 25]. p. 31–45. Available from: https://pubmed.ncbi.nlm.nih.gov/15123036/
46. Lundy SK, Sarkar S, Tesmer LA, Fox DA. Cells of the synovium in rheumatoid arthritis. T lymphocytes [Internet]. Vol. 9, Arthritis Research and Therapy. Arthritis Res Ther; 2007 [cited 2021 Apr 25]. Available from: https://pubmed.ncbi.nlm.nih.gov/17306038/
47. Firestein GS. Evolving concepts of rheumatoid arthritis [Internet]. Vol. 423, Nature. Nature Publishing Group; 2003 [cited 2021 Apr 25]. p. 356–61. Available from:

https://www.nature.com/articles/nature01661

48. Weissmann G. The pathogenesis of rheumatoid arthritis. In: Bulletin of the NYU Hospital for Joint Diseases [Internet]. N Engl J Med; 2006 [cited 2021 Apr 25]. p. 12–5. Available from: https://pubmed.ncbi.nlm.nih.gov/22150039/
49. Autoanticuerpos en la artritis reumatoide [Internet]. [cited 2021 Apr 25]. Available from: https://www.elsevier.es/es-revista-revista-espanola-reumatologia-29-pdf-13040339
50. Aletaha D, Alasti F, Smolen JS. Rheumatoid factor, not antibodies against citrullinated proteins, is associated with baseline disease activity in rheumatoid arthritis clinical trials. Arthritis Res Ther [Internet]. 2015 Aug 26 [cited 2021 Apr 25];17(1). Available from: https://pubmed.ncbi.nlm.nih.gov/26307354/
51. Merino MC, Gruppi A. Origen y desarrollo de linfocitos B1. Una población celular involucrada en defensa y autoinmunidad. Medicina (B Aires). 2006;66(2):165–72.
52. Seyler TM, Park YW, Takemura S, Bram RJ, Kurtin PJ, Goronzy JJ, et al. BLyS and APRIL in rheumatoid arthritis. J Clin Invest [Internet]. 2005 Nov [cited 2021 Apr 25];115(11):3083–92. Available from: https://pubmed.ncbi.nlm.nih.gov/16239971/
53. Hernández AS. Células colaboradoras (TH1, TH2, TH17) y reguladoras (Treg, TH3, NKT) en la artritis reumatoide [Internet]. Vol. 5, Reumatologia Clinica Suplementos. Elsevier; 2009 [cited 2021 Apr 25]. p. 1–5. Available from: http://www.reumatologiaclinica.org/es-celulas-colaboradoras-th1-th2-th17--articulo-S1699258X09000345
54. Sánchez-Ramón S, López-Longo FJ, Carreño L. Interleucinas en la fisiopatología de la artritis reumatoide: más allá de las citocinas proinflamatorias. Reumatol Clin [Internet]. 2010 Mar 1 [cited 2021 Apr 25];6(SUPPL. 3):20–4. Available from: http://www.reumatologiaclinica.org/es-interleucinas-fisiopatologia-artritis-reumatoide-mas-articulo-S1699258X11000222
55. Schett G, Gravallese E. Bone erosion in rheumatoid arthritis: Mechanisms, diagnosis and treatment [Internet]. Vol. 8, Nature Reviews Rheumatology. Nat Rev Rheumatol; 2012 [cited 2021 Apr 25]. p. 656–64. Available from: https://pubmed.ncbi.nlm.nih.gov/23007741/
56. MIKÁN V JF, OLIVEROS A WD. Osteogénesis y enfermedades óseas. Rev MED. 2007;15(2):261–70.
57. Komuro H, Olee T, Kühn K, Quach J, Brinson DC, Shikhman A, et al. The osteoprotegerin/receptor activator of nuclear factor κB/receptor activator of nuclear factor κB ligand system in cartilage. Arthritis Rheum [Internet]. 2001 [cited 2021 Apr 25];44(12):2768–76. Available from: https://pubmed.ncbi.nlm.nih.gov/11762937/
58. Brennan FM, McInnes IB. Evidence that cytokines play a role in rheumatoid arthritis [Internet]. Vol. 118, Journal of Clinical Investigation. J Clin Invest; 2008 [cited 2021

Apr 25]. p. 3537–45. Available from: https://pubmed.ncbi.nlm.nih.gov/18982160/

59. Zwerina J, Redlich K, Polzer K, Joosten L, Kroenke G, Distler J, et al. TNF-induced structural joint damage is mediated by IL-1. Proc Natl Acad Sci U S A [Internet]. 2007 Jul 10 [cited 2021 Apr 25];104(28):11742–7. Available from: https://pubmed.ncbi.nlm.nih.gov/17609389/

60. Van Gaalen FA, Van Aken J, Huizinga TWJ, Schreuder GMT, Breedveld FC, Zanelli E, et al. Association between HLA class II genes and autoantibodies to cyclic citrullinated peptides (CCPs) influences the severity of rheumatoid arthritis. Arthritis Rheum [Internet]. 2004 Jul [cited 2021 Apr 26];50(7):2113–21. Available from: https://pubmed.ncbi.nlm.nih.gov/15248208/

61. Sanmartí R, Gómez-Puerta JA. Biomarcadores en la artritis reumatoide. Reumatol Clin. 2010;6(SUPPL. 3):25–8.

62. Mewar D, Coote A, Moore DJ, Marinou I, Keyworth J, Dickson MC, et al. Independent associations of anti-cyclic citrullinated peptide antibodies and rheumatoid factor with radiographic severity of rheumatoid arthritis. Arthritis Res Ther [Internet]. 2006 Jul 20 [cited 2021 Apr 26];8(4). Available from: https://pubmed.ncbi.nlm.nih.gov/16859535/

63. Rombouts Y, Willemze A, Van Beers JJBC, Shi J, Kerkman PF, Van Toorn L, et al. Extensive glycosylation of ACPA-IgG variable domains modulates binding to citrullinated antigens in rheumatoid arthritis. Ann Rheum Dis [Internet]. 2016 Mar 1 [cited 2021 Apr 26];75(3):578–85. Available from: https://pubmed.ncbi.nlm.nih.gov/25587188/

64. Mendez-Rayo T, Ochoa-Zárate L, Posso-Osorio I, Ortiz E, Naranjo-Escobar J, Tobón GJ. Interpretación de los autoanticuerpos en enfermedades reumatológicas. Rev Colomb Reumatol. 2018;25(2):112–25.

65. Kourilovitch M, Galarza-Maldonado C, Ortiz-Prado E. Diagnosis and classification of rheumatoid arthritis. J Autoimmun [Internet]. 2014 [cited 2021 Apr 26];48–49:26–30. Available from: https://pubmed.ncbi.nlm.nih.gov/24568777/

66. Fisiopatología, tratamiento y modelos experimentales de artritis reumatoide [Internet]. [cited 2021 Apr 26]. Available from: http://scielo.sld.cu/scielo.php?script=sci_arttext&pid=S0034-75152011000200014

67. de Rooy DPC, van der Linden MPM, Knevel R, Huizinga TWJ, van der Helm-van AHM. Predicting arthritis outcomes-what can be learned from the Leiden Early Arthritis Clinic? Rheumatology [Internet]. 2011 Jan [cited 2021 Apr 26];50(1):93–100. Available from: https://pubmed.ncbi.nlm.nih.gov/20639266/

68. Van Nies JAB, Tsonaka R, Gaujoux-Viala C, Fautrel B, Van Der Helm-Van Mil AHM. Evaluating relationships between symptom duration and persistence of rheumatoid arthritis: Does a window of opportunity exist? Results on the Leiden Early Arthritis

Clinic and ESPOIR cohorts. Ann Rheum Dis [Internet]. 2015 May 1 [cited 2021 Apr 26];74(5):806–12. Available from: https://pubmed.ncbi.nlm.nih.gov/25561360/

69. Klareskog L, Catrina AI, Paget S. Rheumatoid arthritis [Internet]. Vol. 373, The Lancet. Elsevier B.V.; 2009 [cited 2021 Apr 26]. p. 659–72. Available from: https://pubmed.ncbi.nlm.nih.gov/19157532/
70. Caplazi P, Baca M, Barck K, Carano RAD, DeVoss J, Lee WP, et al. Mouse Models of Rheumatoid Arthritis. Vet Pathol [Internet]. 2015 Sep 24 [cited 2021 Apr 26];52(5):819–26. Available from: http://journals.sagepub.com/doi/10.1177/0300985815588612
71. MacGregor AJ, Snieder H, Rigby AS, Koskenvuo M, Kaprio J, Aho K, et al. Characterizing the quantitative genetic contribution to rheumatoid arthritis using data from twins. Arthritis Rheum [Internet]. 2000 Jan [cited 2021 Apr 26];43(1):30–7. Available from: https://pubmed.ncbi.nlm.nih.gov/10643697/
72. Bax M, Van Heemst J, Huizinga TWJ, Toes REM. Genetics of rheumatoid arthritis: What have we learned? [Internet]. Vol. 63, Immunogenetics. Springer; 2011 [cited 2021 Apr 26]. p. 459–66. Available from: /pmc/articles/PMC3132380/
73. Goemaere S, Ackerman C, Goethals K, De Keyser F, Van Der Straeten C, Verbruggen G, et al. Onset of symptoms of rheumatoid arthritis in relation to age, sex and menopausal transition. J Rheumatol [Internet]. 1990 Dec 1 [cited 2021 Apr 26];17(12):1620–2. Available from: https://europepmc.org/article/med/2084234
74. Symmons DPM, Chakravarty K. Can immunisation trigger rheumatoid arthritis? [Internet]. Vol. 52, Annals of the Rheumatic Diseases. BMJ Publishing Group; 1993 [cited 2021 Apr 26]. p. 843–4. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1005209/
75. Symmons DPM, Bankhead CR, Harrison BJ, Brennan P, Barrett EM, Scott DGI, et al. Blood transfusion, smoking, and obesity as risk factors for the development of rheumatoid arthritis: Results from a primary care-based incident case-control study in Norfolk, England. Arthritis Rheum [Internet]. 1997 Nov [cited 2021 Apr 26];40(11):1955–61. Available from: https://pubmed.ncbi.nlm.nih.gov/9365083/
76. Di Giuseppe D, Discacciati A, Orsini N, Wolk A. Cigarette smoking and risk of rheumatoid arthritis: A dose-response meta-analysis. Arthritis Res Ther [Internet]. 2014 Mar 5 [cited 2021 Apr 26];16(2). Available from: https://pubmed.ncbi.nlm.nih.gov/24594022/
77. Sugiyama D, Nishimura K, Tamaki K, Tsuji G, Nakazawa T, Morinobu A, et al. Impact of smoking as a risk factor for developing rheumatoid arthritis: A meta-analysis of observational studies. Ann Rheum Dis [Internet]. 2010 Jan [cited 2021 Apr 26];69(1):70–81. Available from: https://pubmed.ncbi.nlm.nih.gov/19174392/
78. Suresh E. Diagnosis of early rheumatoid arthritis: What the non-specialist needs to know

[Internet]. Vol. 97, Journal of the Royal Society of Medicine. Royal Society of Medicine Press; 2004 [cited 2021 Apr 26]. p. 421–4. Available from: /pmc/articles/PMC1079582/

79. Extra-articular Manifestations in Rheumatoid Arthritis [Internet]. [cited 2021 Apr 26]. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3152850/

80. Sahatçiu-Meka V, Rexhepi S, Manxhuka-Kërliu S, Rexhepi M. Extra-articular manifestations of seronegative and seropositive rheumatoid arthritis. Bosn J Basic Med Sci [Internet]. 2010 [cited 2021 Apr 26];10(1):26–31. Available from: https://pubmed.ncbi.nlm.nih.gov/20192927/

81. Turesson C, Matteson EL. Management of extra-articular disease manifestations in rheumatoid arthritis [Internet]. Vol. 16, Current Opinion in Rheumatology. Curr Opin Rheumatol; 2004 [cited 2021 Apr 26]. p. 206–11. Available from: https://pubmed.ncbi.nlm.nih.gov/15103246/

82. Helfand AE, Arlen DI, Banks LF, Black JR, Canter KC, Gorecki GA, et al. Podiatric medicine and public health: Concepts and perspectives. J Am Podiatr Med Assoc [Internet]. 1998 [cited 2021 Apr 26];88(7):353–9. Available from: https://pubmed.ncbi.nlm.nih.gov/9680773/

83. Bal A, Aydog E, Aydog ST, Cakci A. Foot deformities in rheumatoid arthritis and relevance of foot function index. Clin Rheumatol [Internet]. 2006 Sep [cited 2021 Apr 26];25(5):671–5. Available from: https://pubmed.ncbi.nlm.nih.gov/16344914/

84. Foot and ankle in rheumatoid arthritis. Foot and ankle in rheumatoid arthritis. Springer Paris; 2006.

85. Mootanah R, Song J, Lenhoff MW, Hafer JF, Backus SI, Gagnon D, et al. Foot Type Biomechanics Part 2: Are structure and anthropometrics related to function? Gait Posture [Internet]. 2013 Mar [cited 2021 Apr 26];37(3):452–6. Available from: https://pubmed.ncbi.nlm.nih.gov/23107624/

86. Hillstrom HJ, Song J, Kraszewski AP, Hafer JF, Mootanah R, Dufour AB, et al. Foot type biomechanics part 1: Structure and function of the asymptomatic foot. Gait Posture [Internet]. 2013 Mar [cited 2021 Apr 26];37(3):445–51. Available from: https://pubmed.ncbi.nlm.nih.gov/23107625/

87. Chan PSJ, Kong KO. Natural history and imaging of subtalar and midfoot joint disease in rheumatoid arthritis [Internet]. Vol. 16, International Journal of Rheumatic Diseases. Int J Rheum Dis; 2013 [cited 2021 Apr 26]. p. 14–8. Available from: https://pubmed.ncbi.nlm.nih.gov/23441767/

88. Turner DE, Woodburn J. Characterising the clinical and biomechanical features of severely deformed feet in rheumatoid arthritis. Gait Posture [Internet]. 2008 Nov [cited 2021 Apr 26];28(4):574–80. Available from: https://pubmed.ncbi.nlm.nih.gov/18508270/

89. Stolt M, Suhonen R, Leino-Kilpi H. Foot health in patients with rheumatoid arthritis—a scoping review [Internet]. Vol. 37, Rheumatology International. Springer Verlag; 2017 [cited 2021 Apr 26]. p. 1413–22. Available from: https://pubmed.ncbi.nlm.nih.gov/28324133/
90. Riente L, Delle Sedie A, Iagnocco A, Filippucci E, Meenagh G, Valesini G, et al. Ultrasound imaging for the rheumatologist. V. Ultrasonography of the ankle and foot. Clin Exp Rheumatol. 2006;24(5):493–8.
91. GÖKSEL KARATEPE A, GÜNAYDIN R, ADIBELLI ZH, KAYA T, DURUÖZ E. Foot deformities in patients with rheumatoid arthritis: the relationship with foot functions. Int J Rheum Dis [Internet]. 2010 Mar 15 [cited 2021 Apr 26];13(2):158–63. Available from: http://doi.wiley.com/10.1111/j.1756-185X.2010.01465.x
92. Louwerens JWK, Schrier JCM. Rheumatoid forefoot deformity: Pathophysiology, evaluation and operative treatment options [Internet]. Vol. 37, International Orthopaedics. Int Orthop; 2013 [cited 2021 Apr 26]. p. 1719–29. Available from: https://pubmed.ncbi.nlm.nih.gov/23892468/
93. van der Leeden M, Steultjens MPM, Terwee CB, Rosenbaum D, Turner D, Woodburn J, et al. A systematic review of instruments measuring foot function, foot pain, and foot-related disability in patients with rheumatoid arthritis. Arthritis Rheum [Internet]. 2008 Sep 15 [cited 2021 Apr 26];59(9):1257–69. Available from: http://doi.wiley.com/10.1002/art.24016
94. Onodera T, Nakano H, Homan K, Kondo E, Iwasaki N. Preoperative radiographic and clinical factors associated with postoperative floating of the lesser toes after resection arthroplasty for rheumatoid forefoot deformity. BMC Musculoskelet Disord [Internet]. 2019 Feb 19 [cited 2021 Apr 26];20(1). Available from: https://pubmed.ncbi.nlm.nih.gov/30782150/
95. Diaper R, Wong E, Metcalfe SA. The implications of biologic therapy for elective foot and ankle surgery in patients with rheumatoid arthritis [Internet]. Vol. 30, Foot. Churchill Livingstone; 2017 [cited 2021 Apr 26]. p. 53–8. Available from: https://pubmed.ncbi.nlm.nih.gov/28262590/
96. Knupp M, Skoog A, Törnkvist H, Ponzer S. Triple arthrodesis in rheumatoid arthritis. Foot Ankle Int [Internet]. 2008 Mar [cited 2021 Apr 26];29(3):293–7. Available from: https://pubmed.ncbi.nlm.nih.gov/18348825/
97. Hideki Tsuboi MH. Hind-mid-forefoot Deformity in Hallux Valgus Deformity in Rheumatoid Arthritis: Radiographic Evaluation Grouped by Existence of Dorsal Dislocation of Second Metatarsophalangeal Joint. Rheumatol Curr Res. 2013;03(02).
98. Lee SW, Kim SY, Chang SH. Prevalence of feet and ankle arthritis and their impact on clinical indices in patients with rheumatoid arthritis: A cross-sectional study. BMC

Musculoskelet Disord [Internet]. 2019 Sep 11 [cited 2021 Apr 26];20(1):420. Available from: https://bmcmusculoskeletdisord.biomedcentral.com/articles/10.1186/s12891-019-2773-z

99. Baan H, Drossaers-Bakker W, Dubbeldam R, Van De Laar M. We should not forget the foot: Relations between signs and symptoms, damage, and function in rheumatoid arthritis. Clin Rheumatol [Internet]. 2011 Nov [cited 2021 Apr 26];30(11):1475–9. Available from: https://pubmed.ncbi.nlm.nih.gov/21614474/

100. Turner DE, Helliwell PS, Emery P, Woodburn J. The impact of rheumatoid arthritis on foot function in the early stages of disease: A clinical case series. BMC Musculoskelet Disord [Internet]. 2006 Dec 21 [cited 2021 Apr 26];7. Available from: https://pubmed.ncbi.nlm.nih.gov/17184535/

101. Aydoğ E, Bal A, Aydoğ ST, Çakci A. Evaluation of dynamic postural balance using the Biodex Stability System in rheumatoid arthritis patients. Clin Rheumatol [Internet]. 2006 Jul [cited 2021 Apr 26];25(4):462–7. Available from: https://pubmed.ncbi.nlm.nih.gov/16247584/

102. Toprak CŞ, Duruöz MT, Gündüz OH. Static and dynamic balance disorders in patients with rheumatoid arthritis and relationships with lower extremity function and deformities: A prospective controlled study. Arch Rheumatol [Internet]. 2018 Sep 1 [cited 2021 Apr 26];33(3):328–34. Available from: https://pubmed.ncbi.nlm.nih.gov/30632523/

103. Brooks F, Hariharan K. The rheumatoid forefoot. Curr Rev Musculoskelet Med [Internet]. 2013 Dec [cited 2021 Apr 26];6(4):320–7. Available from: https://pubmed.ncbi.nlm.nih.gov/23943297/

104. Loveday DT, Jackson GE, Geary NPJ. The rheumatoid foot and ankle: Current evidence [Internet]. Vol. 18, Foot and Ankle Surgery. Foot Ankle Surg; 2012 [cited 2021 Apr 26]. p. 94–102. Available from: https://pubmed.ncbi.nlm.nih.gov/22443994/

105. Hulsmans HMJ, Jacobs JWG, Van Der Heijde DMFM, Van Albada-Kuipers GA, Schenk Y, Bijlsma JWJ. The course of radiologic damage during the first six years of rheumatoid arthritis. Arthritis Rheum [Internet]. 2000 [cited 2021 Apr 26];43(9):1927–40. Available from: https://pubmed.ncbi.nlm.nih.gov/11014342/

106. Yano K, Ikari K, Nakayama M, Sakuma Y, Imamura H, Tobimatsu H, et al. The impact of hindfoot deformities for the recurrence of hallux valgus after joint-preserving surgeries for rheumatoid forefoot deformities. Foot Ankle Surg [Internet]. 2019 Jun 1 [cited 2021 Apr 26];25(3):348–53. Available from: https://pubmed.ncbi.nlm.nih.gov/30321979/

107. Fukushi JI, Nakashima Y, Okazaki K, Yamada H, Mawatari T, Ohishi M, et al. Outcome of joint-preserving arthroplasty for rheumatoid forefoot deformities. Foot Ankle Int

[Internet]. 2016 Mar 1 [cited 2021 Apr 26];37(3):262–8. Available from: http://journals.sagepub.com/doi/10.1177/1071100715609981

108. Dave MH, Mason LW, Hariharan K. Forefoot Deformity in Rheumatoid Arthritis: A Comparison of Shod and Unshod Populations. Foot Ankle Spec [Internet]. 2015 Oct 22 [cited 2021 Apr 26];8(5):378–83. Available from: https://pubmed.ncbi.nlm.nih.gov/25941210/

109. De Mits S, Mielants H, De Clercq D, Woodburn J, Roosen P, Elewaut D. Quantitative assessment of foot structure in rheumatoid arthritis by a foot digitizer: Detection of deformities even in the absence of erosions. Arthritis Care Res [Internet]. 2012 Nov [cited 2021 Apr 26];64(11):1641–8. Available from: https://pubmed.ncbi.nlm.nih.gov/22807070/

110. Doorn PF, Keijsers NLW, van Limbeek J, Anderson PG, Laan RFJM, Bosch P van t. P, et al. A clinical classification system for rheumatoid forefoot deformity. Foot Ankle Surg [Internet]. 2011 Sep [cited 2021 Apr 26];17(3):158–65. Available from: https://pubmed.ncbi.nlm.nih.gov/21783077/

111. Van Der Leeden M, Steultjens MPM, Ursum J, Dahmen R, Roorda LD, Van Schaardenburg D, et al. Prevalence and course of forefoot impairments and walking disability in the first eight years of rheumatoid arthritis. Arthritis Care Res [Internet]. 2008 Nov 15 [cited 2021 Apr 26];59(11):1596–602. Available from: https://pubmed.ncbi.nlm.nih.gov/18975350/

112. Barn R, Turner DE, Rafferty D, Sturrock RD, Woodburn J. Tibialis posterior tenosynovitis and associated pes plano valgus in rheumatoid arthritis: Electromyography, multisegment foot kinematics, and ultrasound features. Arthritis Care Res [Internet]. 2013 Apr [cited 2021 Apr 26];65(4):495–502. Available from: https://pubmed.ncbi.nlm.nih.gov/22972604/

113. Turner DE, Woodburn J, Helliwell PS, Cornwall MW, Emery P. Pes planovalgus in RA: a descriptive and analytical study of foot function determined by gait analysis. Musculoskeletal Care [Internet]. 2003 [cited 2021 Apr 26];1(1):21–33. Available from: https://pubmed.ncbi.nlm.nih.gov/20217661/

114. Neufeld JD, Weinraub GM, Hernandez ES, Co MS. The surgical reconstruction of rheumatoid midfoot and hindfoot deformities [Internet]. Vol. 27, Clinics in Podiatric Medicine and Surgery. Clin Podiatr Med Surg; 2010 [cited 2021 Apr 26]. p. 261–73. Available from: https://pubmed.ncbi.nlm.nih.gov/20470957/

115. Smyth CJ, Janson RW. Rheumatologic view of the rheumatoid foot. In: Clinical Orthopaedics and Related Research [Internet]. Springer New York LLC; 1997 [cited 2021 Apr 26]. p. 7–17. Available from: https://pubmed.ncbi.nlm.nih.gov/9224234/

116. Matsumoto T, Nakada I, Juji T, Nakamura I, Ito K. Radiologic Patterning of Hallux

Deformity in Rheumatoid Arthritis and Its Relationship to Flatfoot. J Foot Ankle Surg [Internet]. 2016 Sep 1 [cited 2021 Apr 26];55(5):948–54. Available from: https://pubmed.ncbi.nlm.nih.gov/27289217/

117. Matsumoto T, Nakamura I, Miura A, Momoyama G, Ito K. Radiologic patterning of joint damage to the foot in rheumatoid arthritis. Arthritis Care Res [Internet]. 2014 [cited 2021 Apr 26];66(4):499–507. Available from: https://pubmed.ncbi.nlm.nih.gov/24106167/

118. Popelka S, Hromdka R, Vavík P, Tursa P, Pokorn D, Jahoda D, et al. Isolated talonavicular arthrodesis in patients with rheumatoid arthritis of the foot and tibialis posterior tendon dysfunction. BMC Musculoskelet Disord [Internet]. 2010 [cited 2021 Apr 26];11. Available from: https://pubmed.ncbi.nlm.nih.gov/20187969/

119. O'Brien TS, Hart TS, Gould JS. Extraosseous manifestations of rheumatoid arthritis in the foot and ankle. In: Clinical Orthopaedics and Related Research [Internet]. Springer New York LLC; 1997 [cited 2021 Apr 26]. p. 26–33. Available from: https://pubmed.ncbi.nlm.nih.gov/9224236/

120. Seltzer SE, Weissman BN, Braunstein EM, Adams DF, Thomas WH. Computed tomography of the hindfoot with rheumatoid arthritis. Arthritis Rheum [Internet]. 1985 [cited 2021 Apr 26];28(11):1234–42. Available from: https://pubmed.ncbi.nlm.nih.gov/4062998/

121. Wang B, Saltzman CL, Chalayon O, Barg A. Does the Subtalar Joint Compensate for Ankle Malalignment in End-stage Ankle Arthritis? Clin Orthop Relat Res [Internet]. 2015 Jan 1 [cited 2021 Apr 26];473(1):318–25. Available from: https://pubmed.ncbi.nlm.nih.gov/25315275/

122. Jaakkola JI, Mann RA. A review of rheumatoid arthritis affecting the foot and ankle [Internet]. Vol. 25, Foot and Ankle International. AOFAS - American Orthopaedic Foot and Ankle Society; 2004 [cited 2021 Apr 26]. p. 866–74. Available from: https://pubmed.ncbi.nlm.nih.gov/15680099/

123. Michelson J, Easley M, Wigley FM, Hellmann D. Posterior Tibial Tendon Dysfunction in Rheumatoid Arthritis. Foot Ankle Int [Internet]. 1995 [cited 2021 Apr 26];16(3):156–61. Available from: https://pubmed.ncbi.nlm.nih.gov/7599734/

124. Gutierrez M, Pineda C, Salaffi F, Raffeiner B, Cazenave T, Martinez-Nava GA, et al. Is ankle involvement underestimated in rheumatoid arthritis? Results of a multicenter ultrasound study. Clin Rheumatol [Internet]. 2016 Nov 1 [cited 2021 Apr 26];35(11):2669–78. Available from: https://pubmed.ncbi.nlm.nih.gov/27094944/

125. Simonsen MB, Yurtsever A, Næsborg-Andersen K, Leutscher PDC, Hørslev-Petersen K, Hirata RP, et al. A parametric study of effect of experimental tibialis posterior muscle pain on joint loading and muscle forces—Implications for patients with rheumatoid

arthritis? Gait Posture [Internet]. 2019 Jul 1 [cited 2021 Apr 26];72:102–8. Available from: https://doi.org/10.1016/j.gaitpost.2019.06.001

126. Dubbeldam R, Baan H, Nene A V., Drossaers-Bakker KW, Van De Laar MAFJ, Hermens HJ, et al. Foot and ankle kinematics in rheumatoid arthritis: Influence of foot and ankle joint and leg tendon pathologies. Arthritis Care Res [Internet]. 2013 Apr [cited 2021 Apr 26];65(4):503–11. Available from: https://pubmed.ncbi.nlm.nih.gov/22972768/

127. Keenan MAE, Peabody TD, Gronley JK, Perry J. Valgus deformities of the feet and characteristics of gait in patients who have rheumatoid arthritis. J Bone Jt Surg - Ser A. 1991;73(2):237–47.

128. The rheumatoid foot. A clinical study with pathological and roentgenological comments. 1956 - PubMed [Internet]. [cited 2021 Apr 26]. Available from: https://pubmed.ncbi.nlm.nih.gov/2009676/

129. Ibrahim IK, Medani SH, El-Hameed MMA, Imam MH, Shaaban MMA. Tarsal tunnel syndrome in patients with rheumatoid arthritis, electrophysiological and ultrasound study. Alexandria J Med. 2013;49(2):95–104.

130. Baylan SP, Paik SW, Barnert AL, Ko KH, Yu J, Persellin RH. Prevalence of the tarsal tunnel syndrome in rheumatoid arthritis. Rheumatology [Internet]. 1981 Aug [cited 2021 Apr 26];20(3):148–50. Available from: https://pubmed.ncbi.nlm.nih.gov/7280489/

131. Bowen CJ, Hooper L, Culliford D, Dewbury K, Sampson M, Burridge J, et al. Assessment of the natural history of forefoot bursae using ultrasonography in patients with rheumatoid arthritis: a twelve-month investigation. Arthritis Care Res (Hoboken) [Internet]. 2010 [cited 2021 Apr 26];62(12):1756–62. Available from: https://pubmed.ncbi.nlm.nih.gov/20722046/

132. Studler U, Mengiardi B, Bode B, Schöttle PB, Pfirrmann CWA, Hodler J, et al. Fibrosis and adventitious bursae in plantar fat pad of forefoot: MR imaging findings in asymptomatic volunteers and MR imaging-histologic comparison. Radiology [Internet]. 2008 Mar [cited 2021 Apr 26];246(3):863–70. Available from: https://pubmed.ncbi.nlm.nih.gov/18195378/

133. Landorf KB, Keenan AM. An evaluation of two foot-specific, health-related quality-of-life measuring instruments. Foot Ankle Int [Internet]. 2002 [cited 2021 Apr 26];23(6):538–46. Available from: https://pubmed.ncbi.nlm.nih.gov/12095123/

134. Ortega-Avila AB, Ramos-Petersen L, Cervera-Garvi P, Nester CJ, Morales-Asencio JM, Gijon-Nogueron G. Systematic review of the psychometric properties of patient-reported outcome measures for rheumatoid arthritis in the foot and ankle [Internet]. Vol. 33, Clinical Rehabilitation. SAGE Publications Ltd; 2019 [cited 2021 Apr 26]. p. 1788–99. Available from: https://pubmed.ncbi.nlm.nih.gov/31291785/

135. Gijon-Nogueron G, Ndosi M, Luque-Suarez A, Alcacer-Pitarch B, Munuera PV, Garrow A, et al. Cross-cultural adaptation and validation of the Manchester Foot Pain and Disability Index into Spanish. Qual Life Res [Internet]. 2014 Mar [cited 2021 Apr 26];23(2):571–9. Available from: https://pubmed.ncbi.nlm.nih.gov/23975380/
136. Bakker MF, Jacobs JWG, Kruize AA, Van Der Veen MJ, Van Booma-Frankfort C, Vreugdenhil SA, et al. Misclassification of disease activity when assessing individual patients with early rheumatoid arthritis using disease activity indices that do not include joints of feet. Vol. 71, Annals of the Rheumatic Diseases. 2012. 830–835 p.
137. Yano K, Ikari K, Inoue E, Sakuma Y, Mochizuki T, Koenuma N, et al. Features of patients with rheumatoid arthritis whose debut joint is a foot or ankle joint: A 5,479-case study from the IORRA cohort. PLoS One [Internet]. 2018 Sep 1 [cited 2021 Apr 26];13(9). Available from: https://pubmed.ncbi.nlm.nih.gov/30188930/
138. Scott DL, Smith C, Kingsley G. Joint damage and disability in rheumatoid arthritis: An updated systematic review [Internet]. Vol. 21, Clinical and Experimental Rheumatology. 2003 [cited 2021 May 26]. p. S20-7. Available from: https://europepmc.org/article/med/14969046
139. Übersicht über die Operationsverfahren bei rheumatisch bedingten Pathologien des Fußes [Internet]. [cited 2021 May 26]. Available from: https://www.online-oup.de/article/uebersicht-ueber-die-operationsverfahren-bei-rheumatisch-bedingten-pathologien-des-fusses/uebersichtsarbeiten/y/m/781?pageNumber=0
140. Grondal L, Tengstrand B, Nordmark B, Wretenberg P, Stark A. The foot: Still the most important reason for walking incapacity in rheumatoid arthritis - Distribution of symptomatic joints in 1,000 RA patients. Acta Orthop [Internet]. 2008 Apr 1 [cited 2021 May 26];79(2):257–61. Available from: https://pubmed.ncbi.nlm.nih.gov/18484253/
141. Rome K, Gow PJ, Dalbeth N, Chapman JM. Clinical audit of foot problems in patients with rheumatoid arthritis treated at Counties Manukau District Health Board, Auckland, New Zealand. J Foot Ankle Res [Internet]. 2009 May 15 [cited 2021 May 26];2(1). Available from: https://pubmed.ncbi.nlm.nih.gov/19442310/
142. Otter SJ, Lucas K, Springett K, Moore A, Davies K, Cheek L, et al. Foot pain in rheumatoid arthritis prevalence, risk factors and management: An epidemiological study. Clin Rheumatol [Internet]. 2010 Mar [cited 2021 May 1];29(3):255–71. Available from: https://pubmed.ncbi.nlm.nih.gov/19997766/
143. Gijon-Nogueron G, Ramos-Petersen L, Ortega-Avila AB, Morales-Asencio JM, Garcia-Mayor S. Effectiveness of foot orthoses in patients with rheumatoid arthritis related to disability and pain: a systematic review and meta-analysis [Internet]. Vol. 27, Quality of Life Research. Springer International Publishing; 2018 [cited 2021 May 26]. p. 3059–69. Available from: https://pubmed.ncbi.nlm.nih.gov/29922913/

144. Ramos-Petersen L, Nester CJ, Reinoso-Cobo A, Nieto-Gil P, Ortega-Avila AB, Gijon-Nogueron G. A systematic review to identify the effects of biologics in the feet of patients with rheumatoid arthritis [Internet]. Vol. 57, Medicina (Lithuania). MDPI AG; 2021 [cited 2021 May 26]. p. 1–11. Available from: /pmc/articles/PMC7824565/
145. Ramos Petersen L, Morales Asencio JM, García Mayor S, Gijón Noguerón G. Evaluación de la calidad de las guías de práctica clínica de artritis reumatoide con recomendaciones sobre la salud del pie. Rev Española Podol. 2017 Jan;28(1):3–12.
146. Aletaha D, Ward MM, Machold KP, Nell VPK, Stamm T, Smolen JS. Remission and active disease in rheumatoid arthritis: Defining criteria for disease activity states. Arthritis Rheum [Internet]. 2005 Sep [cited 2021 Apr 26];52(9):2625–36. Available from: https://pubmed.ncbi.nlm.nih.gov/16142705/
147. Prevoo MLL, Van'T Hof MA, Kuper HH, Van Leeuwen MA, Van De Putte LBA, Van Riel PLCM. Modified disease activity scores that include twenty-eight-joint counts development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. Arthritis Rheum [Internet]. 1995 [cited 2021 Apr 26];38(1):44–8. Available from: https://pubmed.ncbi.nlm.nih.gov/7818570/
148. Garrow AP, Papageorgiou A, Silman AJ, Thomas E, Jayson MI, Macfarlane GJ. The grading of hallux valgus. The Manchester Scale. J Am Pod Med Assoc. 2001;
149. Redmond AC, Crosbie J, Ouvrier RA. Development and validation of a novel rating system for scoring standing foot posture: The Foot Posture Index. Clin Biomech [Internet]. 2006 Jan [cited 2021 Apr 26];21(1):89–98. Available from: https://pubmed.ncbi.nlm.nih.gov/16182419/
150. Morrison SC, Ferrari J. Inter-rater reliability of the Foot Posture Index (FPI-6) in the assessment of the paediatric foot. J Foot Ankle Res [Internet]. 2009 Oct 21 [cited 2021 Apr 26];2(1). Available from: https://pubmed.ncbi.nlm.nih.gov/19845961/
151. García-Rodríguez A, Martín-Jiménez F, Carnero-Varo M, Gómez-Gracia E, Gómez-Aracena J, Fernández-Crehuet J. Flexible flat feet in children: a real problem? Pediatrics [Internet]. 1999 [cited 2021 Apr 26];103(6). Available from: https://pubmed.ncbi.nlm.nih.gov/10353981/
152. El O, Akcali O, Kosay C, Kaner B, Arslan Y, Sagol E, et al. Flexible flatfoot and related factors in primary school children: A report of a screening study. Rheumatol Int [Internet]. 2006 Sep [cited 2021 Apr 26];26(11):1050–3. Available from: https://pubmed.ncbi.nlm.nih.gov/16670858/
153. Pfeiffer M, Kotz R, Ledl T, Hauser G, Sluga M. Prevalence of flat foot in preschool-aged children. Pediatrics [Internet]. 2006 Aug [cited 2021 Apr 26];118(2):634–9. Available from: https://pubmed.ncbi.nlm.nih.gov/16882817/
154. Evans AM, Rome K, Peet L. The foot posture index, ankle lunge test, Beighton scale and

the lower limb assessment score in healthy children: A reliability study. J Foot Ankle Res [Internet]. 2012 Jan 9 [cited 2021 Apr 26];5(1). Available from: https://pubmed.ncbi.nlm.nih.gov/22230105/

155. Barton CJ, Bonanno D, Levinger P, Menz HB. Foot and ankle characteristics in patellofemoral pain syndrome: A case control and reliability study. J Orthop Sports Phys Ther [Internet]. 2010 [cited 2021 Apr 26];40(5):286–96. Available from: https://pubmed.ncbi.nlm.nih.gov/20436240/

156. De Souza S, Williams R, Lempp H. Patient and clinician views on the quality of foot health care for rheumatoid arthritis outpatients: A mixed methods service evaluation. J Foot Ankle Res [Internet]. 2016 Jan 6 [cited 2021 May 1];9(1):1. Available from: http://www.jfootankleres.com/content/9/1/1

157. Hennessy K, Woodburn J, Steultjens M. Clinical practice guidelines for the foot and ankle in rheumatoid arthritis: A critical appraisal. J Foot Ankle Res [Internet]. 2016 Aug 19 [cited 2021 May 1];9(1). Available from: https://pubmed.ncbi.nlm.nih.gov/27547242/

158. Turner DE, Helliwell PS, Siegel KL, Woodburn J. Biomechanics of the foot in rheumatoid arthritis: Identifying abnormal function and the factors associated with localised disease "impact." Clin Biomech [Internet]. 2008 Jan [cited 2021 May 1];23(1):93–100. Available from: https://pubmed.ncbi.nlm.nih.gov/17904711/

Chapter IV

Appendix

Cuaderno de recogida de datos
Doctorado *Clasificación del grado de afectación del pie en Artritis Reumatoide*
Tutor *Dr. Gijón Noguerón, Gabriel A.*
Doctorando *Pekka Anttila.*
Facultad Ciencias de la Salud, Universidad de Málaga

Proyecto de investigación: Clasificación del grado de afectación del pie en Artritis Reumatoide.

Objetivos:

- El principal objetivo que nos hemos fijado en este estudio es analizar el mayor número de variables asociadas al pie en pacientes con Artritis Reumatoide (AR). Con estos datos buscamos clasificar la deformación que se produce en el pie.
- Objetivos secundarios:
  - Determinar prevalencias de diferentes afecciones del pie, como Hallux Abductus Valgus (Juanete), dedos en garra, pie plano adquirido, asociar nivel de dolor al nivel de deformidad, etc…
  - Disponer de una herramienta útil a nivel podológico para estandarizar tratamientos ortopodológicos (plantillas), y/o tratamiento quirúrgicos.

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 Podología, área de Ortopodología, por el Doctorando Pekka Anttila, dirigido por el Dr Gabriel Gijón Noguerón. Y será llevado a cabo en el Complejo Hospitalario de Granada.

El estudio se inició el año pasado (2016) con la colaboración de la asociación AMARE, y se pretende continuar en el Complejo Hospitalario de Granada con Tutor Clínico, Dr Rafael Caliz, Jefe de Servicio de Reumatología.

El estudio en el que usted participara consta de dos fases, la primera consiste en rellenar, lo más sinceramente posible, diferentes formularios muy utilizados en estudios de podología en pacientes con AR. Podrá contar con la ayuda del personal de investigación y con la posibilidad de aclaración de cualquier duda que se le presente en cualquier momento, esta fase le llevara un tiempo aproximado de 15 minutos.

La segunda fase será realizada por el personal de investigación, coordinado por el Doctorando Pekka Anttila, en ella se utilizaran diferentes métodos/escalas de evaluación del pie, validadas y utilizadas en investigación en el área de Podología. El tiempo requerido se estima entre 10 y 15 minutos.

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.

Beneficios

Los beneficios que esperamos obtener con dicho estudio, son disponer de una herramienta útil en ortopodología con la que evaluar el pie en pacientes con AR y proporcionar un tratamiento específico a cada paciente. Con ella pretendemos abrir nuevas líneas de investigación del área de Ortopodologia.

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:

De acuerdo a la Ley 15/1999 de Protección de Datos de Carácter Personal, los datos personales que se le requieren (p.ej.edad, sexo, datos de salud) son los necesarios para cubrir los objetivos del estudio. En ninguno de los informes del estudio aparecerá su nombre, y su identidad no será revelada a persona alguna salvo para cumplir con los fines del estudio, y en el caso de urgencia médica o requerimiento legal. Cualquier información de carácter personal que pueda ser identificable será conservada y procesada por medios informáticos en condiciones de seguridad.

El acceso a dicha información quedará restringido al personal autorizado que estará obligado a mantener la confidencialidad de la información. Los resultados del estudio podrán ser comunicados a las autoridades sanitarias y, eventualmente, a la comunidad científica a través de congresos y/o publicaciones.

Los datos serán utilizados para los fines específicos de este estudio y en todo caso si fuese necesario podrán ser también utilizados con otros fines de tipo docente o carácter científico. De acuerdo con la ley vigente, tiene usted derecho al acceso de sus datos personales; asimismo, y si está justificado, tiene derecho a su rectificación y cancelación. Si así lo desea, deberá solicitarlo al médico que le atiende en este estudio.

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

Pekka Anttila.

Consentimiento por escrito del paciente o participante

Título del estudio: Clasificación del grado de afectación del pie en Artritis Reumatoide

Yo el abajo firmante:

Nombre:	**Apellidos**:

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

He hablado con el profesional responsable del estudio Pekka Anttila, o en su defecto con cualquier colaborador de dicha investigación.

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.

Yo como investigador principal me comprometo a, y garantizo que los datos obtenidos en este estudio solo serán utilizados para los fines específicos del mismo.

Nombre: *Pekka*	**Apellidos**: *Anttila*

Firma profesional responsable:	**A fecha:** ____/____/_____
	DNI: 74.690.074-N

Nombre:		**Apellidos:**	
Fecha Nacimiento	**Edad:**	**Fecha recogida datos:**	**Nº Registro**(rellenar por profesional)**:**

Años evolución:	**Talla:**	**Peso:**	**Nº zapato:**

Antecedentes personales: Presenta alguna de las enfermedades y o algún proceso clínico que enumeramos a continuación, si es el caso márquela con una X. En caso de duda pregunte a cualquier miembro del grupo de investigación.		
	1	Psoriasis.
	2	Diabetes Mellitus.
	3	Lupus.
	4	Gota.
	5	Artritis Infecciosa.
	6	Espondilitis anquilosante.
	7	Fibromialgia.
	8	Fiebre mediterránea familiar.
	9	Síndrome de Sjögren.
	10	Esclerosis sistémica.
	11	Cirugía osteoarticular en el píe.
	12	Ha tenido algún traumatismo en el pie en los últimos 6 meses.
	13	Enfermedad vascular en Miembros Inferiores.
	14	Enfermedad Neurodegenerativa en Miembros Inferiores.
	15	Sinovitis.
	16	Edema.

ESCALA EVA

Describa su sensación de dolor asignándole un número entre los siguientes valores del 0 al 10

DOLOR EN GENERAL										
SIN DOLOR										**MÁXIMO DOLOR**
0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**

DOLOR EN MANOS										
SIN DOLOR										**MÁXIMO DOLOR**
0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**

DOLOR EN PIES										
SIN DOLOR										**MÁXIMO DOLOR**
0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**

Anexo 8 Escala Manchester HAV

Escala de Manchester.

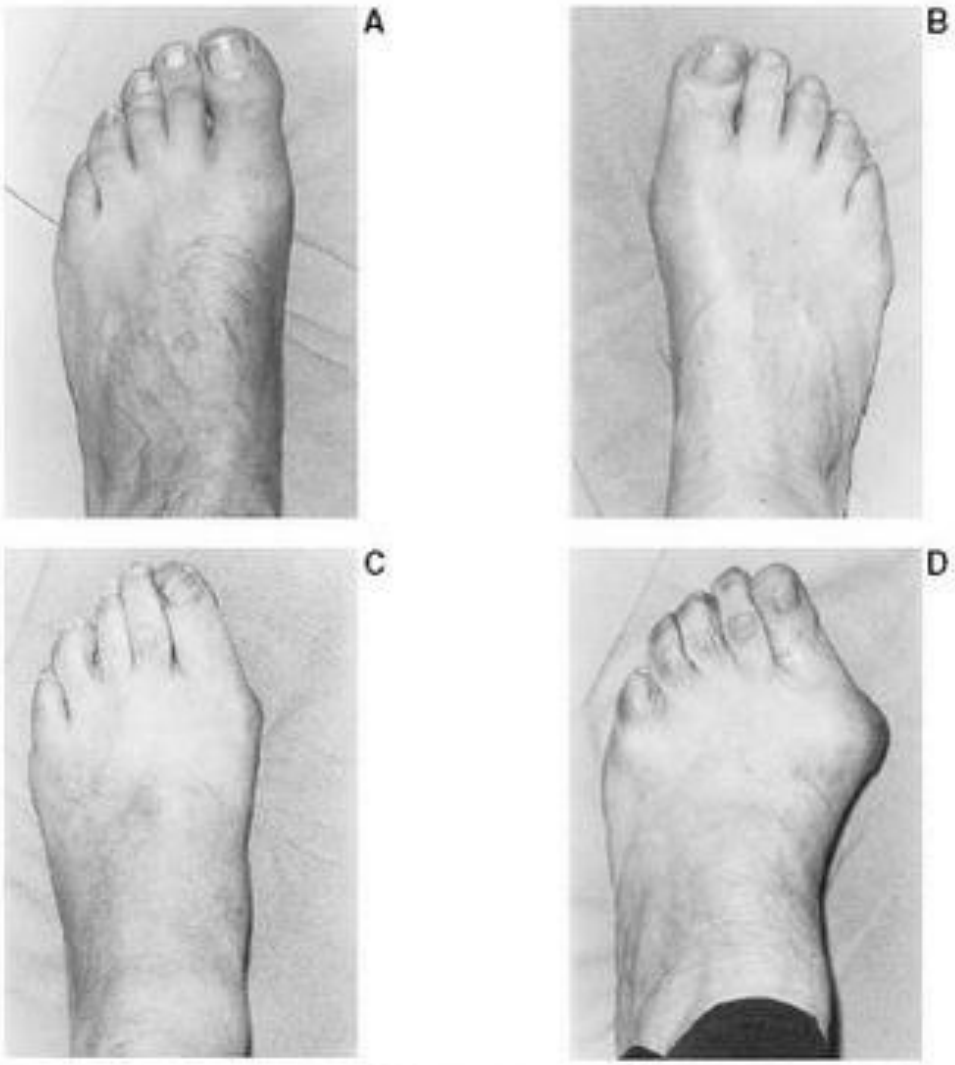


Figure 2. Hallux valgus grading photographs. A, Grade 1 (no deformity); B, grade 2 (mild deformity); C, grade 3 (moderate deformity); D, grade 4 (severe deformity).

A: Grado 1 (no deformidad). B: Grado 2 (deformidad leve).
C: Grado 3 (deformidad moderada). D: Grado 4 (deformidad severa)

Anexo 9 Foot Posture Index

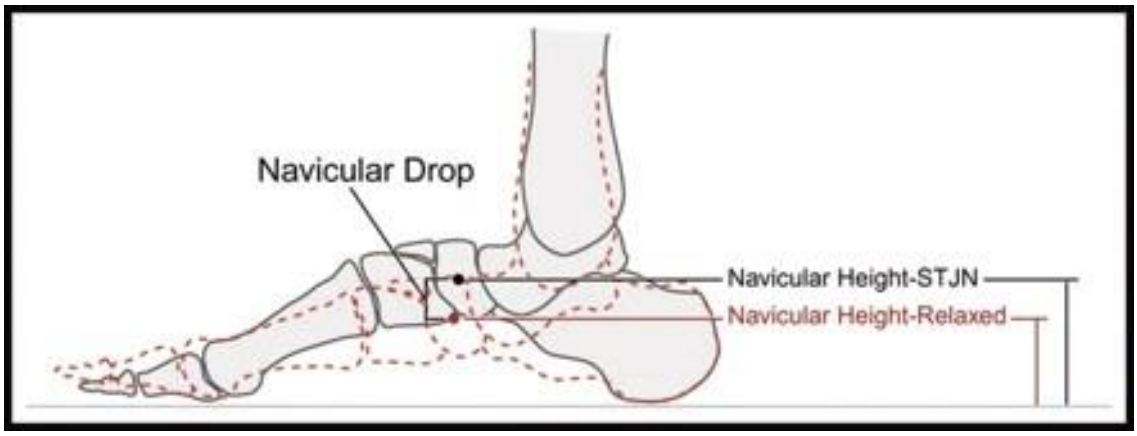
HOJA DE RECOGIDA DE DATOS INDICE POSTURA DEL PIE

NOMBRE DEL PACIENTE	Nº HISTORIA

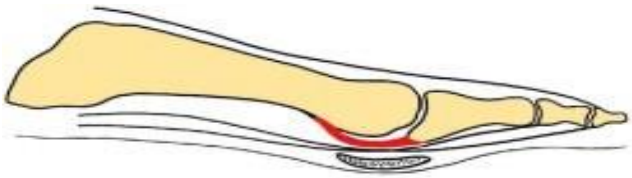
	CRITERIOS	PLANO	PUNTUACION 1 Fecha Comentario		PUNTUACIÓN 2 Fecha Comentario		PUNTUACIÓN 3 Fecha Comentario	
			Izquierdo -2 a +2	Derecho -2 a +2	Izquierdo -2 a +2	Derecho -2 a +2	Izquierdo -2 a +2	Derecho -2 a +2
Retropié	Palpación cabeza del astrágalo	Transverso						
	Curvatura supra e inframaleolar lateral	Frontal / Transverso						
	Calcáneo plano frontal	Frontal						
Antepié	Prominencia región talonavicular	Transverso						
	Congruencia arco longitudinal interno	Sagital						
	Abd / ad antepié respecto retropié	Transverso						
	TOTAL							

Valores de referencia
Normal = 0 a +5
Pronado = +6 a +9. Altamente pronado 10+
Supinado = -1 a -4. Altamente supinado -5 a -12

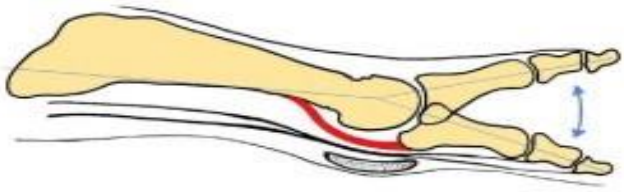
Anexo 10 Navicular Drop



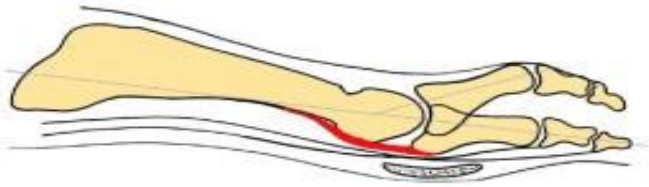
Anexo 11 Clasificación Nijmegen



Grade 0. No clinical changes in the MTP joints, no or mild radiographic changes (Larsen 0-1).



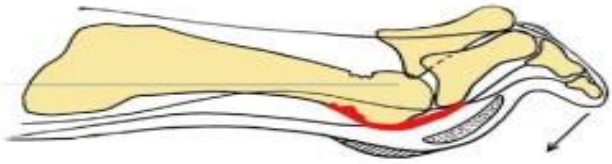
Grade 1. Decreased mobility of one or more of the joints, particularly in plantar flexion, with the ability to reduce the plantar soft tissues under the metatarsal heads, and with adequate quality of the plantar soft tissues. Erosive changes (Larsen 1-5) and/or joint space narrowing can be present.



Grade 2. Loss of plantar flexion in one or more of the MTP joints (up to 0°), and loss of the ability to reduce the plantar soft tissues under the metatarsal heads, and/or with inadequate quality of the plantar soft tissues. Erosive changes (Larsen 1-5) and/or joint space narrowing can be present.

A. hallux valgus of more than 20^0

B. hallux valgus 20^0 or less.



Grade 3. Extension contracture in one or more MTP joint, with or without radiographic subluxation or dislocation. Erosive changes (Larsen 1-5) and/or joint space narrowing can be present.

A. hallux valgus of more than 20^0.

B. hallux valgus of 20^0 or less.

Anexo 12 Los nuevos criterios de artritis reumatoide ACR/EULAR 2010

Los nuevos criterios de AR sólo se aplicarán a una determinada población diana que debe tener las siguientes características:

- Presentar al menos 1 articulación con sinovitis clínica (al menos una articulación inflamada) y que dicha sinovitis no pueda explicarse por el padecimiento de otra enfermedad.
- Tener una puntuación igual o superior a 6 en el sistema de puntuación que se presenta en la tabla y que considera la distribución de la afectación articular, serología del factor reumatoide (FR) y/o ACPA, aumento de los reactantes de fase aguda y la duración igual o superior a 6 semanas[2].

Conjunto de variables y su puntuación de cada una de las variables para el computo global	
Afectación articular	
1 articulación grande afectada	0
2-10 articulaciones grandes afectadas	1
1-3 articulaciones pequeñas afectadas	2
4-10 articulaciones pequeñas afectadas	3
> 10 articulaciones pequeñas afectadas	5
Serología	
FR y ACPA negativos	0
FR y/o ACPA positivos bajos (< 3 VN)	2
FR y/o ACPA positivos alto (> 3 VN)	3
Reactantes de fase aguda	
VSG y PCR normales	0
VSG y/o PCR elevadas	1
Duración	
<6 semanas	0
≥6 semanas	1
Un paciente será clasificado de AR si la suma total es igual o superior a 6	

ACPA: anticuerpos contra péptidos citrulinados; FR: factor reumatoide; PCR: proteína C reactiva; VN: valor normal; VSG: velocidad de sedimentación globular.

Estos criterios también permiten hacer el diagnóstico en aquellos pacientes que presenten una AR evolucionada siempre que:

- Tengan erosiones típicas de AR.
- Presenten una enfermedad de larga evolución (activa o inactiva) cuyos datos retrospectivos permitan la clasificación con los criterios mencionados.
- En escenarios de artritis de muy reciente comienzo, en individuos que no cumplan en un momento dado los criterios pero que los cumplan con la evolución del tiempo

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

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 Dario 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 Espínola García
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

IVYSPRING INTERNATIONAL PUBLISHER

International Journal of Medical Sciences

2021; 18(11): 2269-2275. doi: 10.7150/ijms.56935

Research Paper

Morpho-structural characteristics of feet in patients with rheumatoid arthritis: A cross sectional study

Andres Reinoso-Cobo[1], Pekka Anttila[2], Ana Belen Ortega-Avila[1,3]✉, Pablo Cervera-Garvi[1], Eva Lopezosa-Reca[1], Ana Marchena-Rodriguez[1], Laura Ramos-Petersen[4], Gabriel Gijon-Nogueron[1,3]

1. Department of Nursing and Podiatry, Faculty of Health Sciences, University of Malaga, Arquitecto Francisco Peñalosa 3, Ampliación de Campus de Teatinos, 29071 Malaga, Spain.
2. Applied Science of Metropolia Univesity, Podiatry Department, 01600 Helsinki, Finland.
3. IBIMA. Malaga, Spain.
4. Departamento of Podiatry. Faculty of Health Sciences. Universidad Católica San Antonio de Murcia. Campus de Los Jerónimos. Guadalupe 30107 Murcia Spain.

✉ Corresponding author: Ana Belen Ortega-Avila, E-mail: anaortavi@uma.es.

Received: 2020.12.08; Accepted: 2021.03.22; Published: 2021.03.30

Abstract

Objective: The aim of this study was to evaluate and classify the types and incidences of foot deformities in patients with Rheumatoid Arthritis (RA).

Methods: A cross-sectional study with convenience sample was obtained of 220 patients with foot pain and RA classification criteria (approved by the American College of Rheumatology and the European League against Rheumatism in 2010). A series of outcomes were assessed to measure the morphological characteristics of the feet. The Foot Posture Index (FPI), the Manchester Scale of Hallux Valgus and the Nijmegen classification of forefoot disorders were assessed.

Results: The most common foot posture according to the FPI assessment are the pronated position in the left foot (32.7% of participants) and the neutral position in the right foot (34.1% of participants). The disease progression causes more developed and serious foot deformities. 1.82% of patients present a severe level of Hallux Valgus before 10 years of disease evolution whereas 4.09% of patients present a severe level of Hallux Valgus after 10 years of disease evolution.

Conclusions: The most common foot type in patients with RA is the pronated foot type with deformities in the MTP joints without Hallux Valgus. However, a percentage of patients with RA presents supinated foot type. The evolution of the disease shows some morphological changes in terms of patient's feet. The presence of more developed foot deformities is increased, such us Hallux Valgus or MTP joints deformity (Grade 3 in the Nijmegen classification scale).

Key words: rheumatoid arthritis; foot; Hallux Valgus; joint; foot posture

Introduction

Rheumatoid arthritis (RA) is a chronic, progressive inflammatory disease that can cause limitations and difficulties in activities of daily living (ADLs) and pain. As a result, patients may present gait impairment and difficulties with self-care [1]. The prevalence of RA in the population is approximately 7.7 per 1,000 and it is more prevalent in females, in whom two-thirds of new cases arise. The disease is prevalent in the fourth and fifth decades of life [2].

There are multiple affectations in the upper and the lower limb [3] as well as the quality of life of patients with RA is affected [4] and fatigue [5]. RA is associated with significant pain and deformities, where individuals continue to perform activities with functional capacity restriction. Fatigue and functional disability ensue with the progression of the disease [6].

There is a high prevalence of foot involvement in RA with over 90% of patients reporting foot pain during the course of the disease [7]. It has been suggested that erosive changes may occur in the joints of the hands and feet, particularly in the