UNIVERSITAT DE BARCELONA

Structural damage progression in spine and sacroiliac joints in patients with axial spondyloarthritis

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STRUCTURAL DAMAGE PROGRESSION IN SPINE AND SACROILIAC JOINTS IN PATIENTS WITH AXIAL SPONDYLOARTHRITIS

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CERTIFIQUEN:

Que la Tesi Doctoral "STRUCTURAL DAMAGE PROGRESSION IN SPINE AND SACROILIAC JOINTS IN PATIENTS WITH AXIAL SPONDYLOARTHRITIS" presentada per MARIA LLOP VILALTELLA ha estat realitzada sota la seva direcció i reuneix les característiques metodològiques necessàries per ser defensada davant el tribunal corresponent.

L'Hospitalet de LLobregat, 14 d'octubre de 2020

A la meva família

No hem d'oblidar que quan es va descobrir el radi ningú sabia que seria d'utilitat en els hospitals. Era un treball de ciència pura. I això es prova de que el treball científic no ha de considerar-se des de el punt de vista del seu ús directe. S'ha de realitzar per si mateix, per la bellesa de la ciència i després sempre existirà la possibilitat de que un descobriment científic es converteixi, com el radi, en un benefici per a la humanitat.

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CONTENT

ABBREVIATIONS

AP: antero-posterior

AS: ankylosing spondylitis

ASAS: Assessment in SpondyloArthritis International Society

ASDAS - Ankylosing Spondylitis Disease Activity Score

ASQoL - Ankylosing Spondylitis Quality of Life

axSpA - axial spondyloarthritis

BASDAI: Bath Ankylosing Spondylitis Disease Activity Index

BASFI: Bath Ankylosing Spondylitis Functional Index

BASMI: Bath Ankylosing Spondylitis Metrology Index

BASRI: Bath Ankylosing Spondylitis Radiology Index

bDMARDs: biological disease-modifying antirheumatic drugs

BMO: bone marrow oedema

CI: confidence interval

CRP: C-reactive protein

csDMARDS: Conventional synthetic disease-modifying antirheumatic drugs

CT: Computed tomography

DMARD: disease-modifying antirheumatic drug

ESR: erythrocyte sedimentation rate

EULAR: European League Against Rheumatism

FDA: Food and Drug Administration

GESPIC: German Spondyloarthritis Inception Cohort

HAQ: Health Assessment Questionnaire

HLA: human leucocyte antigen

IBD: inflammatory bowel disease

IBP: inflammatory back pain

IL-17i: interleukin-17 inhibitors

JAK: Janus kinase

MASES: Maastricht Ankylosing Spondylitis Enthesitis Score

MHC: major histocompatibility complex

mNY: modified New York

MRI: magnetic resonance imaging

mSASSS: modified Stoke Ankylosing Spondylitis Spinal Score

nr-AxSpA: non-radiographic axial spondyloarthritis

NSAIDS: non-steroidal anti-inflammatory drug

OASIS: Outcomes in Ankylosing Spondylitis International Study

OMERACT: Outcome Measures in Rheumatology

OR: odds ratio

RASS: radiographic AS Spinal Score

SAE: serious adverse event

SD: standard deviation

SE: standard error

SIJs: sacroiliac joints

SpA: spondyloarthritis

SPARCC: Spondyloarthritis Research Consortium of Canada

TNF: tumour necrosis factor

TNFi: tumour necrosis factor inhibitors

tsDMARDS: targeted synthetic disease-modifying antirheumatic drug

US: ultrasound

VAS: visual analogue scale

Chapter 1

Resum en català

TÍTOL

PROGRESSIÓ DEL DANY ESTRUCTURAL ESPINAL I EN ARTICULACIONS SACROILÍAQUES EN PACIENTS AMB ESPONDILOARTRITIS AXIAL

INTRODUCCIÓ

L'espondiloartritis axial (EspAax) és una malaltia inflamatòria crònica amb símptomes predominantment axials, cursa amb inflamació predominantment en les articulacions sacroilíaques i a la columna (1). La malaltia s'associa en un 90% dels casos amb el gen HLA-B27 . La prevalença, estimada entre el 0.32-1.4% (2, 3), es correlaciona amb el gen HLA-B27. Els pacients amb EspAax poden presentar altres símptomes com artritis perifèrica (mono o ologoartritis dels membres inferiors), entesitis i dactilitis així com manifestacions extra múscul-esquelètiques com la psoriasi, la uveïtis i la malaltia inflamatòria intestinal. Característicament la malaltia es manifesta amb dolor i rigidesa, i pel desenvolupament de nova formació òssia que comporta l'anquilosi de l'esquelet axial (4).

En funció de la presència o absència de sacroilitis radiogràfica, i segons el sistema d'estadiatge dels criteris modificats de Nova York (4), l'EspAax pot ser classificada com EspA radiogràfica (EspAax-r, també coneguda com Espondilitis Anquilosant - EA) o EspA no-radiogràfica (EspA-nr). L'EspAax-nr és considerada com la forma primerenca o més lleu de l'EspAax i els pacients no sempre desenvolupen dany estructural ossi en l'esquelet axial.

Els criteris de classificació ASAS (Assesment in Spondylo Arthriits international Society) (5) es fan servir en la pràctica clínica habitual com a criteris diagnòstics d'EspAax. El seu diagnòstic requereix de la presència de dolor crònic lumbar, de més de 3 mesos de duració, abans dels

45 anys. També requereix de la presència de sacroilitis, determinada per radiografia o per ressonància magnètica a més de com a mínim un tret clínic característic d'EspA, o bé de la presència d'HLA-B27 positiu i de dos trets clínics característics. La sensibilitat dels criteris en diferents estudis varien entre el 67 i el 87% i l'especificitat entre el 62i el 95% (6-8).

Criteris de classificació ASAS per EspAax

Dolor lumbar de ≥ 3 anys de duració amb edat d'inici < 45 anys

Sacroilitis en imatge* més ≥ 1 tret clinic d'EspA**	HLA-B27 més ≥ 2 trets clinics d'EspA**

*Sacroilitis en imatge

- Inflamació activa (aguda) en RM altament sugestiva de sacroilitis associada a EspA.

- Sacroilits radiográfica definida d'acord els criteris modificats de Nova York

**Trets clínics d'EspA
- Dolor lumbar inflamatori
- Artritis
- Entesitis (taló)
- Uveítis
- Dactilitis
- Psoriasis
- Malaltia de Crohn/ Colitis ulcerosa
- Bona resposta a AINEs
- Historia familiar d'EspA
- HLA-B27
- PCR elevada

Una de les gran preocupacions en el camp de les EspA és el desenvolupament de nova formació òssia en la columna degut a la seva contribució en la severitat de la malaltia. Com també és rellevant per a determinar si els tractaments són eficaços en inhibir aquesta progressió estructural (9). Per tant, resulta de vital importància l'avaluació del dany estructural en els pacients amb EspAax. Noves dades (10) suggereixen que els canvis inflamatoris van seguits d'un recanvi de la medul·la òssia subcondral per teixit de reparació

que a la vegada estimulen als osteoblasts, la qual cosa comportarà una nova formació òssia. Diferents estudis previs (11, 12) estableixen que la progressió del dany estructural a nivell de la columna està significativament associat a la presència de sindesmòfits a l'inici, a la presència de reactants de fase aguda (PCR i/o velocitat de sedimentació), al consum de tabac i a una elevada activitat mesurada pel ASDAS (Ankylosing Spondylitis Disease Activity Score). L'associació de la presència de dany radiogràfic en la columna amb la mobilitat reduïda i l'estat funcional és ben coneguda en pacients amb EspAax, recentment aquesta associació també s'ha establert quan hi ha dany en les articulacions sacroilíaques, independentment del dany estructural en la columna (13).

Nombrosos estudis en EspAax-r estan centrats en la progressió radiogràfica a nivell de columna. El mètode d'imatge d'elecció per l'avaluació de la progressió radiogràfica espinal són les radiografies de columna (cervical i lumbar). Les guies ASAS/EULAR recomanen realitzar les radiografies als 2 anys de seguiment (14). Actualment, el mètode mSASSS (modified Stoke Ankylosing Spondylitis Spine Score) és el més utilitzat per avaluar el dany estructural, atesa la seva millor fiabilitat i sensibilitat per avaluar la progressió radiogràfica en comparació a altres mètodes (15), com el BASRI (Bath Ankylosing Spondylitis Radiology Index) (16) o el SASSS (17). L'mSASSS captura les cantonades vertebrals anteriors de la columna cervical i lumbar en projecció lateral, avalua la presència d'erosions, esclerosis, quadratura i sindesmòfits i ponts ossis amb una puntuació total de 72 (18). Les radiografies amb projecció antero-posteriors (AP) són habitualment realitzades de forma complementària a les radiografies amb projecció lateral, no obstant, el seu valor afegit en l'avaluació de la progressió del dany estructural en la columna en l'EspAax no està del tot establerta, a l'hora de detectar dany estructural no visible en radiografies laterals.

El BASRI (BASRI-columna) és un mètode combinat on s'avalua el dany estructural a nivell de la columna cervical i lumbar i a nivell de les articulacions sacroilíaques. El BASRI utilitza la combinació de la projecció AP i lateral per avaluar el dany estructural present a la columna amb una puntuació de 0 a 4. Les articulacions sacroilíaques son avaluades independentment segons el sistema d'estadiatge dels criteris modificats de Nova York (mNY). La puntuació final del BASRI s'obté de la suma de les puntuacions mitjanes de les articulacions sacroilíaques dreta i esquerre a més de la puntuació de la columna cervical i lumbar (18).

Per contra, l'avaluació de la progressió radiogràfica a nivell de les articulacions sacroilíaques ha estat menys estudiada. Està descrit que aproximadament entre un 5-12% dels pacients amb EspAax-nr desenvolupen progressió radiogràfica en les articulacions sacroilíaques en 2 anys (19, 20). Hores d'ara els mètodes convencionals per avaluar el dany estructural de les articulacions sacroilíaques són els criteris mNY, que consisteixen en una escala semi quantitativa del 0 (normal) al 4 (anquilosis total). Reflecteixen 3 canvis estructurals: esclerosis, erosions i afectació de l'espai articular/anquilosis (4). Segons els criteris mNY, la sacroilitis radiogràfica es defineix com la presència d'una puntuació ≥ 2 en ambdós costats o ≥ 3 unilateral. El criteris mNY van ser ideats com a criteris de classificació, i a dia d'avui no han estat validats com a eina per l'avaluació de la progressió del dany estructural en les articulacions sacroilíaques. En aquest context, altres definicions considerades com els canvis en la puntuació total i el percentatge de pacients amb canvi d'almenys un grau en una articulació sacroilíaca podrien ser més sensibles per a detectar progressió radiogràfica en les articulacions sacroilíaques (20, 21).

Les guies EULAR estableixen que les radiografies de les articulacions sacroilíaques són el mètode d'imatge d'elecció davant la sospita d'EspAax (22). Actualment el mètode més

comunament utilitzat per l'avaluació radiogràfica de les articulacions sacroilíaques és la radiografia convencional AP de pelvis. Tot i que les articulacions poden ser estudiades també en radiografies AP lumbars que es realitzen de forma complementària com a part del procés diagnòstic per l'avaluació del dany estructural en la columna. Es desconeix si les articulacions sacroilíaques poden ser avaluades d'una forma vàlida en radiografies AP lumbars.

HIPÒTESIS

- La radiografia AP lumbar presenta un valor afegit en l'avaluació de la progressió del dany estructural en pacients amb EspAax.
- La radiografia AP lumbar aporta una millora en la detecció de progressió radiogràfica en la columna en pacients amb EspAax.
- Els canvis estructurals en les articulacions sacroilíaques poden ser avaluats d'una forma fiable en radiografies AP lumbars utilitzant les radiografies convencionals de pelvis com a referència.

OBEJCTIU PRINCIPAL

- Evaluar el valor afegit de la radiografia AP lumbar en l'avaluació de la progressió del dany estructural en pacients amb EspAax.

OBJECTIUS SECUNDARIS

- Evaluar l'aplicabilitat del mSASSS estès incorporant la radiografia AP lumbar en comparació amb el mSASSS convencional en la detecció de progressió radiogràfica en la columna en pacients amb EspAax.
- Evaluar la fiabilitat i la validació en l'avaluació del dany estructural en les articulacions sacroilíaques mitjançant la valoració de la sacroilitis radiogràfica en les radiografies AP lumbars en comparació a radiografies convencionals de pelvis en pacients amb EspAax.

RESULTATS I DISCUSSIÓ

En el present treball ens proposem testar la nostre principal hipòtesi de que la radiografia AP lumbar presenta un valor afegit en l'avaluació de la progressió del dany estructural en les articulacions sacroilíaques i en la columna en pacients amb EspAax. Per respondre a la pregunta en qüestió, hem elaborat dos estudis, el primer centrat en l'avaluació de la progressió del dany estructural a nivell de columna i el segon en l'avaluació del dany estructural en les articulacions sacroilíaques. En ambdós estudis van ser inclosos pacients amb EspAax del registre alemany GErman SPondyloarthritis Inception Cohort (GESPIC), en funció de la disponibilitat de dades clíniques i de les radiografies inicials i a l'any 2 del seguiment.

El primer estudi està dirigit a avaluar l'aplicabilitat de l'mSASSS estès com a eina per a mesurar la progressió radiogràfica en columna. Com hem esmentat anteriorment, l'avaluació del dany estructural en pacients amb EspAax resulta rellevant pel maneig d'aquests pacients degut a la seva contribució amb la severitat de la malaltia. En aquest context, l'mSASSS estès, és una nova eina que incorpora la radiografia AP lumbar en l'mSASSS, l'actual eina de referència per avaluar el dany estructural en la columna en pacients amb EspAax (18). El mSASSS, avalua la

presència d'erosions, esclerosi, quadratura, sindesmòfits i la creació de ponts ossis que afecten a les cantonades anteriors vertebrals de la columna cervical i lumbar visualitzades en radiografies amb projecció lateral (18).

Estudis previs suggereixen que la projecció AP de la columna lumbar, pot aportar informació addicional sobre la presència de dany estructural en la columna (15, 16). Tot i així, es desconeix les avantatges la de la radiografia AP lumbar en relació a la projecció lateral en l'avaluació de la progressió radiogràfica a nivell de la columna.

Per avaluar l'aplicabilitat de l'mSASSS estès com a eina per mesurar la progressió radiogràfica a nivell de la columna, es va fer una comparació amb l'mSASSS convencional en base 3 aspectes del filtre OMERACT (Outcome Measures in Rheumatology): viabilitat, discriminació i la validesa.

Pel que fa a la viabilitat del mètode, l'estudi es va poder dur a terme en tots els pacients del nostre estudi atès era requisit de l'estudi disposar de radiografia AP lumbar a l'inici i a l'any 2 de seguiment. Tot i que en la pràctica clínica habitual la radiografia AP lumbar es realitza de forma rutinària, cal tenir en compte que incrementa els costos i el temps d'avaluació del dany estructural en aproximadament un 50% en comparació amb l'mSASSS convencional. A més, la radiografia AP lumbar aporta més radiació, augmentant l'exposició total deguda a l'avaluació del dany radiogràfic en aproximadament el 60-70%.

L'estudi va palesar que la fiabilitat dels dos mètodes va ser excel·lent. El coeficient de correlació intraclasse (ICC) va ser de 0.927 i 0.926 a l'inici i de 0.933 i 0.920 al segon any per l'mSASSS estès i convencional respectivament. La puntuació mitjana ± DE a l'inici va ser de 4.25±8.32 i 8.59±17.96 per l'mSASSS i mSASSS estès respectivament. El canvi de puntuació

entre l'inici i el segon any va ser de 0.73±2.34 i de 1.19±3.73 respectivament. Cal destacar que el canvi mínim detectable de l'mSASSS estès va ser superior a l'mSASSS convencional, mentre que la mitjana de resposta estandarditzada va ser igual en els dos mètodes. Amb l'mSASSS estès es van poder detectar nous sindesmòfits després de dos anys en 4 pacients addicionals, nous sindesmòfits o progressió de sindesmòfits existents en 5 pacients addicionals i progressió de ≥ 2 punts en la puntuació total en 14 pacients addicionals la qual cosa implica un augment del 25%, 28% i del 46% en la proporció de pacients amb progressió, d'acord amb les respectives definicions, en comparació amb la puntuació convencional. Aquesta proporció va ser fins i tot superior en pacients amb EspAax-r la qual cosa significa que en malaltia més avançada el valor afegit que aporta la radiografia AP lumbar pot ser superior en comparació a fases més inicials de la malaltia.

L'anàlisi de regressió amb aproximació univariant i multivariant dels dos mètodes va demostrar una associació significativa amb la mobilitat de columna (BASMI) i de funció (BASFI) la qual cosa confirma la validesa interna dels dos mètodes com a paràmetres que evidencien el danys estructurals de la columna en EspAax.

Els resultats obtinguts ens assenyalen que l'mSASSS estès pot ser considerat com a complementari de l'mSASSS convencional atès aporta informació addicional sobre la projecció AP de la radiografia lumbar. No obstant, la informació obtinguda de la radiografia AP lumbar pot ser fins a cert punt redundant, degut a que el mateix dany estructural (el mateix sindesmòfit) pot ser visible tant en la projecció lateral com AP. Aquest fet pot explicar la major variació en les puntuacions inicials (l'mSASSS estès va ser el doble en relació al convencional) que en els percentatges de pacients amb sindesmfòtis (30.5% amb l'mSASSS estès vs 22.9% amb l'mSASSS convencional a l'inici).

El nostre estudi ens permet concloure que l'mSASSS estès presenta una bona fiabilitat i ens aporta una millora en la detecció de la progressió radiogràfica de la columna en pacients amb EspAax en comparació amb l'mSASSS convencional. No obstant, s'ha de tenir en compte els costos addicionals, la radiació addicional (tot i que les radiografies AP lumbars són realitzades habitualment) i el temps addicional que comporta avaluar 24 cantonades vertebrals addicionals.

L'estudi presenta algunes limitacions atès el dany estructural en la columna pot no estar capturat per les radiografies realitzades. Com també succeeix amb l'mSASSS convencional, els sindesmòfits amb localització posterior de la columna cervical, així com l'afectació de les estructures posteriors (articulacions facetàries) tampoc són visibles pe l'mSASSS estès. No obstant, en la majoria de vegades, el dany estructural es desenvolupa de forma simultània en diferents localitzacions de la columna, fet que ens permet assumir que l'mSASSS/mSASSS estès fa possible una aproximació del dany estructural present en tota la columna. De forma similar, el dany present en la columna toràcica no es visualitza correctament degut a la superposició d'estructures anatòmiques toràciques. Malgrat això, els canvis inflamatoris actius (23) i estructurals (24) semblen produir-se en aquesta localització almenys d'una forma tan freqüent com en altres localitzacions. Per aquest motiu, una altre modificació de l'mSASSS ha estat proposada per en Baraliakos et al, el RASSS (Radiographic AS Spinal Score), que afegeixen a l'mSASSS convencional la puntuació de les últimes vertebres dorsals (D10-12) amb la hipòtesi que la majoria de la progressió es troba en aquests segments i que la quantificació de nova formació és superior a l'mSASSS convencional.

A més cal tenir present que la tomografia computada (TC) de baixa dosis té el potencial per a convertir-se en el principal mètode d'avaluació de progressió radiogràfica en el futur atès ha

demostrat detectar més progressió en forma de nous i/o creixement de sindesmòfits en l'EspAax-r (25)

Per tant, amb els resultats obtinguts del primer estudi podem acceptar la nostre hipòtesis de que la incorporació de la radiografia AP lumbar té un valor afegit en l'avaluació de la progressió del dany estructural en la columna en pacients amb EspAax. No obstant, aquesta afirmació ha de ser confirmada en posteriors estudis i utilitzant el TC de baixa dosis com a referència.

En el segon estudi, comparem l'avaluació de la sacroilitis radiogràfica en les radiografies AP lumbars respecte les radiografies convencionals de pelvis. L'avaluació de les articulacions sacroilíaques és fonamental pel diagnòstic i classificació de l'EspAax. El mètode estàndard per avaluar el dany estructural en les articulacions sacroilíaques mitjançant els criteris mNY (1) és encara, a dia d'avui, la radiografia convencional de pelvis (22).

Atesa la complexa anatomia de les articulacions sacroilíaques, s'han proposat diferents projeccions radiològiques per a millorar la fiabilitat i la validació en l'avaluació de la sacroilitis radiogràfica com la projecció de Ferguson (una radiografia AP de pelvis modificada amb un feix de rajos centrat a un angle de 30ª amb inclinació caudal) i la projecció obliqua de cada articulació sacroilíaca. Tot i tenir avantatges teòriques, aquestes projeccions no han aconseguit demostrar una millora significativa en la detecció de sacroilitis respecte les radiografies convencionals de pelvis (26, 27). En el mateix sentit, les articulacions sacroilíaques són visibles en les radiografies AP lumbars realitzades de forma rutinària en el procés diagnòstic de pacients amb dolor lumbar. No obstant, es desconeix si l'avaluació de la sacroilitis radiogràfica en radiografies AP lumbars té una bona fiabilitat i validesa.

Les nostres troballes assenyalen una bona concordança global entre ambdues tècniques radiogràfiques (en un 85% dels casos el pacients van tenir la mateixa classificació d'EspAax-r o EspAax-nr a l'inici i al segon any de seguiment, i en un 84% dels casos va ser descrita la mateixa progressió radiogràfica als dos anys). A més a més, la concordança inter-observador va ser de moderada a bona en presència de sacroilitis radiogràfica (mesurat amb el coeficient kappa de Cohen). La progressió de l'EspAax-nr a EspAax-r segons els criteris mNY es va establir en 7 (6.2%) pacients en l'avaluació de la radiografia convencional de pelvis i en 8 (7.1%) pacients en l'avaluació amb AP lumbar. A més, va haver regressió a EspAax-nr en 4 (3.5%) i en 3 (2.7%) pacients amb les radiografies convencionals de pelvis i AP lumbar respectivament. El percentatge net de progressió de l'EspAax-nr a EspAax-r, que s'explica com la diferència en el nombre de pacients que experimenten empitjorament i millora dividida per la població total de l'estudi, va ser de 2.7 i 4.4% per la radiografia convencional de pelvis i AP lumbar respectivament. La concordança absoluta entre l'avaluació de les dues projeccions radiogràfiques va ser del 84.1%.

Un dels efectes no desitjats més freqüents associats a les radiografies és l'exposició a la radiació. En el nostre cas, ambdues modalitats van tenir una dosi efectiva de radiació similar, d'aproximadament 0.7mSv (28, 29). Atès que en la pràctica clínica habitual la radiografia AP lumbar, que es realitza conjuntament amb la projecció lateral lumbar per avaluar el dany estructural en la columna, l'exposició a radiació extra innecessària es podria estalviar si les articulacions sacroilíaques s'avaluessin amb radiografies AP lumbars. No obstant això, la radiografia convencional de pelvis contínua sent el mètode d'elecció en cas de sospita d'EspAax i no ha de ser substituïda de manera rutinària per una radiografia lumbar. A més a més, l'articulació del maluc, que es pot veure afectada en l'EspA (30), no es visible en les

radiografies AP lumbars com si es ho és en les radiografies convencionals de pelvis. Així doncs, en el cas de pacients amb risc d'afectació del maluc o amb símptomes suggestius, podria ser més convenient realitzar la radiografia de pelvis.

El nostre estudi té algunes limitacions atès no tots els pacients de GESPIC van poder ser inclosos en l'estudi per no disposar de les radiografies apropiades. En 97 dels 210 pacients inicials, les articulacions sacroilíaques eren, de forma parcial o completament, no visibles en radiografies AP lumbars per la qual cosa van ser exclosos de l'anàlisi. Aquest aspecte té implicació en la pràctica clínica habitual degut a que les articulacions sacroilíaques no poden ser avaluades en radiografies AP lumbars en un 50% dels casos. Aquest fet posa en evidència que davant d'un pacient nou amb sospita d'EspAax, la radiografia convencional de pelvis segueix sent la radiografia d'elecció per l'avaluació de la sacroilitis, mentre que la radiografia AP lumbar romandria vàlida per l'avaluació de la sacroilitis només en el cas de disponibilitat en el moment inicial de l'avaluació i si les articulacions sacroilíaques són correctament visualitzades. Un altre limitació és que, vàrem fer servir una cohort de pacients amb diagnòstic establert d'EspAax, dels quals només la meitat tenien una sacroilitis radiogràfica. Aquest fet podria condicionar que el rendiment de les radiografies AP lumbars fora diferent en el cas de ser utilitzades pel diagnòstic de pacients amb dolor lumbar i sospita d'EspAax. Malgrat aquestes limitacions, la classificació (EspAax-r o EspAax-nr) i l'avaluació de la progressió de sacroilitis radiogràfica en pacients amb EspAax coneguda, ens indica que la radiografia AP lumbar ha aconseguit el seu objectiu de manera consistent i ens permet acceptar la nostre hipòtesi.

També cal considerar com a limitació el fet que utilitzem la radiografia convencional de pelvis – un mètode amb poca fiabilitat coneguda – com a referència. La TC és considerada a dia

d'avui el mètode de referència per la detecció del dany estructural en les articulacions sacroilíaques (sacroilitis radiogràfica), tot i que és relativament poc utilitzat com a primer mètode diagnòstic en la pràctica clínica habitual atesa la seva poca disponibilitat i la major exposició a la radiació (31). En els darrers anys, la TC de baixa dosi, que té una radiació similar a la radiografia convencional, ha estat utilitzat per l'avaluació del dany estructural en sacroilíaques (25, 32). A més, la RM de les articulacions sacroilíaques està actualment sent avaluada per la detecció i la puntuació no només del edema ossi sinó també per lesions estructurals, malgrat no haver un consens (25, 33). No obstant, la radiografia convencional de pelvis en la pràctica clínica habitual serveix com la proba d'elecció d'imatge a realitzar davant d'una sospita d'EspAax atesa la seva major disponibilitat i menor cost en comparació al TC de baixa dosis (22, 34). Per tant, es raonable comparar l'aplicabilitat de la radiografia AP lumbar utilitzant a radiografia convencional de pelvis com a referent.

Amb el conjunt dels dos estudis presentats, podem confirmar la nostre principal hipòtesis de que la radiografia AP lumbar presenta un valor afegit en l'avaluació de la progressió del dany estructural en les articulacions sacroilíaques i en la columna en pacients amb EspAax. Així doncs, la radiografia AP lumbar és d'utilitat pel procés diagnòstic i seguiment d'aquests pacients.

INVESTIGACIÓ FUTURA

Durant el treball realitzat en aquests estudis he guanyat experiència en el camp de l'avaluació radiogràfica en la progressió del dany estructural en pacients amb EspAax. Experiència adquirida gràcies a la meva estança en l'Hospital Charité de Berlin (centre de referència en l'àmbit de l'EspA) on he tingut l'oportunitat de realitzar un aprenentatge específic en el

complex camp de l'avaluació del dany estructural tant en columna com en les articulacions sacroilíaques. Seguint aquesta línia de recerca, he realitzat recentment un estudi amb una cohort espanyola per a valorar la progressió radiogràfica de pacients amb EspAax tractats amb fàrmacs anti-TNF. L'estudi "Radiographic progression in patients with axial spondyloarthritis under treatment with TNF inhibitors. Data from REGISPONSERBIO (Spanish Register of Biological Therapy in Spondyloarthritides)" ha estat acceptat com a comunicació oral en el congrés de la Societat Espanyola de Reumatología (SER) i com a "abstract" al congrés europeu (EULAR). Actualment el treball està en fase de redacció amb la intenció de ser adreçat a una revista d'alt impacte en el camp de reumatologia.

CONCLUSIONS

- La incorporació de les radiografies AP lumbars en l'avaluació del dany estructural a nivell de la columna aporta una millora en la detecció de progressió radiogràfica de la columna en pacients amb EspAax.

- La sacroilitis radiogràfica pot ser avaluada en radiografies AP lumbars amb una validesa i fiabilitat similars en comparació amb la radiografia convencional de pelvis en pacients amb EspAax que presentin articulacions sacroilíaques visibles.

- La radiografia AP lumbar afegeix avantatges en l'avaluació de la progressió del dany estructural en pacients amb EspAax per la qual cosa és d'utilitat en el procés de diagnòstic i seguiment d'aquests pacients.

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Chapter 2

General Introduction

Axial spondyloarthritis

Axial spondyloarthritis (axSpA) is a chronic inflammatory rheumatic disease with predominantly axial symptoms, such as inflammation of the sacroiliac joints (SIJs) and spine. The disease is often associated with HLA-B27. Patients with axSpA can develop other typical symptoms, such as peripheral arthritis (mono- or oligoarthritis of the lower limbs), enthesitis and dactylitis, as well as extra-articular manifestations, such as psoriasis, anterior uveitis and inflammatory bowel disease (IBD). The disease characteristically manifests as pain and stiffness, and by new bone formation leading to ankylosis (1).

AxSpA can be classified as into radiographic SpA (r-axSpA, also known as ankylosing spondylitis - AS) or non-radiographic SpA (nr-axSpA) depending on the presence or absence of definite radiographic sacroiliitis respectively, according to the grading system of the modified New York criteria (4). Nr-axSpA can be seen as an earlier or milder form of axSpA, and patients may or may not develop structural bony damage in the axial skeleton.

EPIDEMIOLOGY

The estimated prevalence of axSpA is 0.32% to 1.4%, according to different studies (2, 3). The prevalence of axSpA parallels that of HLA-B27 gene prevalence. For example, the highest estimated prevalence of SpA was found in Northern Arctic indigenous communities, where up to 50% of people have been reported to be HLA–B27 positive (35). Conversely, a lower prevalence has been reported in Asia, Africa, and the Middle East, corresponding with a lower HLA-B27 prevalence in these areas (36).

Age onset of the disease is around the third decade of life, and about 5 years earlier in HLA-B27-positive patients than in HLA-B27-negative patients (37). Furthermore, r-axSpA is slightly more common in men (male-to-female ratio of 2:1 to 3:1); unlike nr-axSpA where the sex distribution is equal (37).

PATHOGENESIS

The aetiology of SpA is still largely unknown, but it is thought to reflect a complex interplay of genetic and environmental factors. Twin studies in r-axSpA have estimated a heritability greater than 90% (38). However, a large familial study (39) showed that only 20% to 44% of genetic predisposition was attributable to major histocompatibility complex (MHC) variants (mainly HLA-B27, but also HLA-B40, HLA-B51, HLA-B7, HLA-A2, and HLA-DPB1), and 7% to 38% to non-MHC variants. Among all genes reported to be associated with r-axSpA, HLA-B27 confers the highest risk and is present in 85% to 90% of patients (40). Nevertheless, first-degree relatives have a 5% to 16% risk of developing the disease, while only 1% to 5% of HLA-B27 individuals develop r-axSpA, suggesting that other genes and environmental factors are involved (40).

A genetic study published in 2007 (41) identified variants among non-HLA proteins as major risk factors for r-axSpA, such as those implicated in the IL-23 signalling pathway and those belonging to the M1 family of zinc metallopeptidases, such as endoplasmic reticulum aminopeptidase 1 (ERAP1). Since the discovery of these variants, multiple non-HLA genes have been associated with r-axSpA. In fact, many of the genes described are associated with type 3 immunity, which is mediated by innate and adaptive immune effector cells that commonly express nuclear receptor RORγt and produce cytokines of the IL-17 family (42).

AxSpA is associated with psoriasis and IBD in about 15% to 20% of cases (37). However, this association may be stronger, as these conditions are sometimes clinically silent (43). The barrier damage of dermal tissue in psoriasis and intestinal mucosae in IBD leads to subsequent exposure of the immune system to commensal microorganisms and pathogens that can contribute to chronic tissue inflammation. Therefore, the “barrier dysfunction” seems to be relevant for the pathogenesis in axSpA (1). In this context, the microbiome has received considerable attention in recent years because commensal microorganisms have been implicated in the disruption of intestinal mucosae. Recent studies have described the implication of the microbiome in the pathogenesis of axSpA in animal models and observed dysbiosis in the gut microbiota in patients with axSpA (44-46).

Additionally, the disease affects tissues exposed to considerable mechanical stress, such as those of the SIJs, the spine, large joints of the lower limbs and the aortic root, as well as entheses. For this reason, several studies have focused on describing the role of mechanical stress in enthesis inflammation and new bone formation in SpA (47, 48).

Thus, the interaction of genetic factors, in particular human leukocyte antigen-B27 (HLA-B27), with different types of stress (including mechanical stress,) leads to the production of pro-inflammatory cytokines (including IL-23) and danger signals (namely, pathogen-associated molecular pattern molecules – PAMPs). Together, IL-23 and danger signals can activate inflammatory leukocytes as well as stromal cell populations to produce key inflammatory cytokines at specific tissue sites, such as bone marrow and the insertion of ligaments on vertebrae. Among these cytokines, soluble tumour necrosis factor (sTNF) and IL-17 are proposed to be strong drivers of the inflammatory component of the disease. Transmembrane

TNF (tmTNF) and IL-22 might simultaneously lead to new bone formation and, ultimately, ankylosis of the axial joints.

CLINICAL FEATURES

Inflammatory back pain

Inflammatory back pain (IBP) onset, becomes persistent after a few months, and is first located in the lumbar region or at the lumbosacral junction and with alternating buttock pain. The pain worsens with inactivity and improves with exercise and non-steroidal anti-inflammatory drugs (NSAIDs). Morning stiffness is often prolonged (> 30 min) and nocturnal pain may awaken patients from sleep.

One of the major concerns of patients with axSpA is progression towards ankylosis of the axial skeleton. Ankylosis results from ossification of the ligaments and the costovertebral and sternocostal joints. Consequently, it leads to loss of spinal movement and abnormal posture (loss of lumbar lordosis, followed by thoracic hyperkyphosis). This restriction can be quantified by applying established methods (such as the modified Schober test for measuring lumbar flexion) (49).

Peripheral arthritis, enthesitis and dactylitis

Arthritis and enthesitis are the most common peripheral manifestations (found in 30%-50% of axial spondyloarthritis at presentation or in the past), which can occur at any time in the course of the disease (1). Peripheral arthritis is typically asymmetric, oligoarticular and involves the lower limbs. Enthesitis is defined as inflammation of the insertion of tendons, ligaments, aponeurosis and capsules into the bone; the most typical enthesitis is heel pain

(posterior or inferior) related to inflammation of the Achilles' tendon or the plantar fascia insertion. Additionally, dactylitis is the combination of synovitis, enthesitis, tenosynovitis and soft tissue swelling, which presents as swelling of a finger, is more common in psoriatic arthritis and is a rare peripheral manifestation of axSpA.

Extra musculoskeletal manifestations

Acute anterior uveitis is the most common extra-musculoskeletal manifestation, is present in 25% to 30% of patients and has a higher incidence among HLA-B27 positive patients (OR 42) (50). The condition typically presents with unilateral eye pain, redness, photophobia and increased lacrimation; moreover, if not treated, it can lead to visual loss that may be irreversible. About 50% of patients with one episode of uveitis will develop recurrent anterior uveitis, and this manifestation can be present in any time of the disease (51).

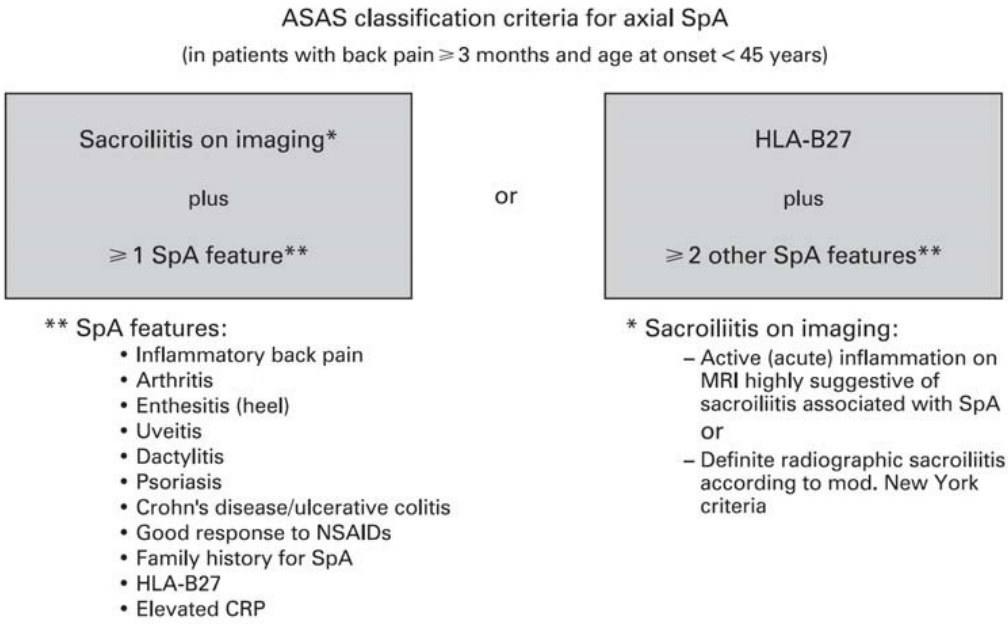
Additionally, psoriasis is present in about 15% to 20% of patients whether IBD in 6% of patients (37, 52).

CLASSIFICATION CRITERIA

The Assessment in SpondyloArthritis International Society (ASAS) criteria were published for axSpA in 2009 (53) and for peripheral spondyloarthritis in 2011 (5) to aid in diagnosing axSpA earlier. The ASAS classification criteria for axSpA (Figure 1) require a history of chronic back pain (pain duration ≥ 3 months) and an age of onset of < 45 years as entry criteria. Next, the patient must show either sacroiliitis on radiography or MRI plus at least one typical clinical SpA feature or presence of HLA-B27 in addition to at least two typical clinical SpA features.

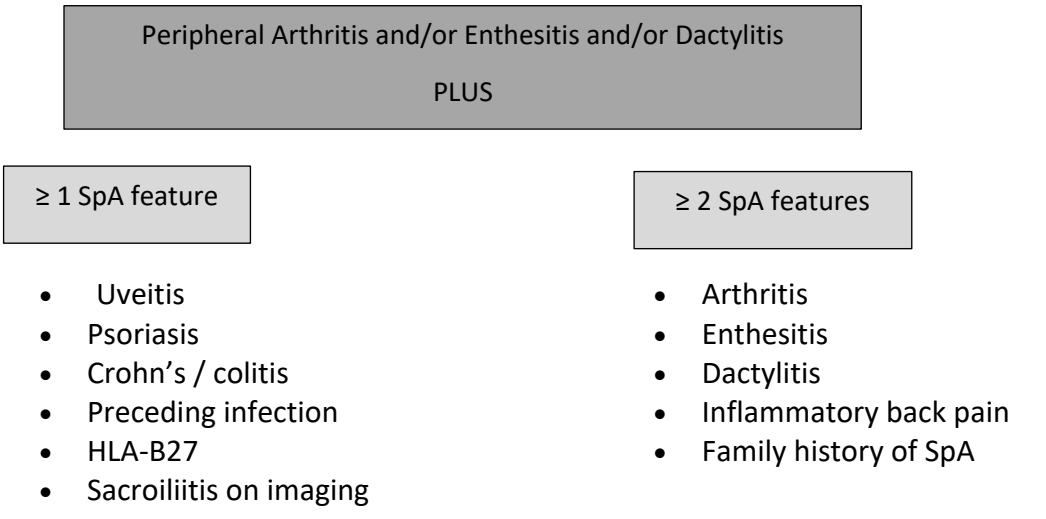
The sensitivity of the criteria ranges between 68% and 87%, and the specificity between 62% and 95% between different studies (6, 7).

Figure 1. ASAS Classification criteria for axSpA



Patients with peripheral symptoms but with no major axial involvement can be classified with the ASAS classification criteria for peripheral SpA (Figure 2). These require a history of arthritis, enthesitis or dactylitis in addition to SpA features.

Figure 2. ASAS classification criteria for peripheral SpA



IMAGING

Imaging is essential for correct diagnosis as well as differential diagnosis of axSpA. Plain radiographs of the spine, SIJs and peripheral joints can reveal various structural changes. Nonetheless, because structural damage generally first arises in the SIJ, imaging of SIJ plays a pivotal role when diagnosing axSpA.

The most common differential diagnoses for axSpA are degenerative or mechanical problems (degenerative disc disease, spondylosis, congenital vertebral anomalies, diffuse skeletal hyperostosis, osteitis condensans and osteoarthritis of SIJs). Other differential diagnoses, although less frequent, are fractures, infectious sacroiliitis, bone metastasis and primary bone tumours (1).

Radiography

According to the European League Against Rheumatism (EULAR) recommendations, SIJ radiography is still the first imaging method recommended when axSpA is suspected (54). However, this method has limitations in patients with early axSpA because structural changes generally take months to years to appear. Furthermore, the interpretation of SIJ radiographs is often challenging. Radiographic sacroiliitis can be graded according to the modified New York grading system (4) as follows: grade I, suspicious; grade II, evidence of erosion and sclerosis; grade III, erosions, sclerosis, joint space narrowing or partial ankylosis; and, finally, grade IV, total ankylosis.

Spinal radiographs typically show squaring of the vertebrae secondary to erosions of the superior and inferior margins of these bodies. Vertebral enthesitis may cause sclerosis of the upper and lower vertebral bodies which appears as the formerly called “shiny

corners". Annulus fibrosus ossification leads to syndesmophyte formation, and over time, bridging of these syndesmophytes results in a bamboo spine.

Magnetic resonance imaging (MRI)

MRI is able to detect inflammatory lesions even before definite lesions are visible on plain radiographs. Therefore, when clinical suspicion of early SpA is high but standard SIJ radiography is normal or ambiguous, MRI should be performed. However, only 30% to 50% of subjects with axSpA are positive for active sacroiliitis on MRI (55). Fat-suppressed T2-weighted sequences that are sensitive for free water (eg, STIR), or fat-suppressed T1W sequences that are sensitive for contrast enhancement such as T1WFS post-Gd are the imaging sequences of choice to visualize lesions indicating signs of activity. Whether, for detection of post-inflammatory changes, such as erosions, sclerosis, ankyloses, and fatty lesions a T1-weighted (T1W) sequence is performed.

The ASAS group definition of active sacroiliitis on MRI for classification of axSpA (56) requires evidence of bone marrow oedema (BMO) in a typical anatomical area (subchondral bone) and must be highly suggestive of SpA. BMO is depicted as a hyperintense signal on STIR images and usually as a hypointense signal on T1-weighted images.

Recently, the ASAS group updated the MRI SIJ lesions considered relevant in SpA patients (57), adding new definitions and revising existing definitions for inflammatory lesions and structural lesions. Therefore, additional definitions of inflammatory lesions other than BMO include:

- **Capsulitis**: Depicted as an increased signal on STIR and/or T1FS post-Gd observed at the perimeter of the joint (anterior or posterior on axial images, cranial or caudal on semicoronal images).

- **Joint space enhancement**: Increased signal on contrast-enhanced images in the joint space of the cartilaginous portion of the SIJ.

- **Inflammation at the site of erosion**: Increased signal on STIR and/or T1FS post-Gd at the site of erosion.

- **Enthesitis**: Increased signal in bone marrow and/or soft tissue on STIR and/or T1FS post-Gd at sites where ligaments and tendons attach to bone, but not including the inter-osseous ligaments of the sacroiliac joint.

- **Joint space fluid**: Bright signal in the joint space on STIR images equivalent to cerebrospinal fluid.

Likewise, MRI SIJ lesion definitions indicating signs of structural change include:

- **Erosion**: Defect in subchondral bone associated with full-thickness loss of the dark appearance of the subchondral cortex at its expected location, with loss of signal on a T1W non-fat-suppressed sequence compared with the normal bright appearance of adjacent bone marrow.

- **Fat lesion (also known as fat metaplasia)**: Bright signal seen on a T1W non-fat-suppressed sequence that is brighter than normal bone marrow, which meets the following requirements: a) homogeneously bright; b) located in a typical anatomical

area (subchondral bone); and c) sharply defined along its non-articular border with normal bone marrow.

- **Fat metaplasia in an erosion cavity (also known as "backfill"**): Bright signal on a T1-weighted sequence in a typical location for an erosion or confluent erosions, with signal intensity greater than normal bone marrow, that is a) associated with complete loss of the dark appearance of the subchondral cortex at its expected location and b) clearly demarcated from adjacent bone marrow by an irregular band of dark signal reflecting sclerosis at the border of the original erosion.

- **Sclerosis**: Very low signal on all sequences located in a typical anatomical area (subchondral bone).

- **Ankylosis**: Abnormal bright signal on a T1W non-fat-suppressed sequence with similar signal intensity to bone marrow, which is in the expected location of the sacroiliac joint space and bridges the joint so that there is continuity of bone marrow signal between the ilium and sacrum. It is associated with full-thickness loss of the dark appearance of the subchondral cortex on both sides of the joint.

- **Bone bud**: Abnormally bright signal on a T1W non-fat-suppressed sequence with similar signal intensity to bone marrow, which is in the expected location of the SIJ space but does not bridge the joint so that it is continuous with the subchondral bone of either the ilium or the sacrum but not both. It is associated with full-thickness loss of the dark appearance of the subchondral cortex on the corresponding side of the joint, at its expected location.

Actually, the presence of other inflammatory lesions alone, with no concomitant BMO, is insufficient for the definition of “active sacroiliitis on MRI”. Additionally, in the absence of MRI signs of BMO, the presence of structural lesions does not meet the definition of “active sacroiliitis on MRI” (56).

The interpretation of BMO representing inflammatory lesions as “highly suggestive of SpA”, includes identification of inflammatory lesion on at least two consecutive slices of an MRI scan or on a single slice if there is more than one inflammatory lesion present. Moreover, if an inflammatory lesion appears to be present but it is hard to determine whether the lesion meets the criterion “highly suggestive of SpA”, then the decision may be influenced by the presence of concomitant structural damage, especially erosion, and/or other signs of inflammation, which in themselves do not suffice to meet the criterion (31, 56).

Computed tomography

Computed tomography (CT) of SIJs is considered to be the gold standard for the detection of structural damage in the SIJs (especially erosions), although it is rarely used as the primary diagnostic method because of the lower feasibility in clinical practice and higher radiation exposure (31). Additionally, conventional radiography and MRI of SIJs usually allow a comprehensive assessment of structural damage. However, in the last years, low-dose CT, which has a radiation exposure similar to conventional radiography, has been established for the assessment of structural damage in the SIJs (32).

Ultrasound

In contrast to the other image modalities previously described, ultrasound (US) has utility for peripherical manifestations in patients with SpA, specifically for evaluating peripheral enthesitis. B-mode and Doppler US (colour and power) both reveal the structure and vascularity of the enthesis. Together, they are helpful in detecting subclinical enthesitis, measuring disease activity and evaluating treatment effect (58, 59).

In recent years, several enthesitis scoring systems have been published. More recently, a final reliable score and definition of enthesitis for SpA by the US OMEREACT task force has been described (59).

ASSESSMENT

As the ASAS/EULAR recommendations state, "Disease monitoring of patients with axSpA should include patient-reported outcomes, clinical findings, laboratory tests and imaging, all with the appropriate instruments and relevant to the clinical presentation. The frequency of monitoring should be decided on an individual basis depending on symptoms, severity and treatment" (54).

Patient-reported outcomes

Several patient-reported outcomes have been reported in the last decades to assess levels of pain, disease activity, quality of life and physical function.

The Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) (60) was first described in 1994 to assess disease activity. This index is simple to use, as it comprises only six

questions related to fatigue, axial involvement, peripheral articular involvement, enthesopathy and morning stiffness (two questions). The BASDAI score ranges from 0-10, with higher values indicating more active disease. A score above 4 is considered the cut-off to determine whether the disease is active. Additionally, a change of at least 50% in the BASDAI is usually considered as reflecting a clinically relevant improvement.

The Ankylosing Spondylitis Disease Activity Score (ASDAS) is a more recent disease activity score, which combines patient-reported outcomes and C-reactive protein (CRP) (or erythrocyte sedimentation rate [ESR]) into one index (Box 1) (61). Active disease is defined as an ASDAS score of at least 2.1. The cut-offs between the disease activity states are: inactive disease ≤ 1.3, low disease activity 1.3-2.0, high disease activity 2.1-3.5, and very high disease activity ≥ 3.5 (62). The ASDAS cut-off for clinically important improvement is ≥ 1.1 and the cut-off for a major improvement is ≥ 2.0 (63).

Box 1**.** Parameters used to calculate Ankylosing Spondylitis Disease Activity Score (ASDAS)

1. Total back pain (BASDAI question 2)
2. Duration of morning stiffness (BASDAI question 6)
3. Patient global assessment of disease activity
4. Peripheral pain/swelling (BASDAI question 3)
5. C-reactive protein (mg/l) or erythrocyte sedimentation rate (mm/hr)

In the recent EULAR recommendations, ASDAS is the preferred measure to assess disease activity (54). ASDAS correlates better than BASDAI in patients' and physicians' level of disease activity (64). Frequently, there is concordance between BASDAI ≥ 4 and

ASDAS ≥ 2.1; however, in discordant cases, an elevated ASDAS has been more predictive of good response than elevated BASDAI (65). Moreover, ASDAS cut-offs for disease activity and response criteria were based on a thorough validation process, while BASDAI cut-offs were arbitrarily chosen (63). Hence, ASDAS is preferred over BASDAI.

Functional impairment is mostly evaluated using the Bath Ankylosing Spondylitis Functioning Index (BASFI) (66). The score ranges from 0 to 10, with higher values indicating worse functioning. Other instruments available to assess functional impairment and quality of life are The Health Assessment Questionnaire (HAQ), Ankylosing Spondylitis Quality of Life Questionnaire (ASQoL), the 36-Item Short Form Survey Instrument (SF-36), etc.

Recently, a new patient-reported outcome has been described: the ASAS Health Index (ASAS Hi) (67). This index is a valid, reliable and responsive measure of functioning and health in patients with axial and peripheric SpA. It is composed of 7 items with a dichotomous response option addressing all important aspects of patient complaints. ASAS Hi correlates strongly with disease activity, functional disability and patient global assessment, but correlates weakly with physician global opinion (67).

Clinical findings

The most commonly used instrument to evaluate range of motion is the Bath AS Metrology Index (BASMI) (68), a composite index combining information from five different tools: cervical rotation, tragus-to-wall distance, spinal lateral flexion, lumbar flexion (modified Schober's test) and inter-malleolar distance. Three different

definitions have been published: the 2-step definition, the 10-step definition and the linear definition. ASAS recommends the 10-step definition or the linear definition (69, 70).

To evaluate peripheral involvement, ASAS recommends the assessment of the number of swollen joints (44-joint count) and the assessment of enthesitis using a validated enthesitis index (71). The Maastricht Ankylosing Spondylitis Enthesitis Score (MASES) (72) (range 0-13) and the Spondyloarthritis Research Consortium of Canada (SPARCC) (73) are the more common used indices to evaluate enthesitis.

MANAGEMENT

The treat-to-target concept was newly added in the 2014 recommendations by an international task force (74). The value of targeting disease activity appears to be relevant because inflammation leads to the signs and symptoms of the disease, functional impairment as well as structural changes (12, 75). However, controversy remains as to what this target should be; inactive disease is the ultimate goal, but as may be an unrealistic goal low disease activity seems to be an acceptable target in some patients (54). Moreover, treatment target should be a shared decision between patient and rheumatologist, taking all relevant situational factors into consideration (54, 74).

ASAS has proposed composite indices for monitoring disease activity in clinical trials:

• One set of responder criteria (ASAS-20 improvement criteria and ASAS-40 improvement criteria (76, 77); box 2 and box 3 respectively)

• One set of remission criteria (ASAS partial remission criteria (76); box 4)

Box 2. ASAS-20 improvement criteria

- Improvement of $\geq$ 20% and $\geq$ 1 unit (on a 0-10 scale) in at least 3 of the 4 domains:
  - Patient global
  - Pain (spinal pain or BASDAI question 2)
  - Function (BASFI)
  - Inflammation (mean of BASDAI question 5 and 6)
- No worsening of $\geq$ 20% and $\geq$ 1 unit in remaining domain.

Box 3. ASAS-40 improvement criteria

- Improvement of $\geq$ 40% and $\geq$ 2 units (on a 0-10 scale) in at least 3 of the 4 domains:
  - Patient global
  - Pain (spinal pain or BASDAI question 2)
  - Function (BASFI)
  - Inflammation (mean of BASDAI question 5 and 6)
- No worsening in remaining domain.

Box 4. ASAS partial remission criteria

- Value not above 2 units (on a 0-10 scale) in each of the 4 domains:
  - Patient global
  - Pain (spinal pain or BASDAI question 2)
  - Function (BASFI)
  - Inflammation (mean of BASDAI question 5 and 6)

TREATMENT

The ASAS/EULAR management recommendations were updated in 2016 (54), similarly in 2019 were updated the American College of Rheumatology/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network Recommendations for the Treatment of SpA (33). In both, treatment with non-steroidal anti-inflammatory drugs (NSAIDs) are recommended as first-line therapies in patients with SpA in combination with non-pharmacological treatment.

Non-pharmacological treatment

Education is an important aspect for the successful management of patients with SpA. Once the diagnosis is made, the patient should be given a clear description of the nature of the disease, including an explanation of the various potential clinical symptoms and presentations as well as the possible progression of the target symptom. Moreover, it is essential for patients to make informed shared decisions as this has proven to be efficacious (78-80).

Physical activity is effective in reducing pain and preserving function (81, 82). Physical activity recommendations include four domains (cardiorespiratory fitness, muscle strength, flexibility and neuromotor performance) (82). Planning physical activity requires a shared decision between healthcare providers and patients (82). Overall, supervised exercises are more effective compared with home exercises (83).

Non-steroidal anti-inflammatory drugs

NSAIDs are recommended as first-line treatment for patients with axSpA due to their high effectiveness in reducing back pain and stiffness when administered at a full anti-inflammatory dosage (54, 84, 85). Moreover, there are no significant differences in efficacy and adverse events between traditional and COX-2 NSAIDs (86).

NSAIDs should be used according to the patient's symptoms, and up to 35% of patients with early disease (< 3 years of disease duration) starting NSAIDs achieved ASAS partial remission (84). Moreover, patients usually respond quickly, within the first 2 weeks of NSAID therapy, and in responders, the response rate increases further in the first 24 weeks (84). Although the safety of long-term NSAID therapy is a concern, continuous use is preferred in responders if symptoms persist, whether dose reduction or discontinuation should be considered only if the patient is in remission (54). Despite NSAID safety data in r-axSpA patients has been recently reported in two reviews of randomised controlled trials (86, 87), showing non increasing side effects as compared to placebo, data was only available for 12 weeks of follow-up. Moreover, two studies suggest that infrequent NSAID use may be associated with increased mortality (88, 89). This may be because NSAID treatment is associated with reduced inflammation and increased mobility in patients with axSpA, factors that might reduce cardiovascular morbidity. However, the potential risks of long-term treatment, including cardiovascular, gastrointestinal, and renal risks, should be taken into account (1).

Conventional synthetic disease-modifying antirheumatic drugs and glucocorticoids

Conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), such as methotrexate, sulfasalazine and leflunomide, are not generally efficacious for axial

symptoms. Nonetheless, sulfasalazine might have a limited role in peripheral manifestations, based on old studies (54, 90). In axial disease, although a recent placebo-controlled study of sulfasalazine demonstrated an improvement in axial symptoms and a second study of sulfasalazine compared with etanercept showed modest clinical and imaging responses in the sulfasalazine group as compared with etanercept group (8, 91), there is still scant evidence on the use of sulfasalazine for axial symptoms. Therefore, sulfasalazine could play a role in treating axial disease in patients with contraindications for TNF inhibitors (33, 54). Regarding other csDMARDs, a study with 20 mg methotrexate showed no improvement in axial symptoms, but did show a decrease in swollen joint counts (92). Nonetheless, there is still more evidence supporting the use of sulfasalazine in peripheral manifestations regarding other csDMARDs (33). Additionally, it is not recommended that a csDMARD (usually methotrexate) should be combined with a TNF inhibitor to prevent the development of anti-drug antibodies (ADAs) (1).

Glucocorticoid injections directed to the local site of musculoskeletal inflammation may be considered to treat arthritis and enthesitis. Nonetheless, long-term treatment with systemic glucocorticoids is not recommended because high doses of prednisolone of about 50 mg per day or higher are needed to achieve a modest effect in disease activity (93).

Targeted synthetic disease-modifying antirheumatic drugs

More recently, targeted synthetic DMARDs (tsDMARDs) such as Janus kinase (JAK) inhibitor tofacitinib, showed in a phase II study a benefit in both clinical and imaging outcomes of axial disease over 12 weeks in r-axSpA (94). Additionally, filgotinib, a

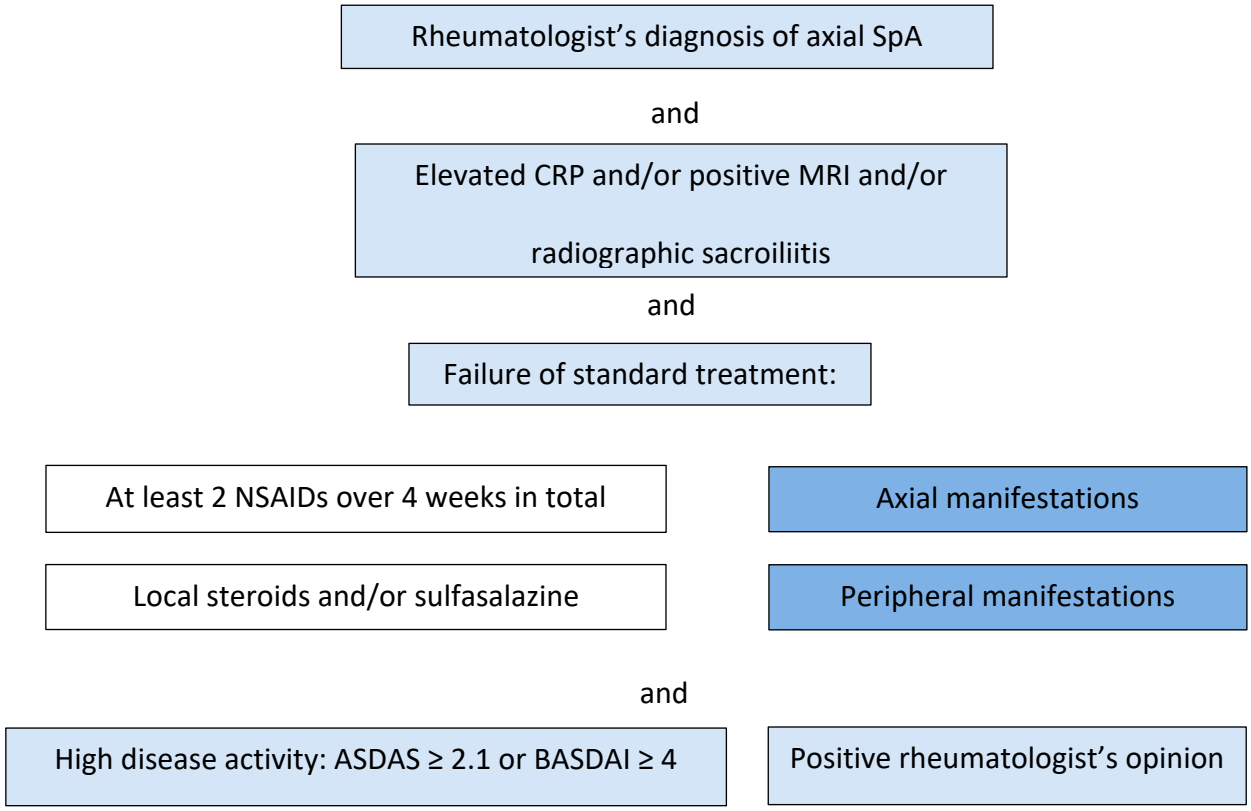
specific JAK1 inhibitor was evaluated in a phase II, randomized, placebo-controlled trial in patients with r-axSpA showing an improvement as compared to placebo in clinical outcomes over 12 weeks (95). Another specific JAK1 inhibitor, upacitinib, is currently been evaluated in a phase IIb/III randomized controlled trial that aimed to assess its efficacy and safety in patients with active r-axSpA (ClinicalTrials.gov ID: NCT03178487 /SELECT Axis 1).

Biological disease-modifying antirheumatic drugs

Biological disease-modifying antirheumatic drugs (bDMARDs) should be considered in patients with persistently high disease activity despite conventional treatment (33, 54). The bDMARDs indicated for the treatment of axSpA are tumour necrosis factor inhibitor (TNFi) and IL-17 inhibitors (IL-17i). bDMARDs can be further subdivided into originator and biosimilar DMARDs. Current practice is to start with TNFi therapy, as more evidence and experience is available (54).

Figure 3 summarises the different requirements before a bDMARD could be started (54). Five TNFi drugs are available for the indication of r-axSpA: infliximab, etanercept, adalimumab, golimumab, and certolizumab. Except for infliximab, all of these drugs are indicated for both radiographic and non-radiographic axSpA. Treatment with any of these TNFi leads to good or very good improvement in all articular manifestations, CRP levels, and MRI-detectable inflammation in the SIJs or spine in active patients. Elevated CRP followed by inflammation on MRI are the best predictors of good response to TNFi therapy, both in patients with r-axSpA and nr-axSpA (96, 97) .

Figure 3. ASAS-EULAR recommendations for the treatment of patients with axSpA with bDMARD.



Efficacy of the five TNFi drugs for musculoskeletal signs and symptoms are very similar. However, there are differences regarding musculoskeletal manifestations. Monoclonal antibodies (infliximab, adalimumab, certolizumab and golimumab) are efficacious in the treatment of IBD whereas etanercept is not. Moreover, etanercept has shown contradictory results for uveitis, while monoclonal antibodies have shown efficacy in preventing the recurrence of uveitis. Finally, etanercept seems to be less efficacious for psoriatic skin involvement than other TNFi drugs, although no head-to-head comparisons are available (33, 54).

Biosimilar treatments have shown comparable levels of safety and efficacy than the originator. Because cost is potentially an important consideration when choosing treatments, the EULAR/ASAS and ACR recommendations consider that either treatments can be chosen to initiate new courses of TNFi (33, 54). However, ACR recommendations stress that switching to a biosimilar treatment during the course of treatment should not be mandated (33).

Treatments targeting interleukin-17, secukinumab, and more recently ixekizumab have been incorporated in the latest treatment guidelines of axSpA (33, 54). Both are approved for the treatment of patients with r-axSpA, based on phase III trials showing a significant and clinically meaningful reduction in disease activity versus placebo through 52 weeks of follow-up (98-100). In nr-axSpA, a recent phase 3 study (101) reported good results with ixekizumab treatment, and on the basis of this study, ixekizumab has recently been approved for this indication in Europe and U.S. Conversely, based in the recent phase III PREVENT study presented in the ACR Congress (102), secukinumab has also been approved for the treatment of nr-axSpA. Nevertheless, the role of interleukin-17 inhibitors (IL-17i) in the treatment of axSpA remains to be determined as larger clinical experience grows.

IL-17i drugs have proven efficacy for the treatment of psoriasis and psoriatic arthritis, and have also shown promising results in preventing the recurrence of uveitis (103). However, when IL-17i were investigated for the management of IBD, no benefit was found and worsening of disease was reported in some patients (104).

It is recommended that bDMARD response be assessed 3 months after treatment initiation (54). The response should be defined by the same outcome measures used to initiate either ASDAS or BASDAI. In the case of ASDAS, a clinically important improvement of ≥ 1.1 is required, whereas BASDAI requires an improvement of ≥ 2.0. Importantly, this evaluation should coincide with a positive opinion from the rheumatologist (54). When the established outcomes are not achieved, switching to another TNFi or an anti-IL-17 therapy should be considered. Although more evidence is needed, it seems reasonable to switch to another class of drugs, an IL-17i, in patients with primary nonresponse to the first TNFi. In patients with secondary nonresponse to TNFi, switching to another TNFi seems to be a good approach (33, 54).

Discontinuation of TNFi in patients with axSpA who had achieved sustained remission led to a relapse in 53% to 58% of cases, in nr-axSpA and r-axSpa respectively (105, 106). Hence, discontinuation of TNFi is generally not recommended. In contrast, tapering of biological therapy is recommended for these patients (54), as tapering has been tolerated by 52% to 86% of patients (107, 108) and a recent randomized trial supports the non-inferiority of reduced-dose TNFi doses compared with full doses to maintain low disease activity after 1 year in patients with SpA in sustained clinical remission (109).

Treatment options for inhibition of radiographic progression

Over the last few years, research has focused on whether therapy for axSpA inhibits radiographic progression. An inhibitory effect of continuous NSAIDs over on-demand NSAID therapy for 2 years was reported in patients with r-axSpA in two randomised trials (110, 111). Similar results were found in a study comparing high-dose with low-dose

NSAID therapy (112). However, these findings were not supported by a recent randomised trial that found no significant differences between continuous and on-demand treatment (113).

As mentioned before, it is thought that inflammation of subchondral bone marrow leads to local repair processes and subsequent new bone formation (10). Therefore, early anti-inflammatory treatment could play a role in preventing new bone formation and in subsequent radiographic progression (114). Furthermore, it seems that long-term TNFi exposure (≥ 4 years) might confer beneficial effects on spinal radiographic progression in r-axSpA (114). However, no significant differences in spinal radiographic progression are apparent between patients receiving and not receiving TNFi over the first 2 years (115, 116). In nr-axSpa, further data are needed to prove that TNFis are more effective than nonbiologic therapy in reducing the likelihood of spinal radiographic progression, as only 2 studies without a control cohort are available (14, 117).

There are a few studies evaluating the TNFi structural effect in SIJs. Dougados et al. (118) reported a significant improvement in total SIJ score in the etanercept arm as compared with the control arm over 2 years of follow-up, reporting a change in total SIJ score between groups of −0.22 (95% CI −0.38 to −0.06), p 0.008. Furthermore, significant differences were found in terms of net progression rate (change in mNY criteria). A more recent study (119) reported slower progression of structural damage in SIJs during long-term TNFi treatment (up to 6 years).

The MEASURE-I study assessed radiographic progression in r-axSpA patients receiving secukinumab therapy, describing lower progression rates (change mSASSS score) over 2

years of treatment (98). A further extension of the study (120) described that mSASSS progression remained stable over 4 years of treatment, with a numerically lower mSASSS change from baseline with secukinumab 150 mg versus 75 mg. However, a recent study comparing the MEASURE-I study versus the ENRADAS historical cohort of patients who did not receive biological therapy despite finding a change in mSASSS over 2 years lower in MEASURE-I versus the ENRADAS cohort, no significant differences were found (121).

Hence, further studies with a comparative group and larger numbers of patients are required to confirm if secukinumab is more effective than TNFi or NSAIDs in reducing the likelihood of spinal radiographic progression. Currently, there is an ongoing head-to-head study designed to evaluate the superiority of secukinumab over biosimilar adalimumab in reducing spinal radiographic progression in r-axSpA (122) which will hopefully give us additional information to make further conclusions.

Chapter 2

Rationale

RATIONALE

At present, conventional radiographs are still currently recommended as the standard imaging technique for the initial evaluation and subsequent assessment of structural damage progression in the spine and in SIJs in axSpA patients. Pelvic radiograph is the radiograph most often used to assess radiographic sacroiliitis, and lateral views of cervical and lumbar spine radiographs are taken to assess radiographic spinal progression. However, although AP lumbar radiography is often performed in the diagnostic work-up and follow-up of patients with axSpA, its value in assessing structural damage in the spine and SIJs is unknown.

AP lumbar radiographs may capture structural damage present in the spine but not captured by lateral view. However, it is not known whether AP lumbar radiographs, which are often performed routinely, could provide additional information on the presence of structural damage in the spine.

Similarly, SIJs are often depicted on AP lumbar radiographs, but there are no data on whether SIJs can be assessed with a similar reliability and validity as pelvic radiographs. If the patient has already undergone AP lumbar radiography when he or she is first assessed, no additional pelvic radiographs needs to be performed to assess SIJs in the diagnostic work-up of patients with suspected axSpA.

Chapter 3

Hypothesis

HYPOTHESIS:

1) AP lumbar radiographs have added value for the assessment of structural damage progression in axSpA patients.
2) AP lumbar radiographs have added value for the assessment of structural damage progression in the spine in patients with axSpA.
3) Structural changes in SIJs can be reliably assessed on AP lumbar radiographs using conventional pelvic radiographs as a reference.

Chapter 4

Objectives

OBJECTIVES:

MAIN OBJECTIVE:

1) To evaluate the added value of AP lumbar radiographs for the assessment of structural damage progression in axSpA patients.

SECONDARY OBJECTIVES:

2) To evaluate the performance of the extended mSASSS score, which includes AP lumbar radiographs compared with the conventional mSASSS, in detecting radiographic spinal progression in patients with axSpA.

3) To investigate the reliability and validity of structural damage assessment in SIJs by assessing radiographic sacroiliitis on AP lumbar radiographs as compared with conventional pelvic radiographs in patients with axSpA.

Chapter 5

1. Incorporation of the anteroposterior lumbar radiographs in the modified Stoke Ankylosing Spondylitis Spine Score improves detection of radiographic spinal progression in axial spondyloarthritis.

- **Reference: Llop M**; Rios Rodriguez V; Redeker I; Sieper J; Haibel H; Rudwaleit M; Poddubnyy D. Incorporation of the anteroposterior lumbar radiographs in the modified Stoke Ankylosing Spondylitis Spine Score improves detection of radiographic spinal progression in axial spondyloarthritis. Arthritis research & therapy. 21, pp. 126. 2019. ISSN1478-6354

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Incorporation of the anteroposterior lumbar radiographs in the modified Stoke Ankylosing Spondylitis Spine Score improves detection of radiographic spinal progression in axial spondyloarthritis

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Abstract

Background: To evaluate the performance of the extended modified Stoke Ankylosing Spondylitis Spine Score (mSASSS) incorporating information from anteroposterior (AP) lumbar radiographs as compared to the conventional mSASSS in detection of radiographic spinal progression in patients with axial spondyloarthritis (axSpA)

Methods: A total of 210 patients with axSpA, 115 with radiographic axSpA (r-axSpA), and 95 with non-radiographic axSpA (nr-axSpA), from the GErman SPondyloarthritis Inception Cohort (GESPIC), were included in the analysis based on the availability of spinal radiographs (cervical spine lateral, lumbar spine lateral, and AP views), at baseline and year 2. Two trained readers independently scored lateral cervical and lumbar spine images according to the mSASSS system (0–3 per vertebral corner, 0–72 in total). In addition, all vertebral corners of vertebral bodies visible on lumbar AP radiographs (lower T12 to upper S1) were assessed according to the same scoring system that resulted in a total range for the extended mSASSS from 0 to 144. Reliability and sensitivity to detect radiographic spinal progression of the extended mSASSS as compared to the conventional mSASSS were evaluated.

Results: The reliability of conventional and extended scores was excellent with intraclass correlation coefficients (ICCs) of 0.926 and 0.927 at baseline and 0.920 and 0.933 at year 2, respectively. The mean ± SD score for mSASSS and extended mSASSS at baseline were 4.25 ± 8.32 and 8.59 ± 17.96, respectively. The change score between baseline and year 2 was 0.73 ± 2.34 and 1.19 ± 3.73 for mSASSS and extended mSASSS, respectively. With the extended mSASSS, new syndesmophytes after 2 years were detected in 4 additional patients, new syndesmophytes or growth of existing syndesmophytes in 5 additional patients, and progression by ≥ 2 points in the total score in 14 additional patients meaning a 25%, 28%, and 46% increase in the proportion of patients with progression according to the respective definition as compared to the conventional score.

Conclusions: Incorporation of lumbar AP radiographs in the assessment of structural damage in the spine resulted into detection of additional patients with radiographic spinal progression not captured by the conventional mSASSS score.

Keywords: Axial spondyloarthritis, mSASSS, Radiographic spinal progression, Radiographs, X-rays

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Introduction

Axial spondyloarthritis (axSpA) can be classified into radiographic SpA (r-axSpA, also known as ankylosing spondylitis—AS) or non-radiographic SpA (nr-axSpA) depending on the presence or absence of definite radiographic sacroiliitis according to the grading system of the modified New York (mNY) criteria [1]. New bone formation with development of syndesmophytes between vertebrae represents the morphological substrate of structural damage in the spine in axSpA. Since development of structural damage is usually assessed on conventional radiographs, it is referred to as radiographic spinal progression. Structural damage in the spine and disease activity are two major determinants of spinal mobility and physical function in axSpA [2–4]. Currently, the modified Stoke Ankylosing Spondylitis Spine Score (mSASSS) [5] is considered as the gold standard for assessment of structural damage in the spine in axSpA [6]. Compared to the Bath Ankylosing Spondylitis Radiology Index (BASRI) [7] and SASSS [8], mSASSS has a better reliability and sensitivity to change [9].

The mSASSS assesses the presence of erosions, sclerosis, squaring, non-bridging syndesmophytes, and bony bridges affecting the anterior vertebral corners of the cervical and lumbar spine on radiographs in lateral views [5]. Previous studies suggested that anteroposterior (AP) view of the lumbar spine, which are frequently performed routinely, could provide additional information on the presence of structural damage in the spine [7, 9]. The added value of the AP lumbar radiographs in the assessment of radiographic spinal progression in axSpA as compared to lateral views only is, however, not known.

The aim of the current study was to evaluate the performance of the extended mSASSS score incorporating information of the AP lumbar radiographs compared to the conventional mSASSS.

Patients and methods

Patients

Patients with axSpA from the GErman SPondyloarthritis Inception Cohort (GESPIC) were included in the current analysis based on the availability of clinical data and radiographs at baseline and year 2. A detailed description of the entire cohort as well as of the radiographic subset has been reported previously [10–12]. Briefly, patients included in GESPIC had a definite clinical diagnosis of axSpA according to the treating rheumatologist with symptom duration of up to 5 years for the non-radiographic form and up to 10 years for the radiographic form of axSpA. The final classification as nr-axSpA or r-axSpA was performed based on the central reading of the radiographs as previously reported [10]. Treatment of the patients was defined by local rheumatologists and followed national and international guidelines; however, since the cohort had started prior to introduction of tumor necrosis factor inhibitors (TNFi) in the clinical practice, the vast majority of the patients were off TNFi therapy at inclusion and during first 2 years of observation.

Radiographic assessments

Radiographs of cervical (lateral view) and lumbar spine (lateral and AP views) were obtained at baseline and after 2 years. Images were centrally collected, digitized, anonymized, and scored independently by two trained readers (DP and HH), who were blinded to the chronological order of the images and to all clinical data. According to the mSASSS, anterior corners of the vertebral bodies from lower C2 to upper T1 (cervical spine) and from lower T12 to upper S1 (lumbar spine) were scored as follows: 0 = normal, 1 = erosion, sclerosis, and/or squaring, 2 = non-bridging syndesmophyte, and 3 = bridging syndesmophyte, giving a range for the entire score from 0 to 72 [5]. No adjudication was performed. The final mSASSS score included in the analysis was calculated as a mean of the mSASSS scores of both readers. In addition, left and right, upper and lower vertebral corners of vertebral bodies visible on lumbar AP radiographs from lower Th12 to upper S1 were scored according the same grading system. The combination of the scores from both lateral cervical and lumbar views and lumbar AP views composed the "extended mSASSS" with a total range from 0 to 144. The final extended mSASSS was calculated as a mean of the scores of both readers. Syndesmophytes were considered to be present if both readers gave a score of ≥ 2 to a vertebral corner.

Missing scores of single vertebral corners were substituted with scores for the respective vertebral corners at other time point, if available, or with a score of zero if scores for both time points were missing.

Data analysis

To assess the applicability of the extended mSASSS as a tool for the measurement of radiographic spinal progression, it was compared to the conventional mSASSS according to the three aspects of the Outcome Measures in Rheumatology (OMERACT) filter: feasibility, discrimination, and truth [13].

Feasibility

The feasibility aspect of the OMERACT filter refers to the pragmatic reality on applying or using a specific measure; which is decisive on its success: "Can the measure be applied easily, given constraints of time, money, and interpretability?" [13]. The feasibility was assessed in the context of time, radiation exposure, and cost excess associated with extended mSASSS compared to the conventional one.

Discrimination

The discrimination aspect addresses the question: "Does the measure discriminate between situations of interest?" This aspect of the OMERACT filter focuses on reliability and sensitivity to change [13].

We used the intraclass correlation coefficient (ICC) and Cohen's kappa coefficient to measure the inter-observer reliability for continuous and categorical variables, respectively. The analysis was performed for the overall scores as well as separately for the components of the scores (cervical spine lateral view, lumbar spine lateral view, lumbar spine AP view). Additionally, a Bland and Altman plot was drawn and the smallest detectable change (SDC) was determined to assess the sensitivity to change of both methods (mSASSS and extended mSASSS). The SDC expresses the smallest change in scores that can be detected without measurement error, and it was calculated as follows:

$SDC = 1.96 \times SEM$,

where SEM denotes the standard error of measurement of the change score obtained from a two-way analysis of variance by taking the square root of the error variance [14].

To measure the sensitivity to change, we used the following definitions of progression: (1) change of the absolute score (calculated as means of the scores of both readers), (2) change of the score by ≥ 2 points after 2 years, (3) development of at least one new syndesmophyte (score of 0 or 1 at baseline and score of 2 or 3 after 2 years at the same vertebral corner in the opinion of both readers), and (4) development of new syndesmophytes (as described above) or growth of existing syndesmophytes (score of 2 at baseline and 3 after 2 years at the same vertebral corner) in the opinion of both readers. The sensitivity to change was evaluated in the entire group and in r-axSpA and nr-axSpA subgroups. We also analyzed both status and progression scores in the components of the mSASSS and the extended mSASSS (cervical spine lateral view, lumbar spine lateral view, lumbar spine AP view). A variance component analysis was performed.

Truth

The truth aspect addresses the question: "Is the measure truthful, does it measure what is intended? Is the result unbiased and relevant?" [13]. Earlier studies showed an association between the mSASSS and spinal mobility/functional status in axSpA [2–4]. With a linear regression analysis, we investigated the relationship between both scores and spinal mobility (assessed by the Bath Ankylosing Spondylitis Metrology Index—BASMI, an original two-step definition) and function (assessed by the Bath Ankylosing Spondylitis Functional Index—BASFI).

Statistical analysis was performed with IBM SPSS Statistics version 24 (IBM, Armonk, NY, USA) and SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

A total of 210 patients with axSpA, 115 with r-axSpA and 95 with nr-axSpA, were included in the analysis based on availability of the full sets of radiographs: lumbar (AP and lateral views) and cervical (lateral view) spine at baseline and after 2 years. Demographic, clinical, and radiographic data of the patients at baseline and year 2 are presented in Table 1.

Feasibility

In this study, lumbar AP radiographs were available in all 210 patients that was a requirement of the inclusion in the radiographic subset. Although AP lumbar radiograph is a routine projection in the clinical practice, it increases the costs of the radiographic investigation of the spine by approximately 50% and the time required for the reading according to the extended mSASSS by 50–100% (since additional 24 vertebral corners should be assessed) as compared to conventional mSASSS. Furthermore, AP lumbar radiographs are associated with additional radiation exposure, increasing the overall exposure associated with the assessment by approximately 60–70%.

Discrimination

The status scores and progression data for the both scores is presented in Table 2. The mean ± standard deviation (SD) score at baseline for the whole group included in the analysis was 8.59 ± 17.96 and 4.25 ± 8.32 for the extended mSASSS and conventional mSASSS, respectively. The absolute change score between baseline and year 2 was 1.19 ± 3.73 and 0.73 ± 2.34 for the extended mSASSS and conventional mSASSS, respectively (Table 2). In the separate analysis of the components of the score, the progression rates were comparable across the components (Table 3).

There was an excellent agreement between readers on the status scores with ICCs of 0.93 (95% CI 0.91–0.94) and 0.93 (95% CI 0.90–0.94) at baseline and 0.93 (95% CI 0.91–0.95) and 0.92 (95% CI 0.90–0.94) at year 2 for the extended and conventional mSASSS, respectively. The agreement for the change score was moderate with ICC of 0.45 (95% CI 0.33, 0.55) and 0.43 (95% CI 0.31, 0.53) for the extended and conventional mSASSS, respectively. For the outcome progression by ≥ 2 points after 2 years, there was a fair agreement for both methods: Cohen's kappa 0.20 (95% CI 0.06, 0.34) and 0.21 (95% CI 0.06, 0.36) for extended and conventional mSASSS, respectively. The agreement for development of new syndesmophytes was moderate with Cohen's

Table 1 Baseline demographic and clinical characteristics of the included patients with axial spondyloarthritis

Parameter	Non-radiographic axial SpA (*n* = 95)	Radiographic axial SpA (*n* = 115)	All patients (*n* = 210)
Age, mean ± SD years	38.7 ± 9.9	36.1 ± 11.0	37.3 ± 10.6
Symptom duration, mean ± SD years	3.1 ± 2.2	5.0 ± 2.8	4.2 ± 2.7
Duration since diagnosis, mean ± SD years	1.0 ± 1.3	2.0 ± 2.0	1.5 ± 1.8
Male sex, *n* (%)	32 (33.7)	75 (65.2)	107 (51.0)
HLA-B27 positive, *n* (%)	69 (73.4)	97 (84.3)	166 (79.4)
Peripheral arthritis, *n* (%)	16 (16.8)	15 (13.0)	31 (14.8)
Enthesitis†, *n* (%)	23 (24.2)	23 (20.0)	46 (21.9)
Uveitis, ever, *n* (%)	15 (15.8)	27 (23.5)	42 (20.0)
Psoriasis, ever, *n* (%)	11 (11.6)	17 (14.8)	28 (13.3)
Inflammatory bowel disease, ever, *n* (%)	1 (1.1)	3 (2.6)	4 (1.9)
Family history for SpA, *n* (%)	16 (16.8)	19 (16.5)	35 (16.7)
BASDAI, mean ± SD, 0–10	4.2 ± 2.0	3.8 ± 2.2	4.0 ± 2.1
BASFI, mean ± SD, 0–10	2.8 ± 2.2	3.0 ± 2.4	2.9 ± 2.3
Treatment with NSAIDs, *n* (%)	65 (68.4)	78 (67.8)	143 (68.1)
Treatment with csDMARDs, *n* (%)	26 (28.6)	35 (32.4)	61 (30.7)
Treatment with systemic steroids, *n* (%)	6 (6.7)	6 (5.6)	12 (6.1)
Treatment with a TNFα blocker, *n* (%)	1 (1.1)	4 (3.7)	5 (2.5)
Smoking, current, *n* (%)	24 (25.3)	39 (33.9)	63 (30.0)

† Twelve enthesitis sites of the lower limbs plus optional symptomatic sites elsewhere were assessed
BASDAI Bath Ankylosing Spondylitis Disease Activity Index, *BASFI* Bath Ankylosing Spondylitis Functional Index, *csDMARDs* conventional synthetic disease-modifying antirheumatic drugs, *NSAIDs* nonsteroidal antiinflammatory drugs, *SD* standard deviation, *SpA* spondyloarthritis, *TNFα* tumor necrosis factor α

Table 2 Status and change scores of mSASSS and extended mSASSS

	All patients (*n* = 210)		Radiographic axial SpA (*n* = 115)		Non-radiographic axial SpA (*n* = 95)	
	mSASSS	Extended mSASSS	mSASSS	Extended mSASSS	mSASSS	Extended mSASSS
Status score at baseline, mean ± SD	4.2 ± 8.3	8.6 ± 18.0	5.9 ± 10.3	12.8 ± 22.5	2.3 ± 4.2	3.5 ± 7.4
Status score at year 2, mean ± SD	5.0 ± 9.6	9.8 ± 20.0	6.8 ± 11.7	14.5 ± 24.9	2.8 ± 5.3	4.1 ± 8.9
Change score, mean ± SD	0.7 ± 2.3	1.2 ± 3.7	1.0 ± 2.8	1.7 ± 4.6	0.5 ± 1.6	0.6 ± 2.2
Smallest detectable change	4.1	6.4	4.7	7.5	3.3	4.6
Change score ≥ smallest detectable change, *n* (%)	14 (6.7)	12 (5.7)	7 (6.1)	8 (7.0)	4 (4.2)	6 (6.3)
Presence of syndesmophytes at baseline, *n* (%)	48 (22.9)	64 (30.5)	35 (30.4)	48 (41.7)	13 (13.7)	16 (16.8)
Presence of syndesmophytes at year 2, *n* (%)	50 (23.8)	65 (31.0)	36 (31.3)	50 (43.5)	14 (14.7)	15 (15.8)
Total number of syndesmophytes at baseline, mean ± SD	0.9 ± 2.6	1.9 ± 5.2	1.5 ± 3.3	3.2 ± 6.6	0.3 ± 1.1	0.5 ± 1.9
Total number of syndesmophytes at year 2, mean ± SD	1.1 ± 3.1	2.2 ± 6.0	1.7 ± 3.8	3.5 ± 7.6	0.4 ± 1.4	0.6 ± 2.4
Change score ≥ 2 points after 2 years, *n* (%)	30 (14.3)	44 (21.0)	23 (20.0)	35 (30.4)	7 (7.4)	9 (9.5)
Development of new syndesmophytes after 2 years, *n* (%)	16 (7.6)	20 (9.5)	13 (11.3)	17 (14.8)	3 (3.2)	3 (3.2)
Development of new /growth of existing syndesmophytes after 2 years, *n* (%)	18 (8.6)	23 (11.0)	15 (13.0)	20 (17.4)	3 (3.2)	3 (3.2)

mSASSS modified Stoke Ankylosing Spondylitis Spine Score, *SD* standard deviation

Table 3 Status and change scores of the components of the mSASSS and the extended mSASSS

	Cervical spine lateral view	Lumbar spine lateral view	Lumbar spine AP view
Change score ≥ 2 points after 2 years, *n* (%)	29 (13.8)	18 (8.6)	25 (11.9)
Total number of syndesmophytes at baseline, mean ± SD	0.5 ± 1.6	0.4 ± 1.5	1.0 ± 3.0
Total number of syndesmophytes at year 2, mean ± SD	0.6 ± 1.7	0.6 ± 1.8	1.1 ± 3.3
Development of new syndesmophytes after 2 years, *n* (%)	8 (3.8)	8 (3.8)	9 (4.4)
Development of new/growth of existing syndesmophytes after 2 years, *n* (%)	8 (3.8)	10 (4.8)	10 (4.8)

mSASSS includes scores of the cervical and lumbar lateral views; extended mSASSS includes additionally the lumbar spine AP view
AP anteroposterior, *mSASSS* modified Stoke Ankylosing Spondylitis Spine Score, *SD* standard deviation

kappa of 0.39 (95% CI 0.28, 0.57) and of 0.43 (95% CI 0.28, 0.57) for extended and conventional mSASSS, respectively. The agreement was moderate also for the outcome development of new syndesmophytes or growth of existing syndesmophytes with Cohen's kappa of 0.44 (95% CI 0.29, 0.58) and 0.42 (95% CI 0.29, 0.55) for the extended and conventional mSASSS, respectively. An analysis of the score components revealed a comparable variability of the scores obtained in the cervical spine and in both planes of the lumbar spine (Table 4). The variance component analysis revealed that the patient-related variance contributed most to the total variance of both mSASSS and extended mSASSS score (Table 5); the same finding was observed when the variance of score components was analyzed separately (Table 6).

The Bland and Altman plots illustrating the inter-reader reliability of the extended and conventional scores are presented in Fig. 1. The SDC was higher for the extended mSASSS than for the conventional one (Table 2). Regarding the presence of syndesmophytes in the opinion of both readers at baseline, extended mSASSS detected syndesmophytes in 64 patients (30.5%) and conventional mSASSS in 48 patients (22.9%); the mean total number of syndesmophytes at baseline was 1.92 ± 5.24 and 0.94 ± 2.61 for the extended mSASSS and conventional mSASSS, respectively. Importantly, the extended mSASSS detected new syndesmophytes in 4 additional patients, new syndesmophytes or progression of existing syndesmophytes in 5 additional patients, and progression by ≥ 2 units in the total score in 14 additional patients meaning a 25%, 28%, and 46% increase in the proportion of patients with progression according to the respective definition as compared to the conventional mSASSS (Table 2).

When the two subgroups of patients (r-axSpA and nr-axSpA) were analyzed separately, the mean ± SD score at baseline as well as progression rates over 2 years were lower in the nr-axSpA group for both scoring systems (Table 2).

Truth

In the univariable analysis, both extended and conventional mSASSS were significantly associated with BASMI and BASFI (Table 7). In the multivariable analysis that was adjusted for disease activity parameters (BASDAI and CRP), the association of both scores with spinal mobility/function remained significant (Table 7).

Discussion

In the present study, we evaluated the added value of incorporation of AP lumbar radiographs in the mSASSS scoring system for the assessment of structural damage in the spine in patients with axSpA. The extended mSASSS showed a good reliability and provided some improvement of the detection of radiographic spinal

Table 4 Inter-observer reliability of the components of the mSASSS and the extended mSASSS

	Cervical spine lateral view	Lumbar spine lateral view	Lumbar spine AP view
ICC for the status score at baseline	0.91 (0.88, 0.93)	0.91 (0.88, 0.93)	0.86 (0.83, 0.90)
ICC for the status score at year 2	0.86 (0.82, 0.89)	0.92 (0.90, 0.94)	0.88 (0.84, 0.90)
ICC for the change score	0.49 (0.39, 0.59)	0.43 (0.32, 0.54)	0.30 (0.19, 0.44)
Kappa for the change score ≥ 2 points after 2 years	0.13 (− 0.04, 0.29)	0.38 (0.18, 0.57)	0.36 (0.18, 0.54)
Kappa for the development of new syndesmophytes after 2 years	0.38 (0.20, 0.55)	0.59 (0.42, 0.77)	0.40 (0.24, 0.57)
Kappa for the development of new/growth of existing syndesmophytes after 2 years	0.34 (0.17, 0.52)	0.62 (0.46, 0.79)	0.48 (0.32, 0.64)

Data are presented as intraclass correlation coefficient (ICC) and Cohen's kappa coefficient to measure the inter-observer reliability for continuous and categorical variables, respectively, with a 95% CI
AP anteroposterior, *mSASSS* modified Stoke Ankylosing Spondylitis Spine Score, *CI* confidence interval, *ICC* intraclass correlation coefficient

Table 5 Inter-observer reliability of the mSASSS and the extended mSASSS, expressed in variance components

	Status score at baseline			Status score at year 2			Change score		
	Residual variance component	Observer variance component	Patient variance component	Residual variance component	Observer variance component	Patient variance component	Residual variance component	Observer variance component	Patient variance component
mSASSS	7.45	0.03	92.52	7.95	0.05	92.00	57.42	0.00	42.58
Extended mSASSS	7.28	0.01	92.71	6.67	0.00	93.33	54.99	0.00	45.01

mSASSS modified Stoke Ankylosing Spondylitis Spine Score

progression in patients with axSpA as compared to the conventional mSASSS that has to be weighed against additional costs, additional radiation exposure (although AP lumbar radiographs are often performed routinely), and additional time investment associated with reading of additional 24 vertebral corners.

Extended mSASSS can be considered as supplementary to the conventional mSASSS as it adds information from the AP lumbar spine view. The information obtained from the AP lumbar radiograph can also be to some extent redundant, since the same structural damage (same syndesmophyte) can be visible on both lateral and AP views. This fact explains, for instance, a larger difference in status scores (the extended mSASSS was double as high as the conventional one) than in percentages of patients with syndesmophytes (30.5% with extended mSASSS vs. 22.9% with conventional mSASSS at baseline).

The most relevant question is, however, if the extended mSASSS is able to detect patients with radiographic spinal progression not captured by the conventional method. Indeed, with the extended mSASSS, new syndesmophytes after 2 years were detected in 4 additional patients, new syndesmophytes or growth of existing syndesmophytes in 5 additional patients, and progression by ≥ 2 points in the total score in 14 additional patients that gave a 25%, 28%, and 46% increase in the proportion of patients with progression according to the respective definition as compared to the conventional score. These proportions were even higher in patients with r-axSpA meaning that in more advanced disease the added value of the lumbar AP assessment might be greater than in early disease [15]. In our analysis, the subgroup of patients with r-axSpA had a higher level of structural damage at baseline and higher progression rates after 2 years compared to nr-axSpA patients. At the same time, in advanced disease with extended ankylosis, one can expect a larger extent of structural damage that would be captured on both lateral and AP views that might result into a reduction of the added value of the AP lumbar radiographs.

The extended mSASSS—similarly to the conventional mSASSS—captures only a part of the structural damage visible on radiographs. Syndesmophytes with posterior localization or in the lateral aspects of the cervical spine, as well as involvement of posterior structures (i.e., facet joints), are not captured by any score. In the majority of cases, however, structural damage develops more or less simultaneously in different aspects of the spinal column that allows the assumption that the mSASSS/extended mSASSS is as a proxy for the overall structural damage in the spine. In the univariable and multivariable regression analyses, both scores showed a significant association with spinal mobility (BASMI) and function (BASFI) that confirms the construct validity of both scores as parameters truly reflecting structural damage in the spine in axSpA. A potentially important limitation of any radiographs is the exclusion of the thoracic spine from scoring due to anatomical overlap with other thoracic structures. However, active inflammatory [16]

Table 6 Inter-observer reliability of the components of the mSASSS and the extended mSASSS, expressed in variance components

	Cervical spine lateral view			Lumbar spine lateral view			Lumbar spine AP view		
	Residual variance component	Observer variance component	Patient variance component	Residual variance component	Observer variance component	Patient variance component	Residual variance component	Observer variance component	Patient variance component
Status score at baseline	8.87	0.06	91.07	9.05	0.00	90.95	13.23	0.22	86.55
Status score at year 2	13.71	0.19	86.10	7.49	0.00	92.51	12.14	0.13	87.73
Change score	50.49	0.18	49.33	57.11	0.00	42.89	69.54	0.00	30.46

AP anteroposterior, *mSASSS* modified Stoke Ankylosing Spondylitis Spine Score

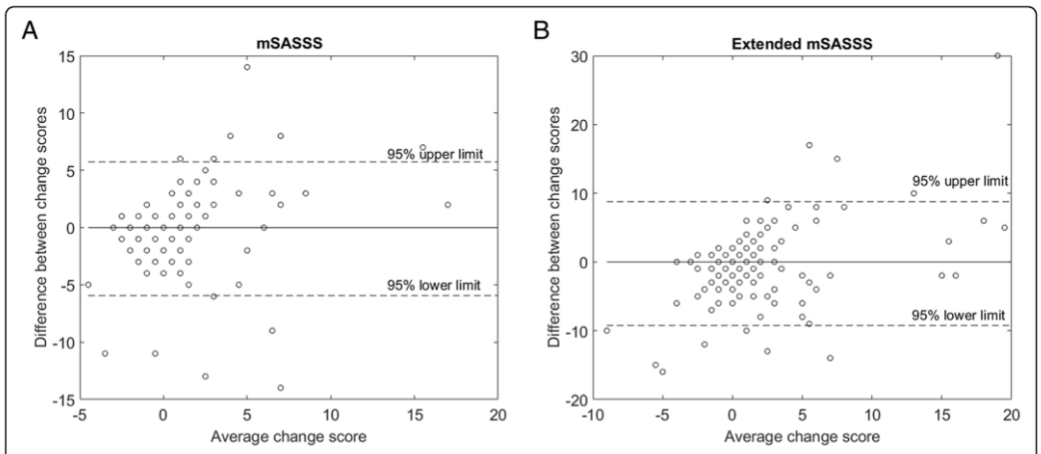

Fig. 1 Bland and Altman plots for mSASSS (**a**) and extended mSASSS (**b**)

and structural changes [17] seem to occur here at least as frequent as in other spine regions. For this reason, another modification of the mSASSS was proposed by Baraliakos et al: the Radiographic AS Spinal Score (RASSS), which adds to the mSASSS the score of the lower thoracic vertebrae (T10–T12), under the hypothesis that most of progression is found in these segments, and the quantification of new bone formation is superior to the conventional mSASSS [18]. Nevertheless, a recent study that compared the mSASSS with the RASSS [19] concluded the limitation of the RASSS in the feasibility aspect (in 64% of radiographs of the lumbar spine, the lower thoracic vertebrae were not visible, and therefore, the RASSS could not be calculated). Due to low reliability, no thoracic spine radiographs and no AP cervical radiographs were collected in GESPIC for the assessment of structural damage.

Other imaging methods without technical limitations of plain radiographs—such as low-dose computed tomography (CT)—have a potential to become the primary methods of radiographic spinal progression in axSpA in the future [17].

Conclusions

The incorporation of the AP radiographs of the lumbar spine in the assessment of structural damage in the spine provides improvement of detection of radiographic spinal progression in axSpA.

Abbreviations

AP: Anteroposterior; AS: Ankylosing spondylitis; axSpA: Axial spondyloarthritis; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; BASMI: Bath Ankylosing Spondylitis Metrology Index; BASRI: Bath Ankylosing Spondylitis Radiology Index; CI: Confidence interval; CRP: C-reactive protein; CT: Computed tomography; GESPIC: GErman SPondyloarthritis Inception Cohort; ICCs: Intraclass correlation coefficients; mNY: Modified New York; mSASSS: Modified Stoke Ankylosing Spondylitis Spine Score; nr-axSpA: Non-radiographic axial spondyloarthritis; OMERACT: Outcome Measures in Rheumatology; r-axSpA: Radiographic axial spondyloarthritis; SD: Standard deviation; SDC: Smallest detectable change; SEM: Standard error of measurement; TNFi: Tumor necrosis factor inhibitor

Table 7 Association between mSASSS or extended mSASSS score with BASFI or BASMI at baseline in the linear regression analysis

	Univariable analysis	Multivariable model 1*	Multivariable model 2*
	β (95% CI)	*β* (95% CI)	*β* (95% CI)
Outcome: BASFI			
mSASSS	0.046 (0.008, 0.083)	0.033 (0.010, 0.056)	–
Extended mSASSS	0.021 (0.003, 0.038)	–	0.014 (0.004, 0.025)
Outcome: BASMI			
mSASSS	0.093 (0.068, 0.117)	0.082 (0.059, 0.106)	–
Extended mSASSS	0.045 (0.034, 0.056)	–	0.040 (0.029, 0.050)

*Adjusted for BASDAI and CRP at baseline

BASDAI Bath Ankylosing Spondylitis Disease Activity Index, *BASFI* the Bath Ankylosing Spondylitis Functional Index, *BASMI* Bath Ankylosing Spondylitis Metrology Index, *mSASSS* modified Stoke Ankylosing Spondylitis Spine Score

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Availability of data and materials
For information of the availability of the data included in the GESPIC database, contact Prof. Dr. Poddubnyy.

Declarations
We confirm that the article has not been published before and is not under consideration for publication elsewhere, and that it has been approved by all authors.

Authors' contributions
ML, VR, and IR contributed to the data analysis and interpretation and drafting of the manuscript. JS and MR contributed to the initiation of GESPIC, data collection, data interpretation, and drafting of the manuscript. HH contributed to the data collection, data interpretation, and drafting of the manuscript. DP contributed to the data collection, analysis and interpretation, and drafting of the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate
All patients signed an informed consent to participate in GESPIC, and the study was approved by the central ethics committee.

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Not applicable.

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Chapter 6

2. Assessment of radiographic sacroiliitis in antero-posterior lumbar versus conventional pelvic radiographs in axial spondyloarthritis

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Original article

Assessment of radiographic sacroiliitis in anteroposterior lumbar *vs* conventional pelvic radiographs in axial spondyloarthritis

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Abstract

Objective. The aim was to investigate the reliability and validity of radiographic sacroiliitis assessment in anteroposterior (AP) lumbar radiographs compared with conventional pelvic radiographs in patients with axial spondyloarthritis (axSpA).

Methods. Patients from the German Spondyloarthritis Inception Cohort were selected based on the availability of pelvic and AP lumbar radiographs with visible SI joints at baseline and year 2. Two readers scored the images independently in a random order according to the modified New York criteria. The sacroiliitis sum score was calculated as the mean of both readers. Patients were classified as radiographic (r-)axSpA if radiographic sacroiliitis of grade $\geq$2 bilaterally or grade $\geq$3 unilaterally was present in the opinion of both readers and as non-radiographic (nr-)axSpA otherwise. The reliability and validity of sacroiliitis assessment in AP lumbar radiographs was assessed using intraclass correlation coefficients (ICCs), absolute agreement and κ statistics.

Results. A total of 226 sets of radiographs were scored from 113 patients included in the study. The ICC for the sacroiliitis sum score was 0.91 at both baseline and year 2. A total of 62 (54.9%) and 55 (48.7%) patients were classified as r-axSpA at baseline and 65 (57.5%) and 60 (53.1%) patients at year 2 based on evaluation of pelvic and AP lumbar radiographs, respectively. The absolute agreement between the methods on the classification was 84.9 and 85.0% at baseline and year 2, respectively, with the κ of 0.70 at both time points.

Conclusion. Radiographic sacroiliitis can be assessed in AP lumbar radiographs with a similar reliability to conventional pelvic radiographs.

Key words: axial spondyloarthritis, ankylosing spondylitis, sacroiliitis, radiograph, sacroiliac joint

Introduction

The evaluation of SI joints is essential for the diagnosis and classification of axial spondyloarthritis (axSpA). The standard method to assess structural damage in the SI joints, such as sclerosis, erosions, joint space widening/narrowing and partial/total ankylosis, is still the conventional pelvic radiograph [1]. The pelvic radiograph is also the reference technique to score the severity of sacroiliitis according to the modified New York (mNY) criteria [2]. Depending on the presence or absence of definite radiographic sacroiliitis, axSpA is classified as radiographic (r-axSpA) or non-radiographic (nr-axSpA).

Reading radiographs of the SI joints can be challenging because of the complexity of the pelvic anatomy, the oblique orientation of the SI joints and the interference of overlying bowel gas and soft tissues. These difficulties lead to poor intra- and inter-reader reliability [3], and variations remain large, without improvement, even when readers have received targeted training [4]. It seems particularly challenging to score early lesions in the SI joints, specifically grades 1 or 2 according to the mNY criteria [4].

Newer imaging techniques, such as CT and MRI, are gaining more relevance for detection of abnormalities in SI joints [5]. CT is considered the gold standard for the

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CLINICAL SCIENCE

Rheumatology key messages

- Radiographic assessment of SI joints remains the first-line imaging method if axial spondyloarthritis is suspected.
- Anteroposterior lumbar radiographs can be used to assess SI joints if they are well depicted.
- There is a good agreement between both radiographic techniques on detection of definite radiographic sacroiliitis.

detection of structural SI joint lesions, but it is associated with high radiation exposure [6]. Over recent years, MRI has been widely accepted for the detection of active inflammatory lesions of the SI joints [1]. Nevertheless, the value of MRI for detection of structural damage in SI joints is still under investigation [7, 8].

Previous studies have compared several methods of SI joint radiography: conventional pelvic radiograph, oblique SI joint view and the Ferguson view; this last one is a modified AP pelvic radiograph with the central rays angled 30° caudally. None of them has shown strong evidence to support the use of specific SI joint views over the standard conventional pelvic radiograph for the diagnosis and grading of sacroiliitis [9, 10].

In the standard AP lumbar radiograph, SI joints are often depicted and available for assessment [11]. Although this view is often performed as a part of the diagnostic work-up in patients suffering from back pain, it is not clear whether sacroiliitis can be assessed reliably on an AP lumbar radiograph. The aim of our study was to investigate the reliability and validity of radiographic assessment of sacroiliitis in the AP lumbar radiograph compared with the conventional pelvic radiograph in patients with axSpA.

Methods

Patient selection

Patients from the German Spondyloarthritis Inception Cohort (GESPIC) were selected based on the availability of sets of pelvic and AP lumbar radiographs with visible SI joints at baseline and after 2 years of follow-up.

All patients included in the GESPIC had a clinical diagnosis of axSpA according to the local rheumatologist, restricting the duration of symptoms to $\leq$10 years for r-axSpA and to $\leq$5 years for nr-axSpA [12].

The study protocol was approved by the central ethics committee of the coordinating centre (Charité Universitätsmedizin, Campus Benjamin Franklin, Berlin, Germany) and by all local ethics committees of the participating centres. Written informed consent was obtained from all patients.

Radiographic assessment

Pelvic and AP lumbar radiographs were obtained at baseline and after 2 years of follow-up. The images were centrally collected, digitized and anonymized. The selection of AP lumbar radiographs was done by one of the readers (M.L.) based on the presence of all relevant anatomical structures (both SI joints, sacral and iliac subchondral bone and the entire joint space).

Two trained and calibrated readers (V.R.R. and M.L.), who were blinded to all clinical data and time points, scored the SI joints from pelvic and AP lumbar images independently in a concealed and randomly selected order according to the grading system of the mNY criteria [2]: grade 0=normal; grade 1=suspicious changes; grade 2=minimal abnormality (small localized areas with erosion or sclerosis, without alteration in the joint width); grade 3=unequivocal abnormality (moderate or advanced sacroiliitis with erosions, evidence of sclerosis, widening, narrowing or partial ankylosis); and grade 4=severe abnormality (total ankylosis). Readers could mark a joint as 'not evaluable' if no judgement on the sacroiliitis grade could be made due to lack of visibility of the joint.

Patients were classified as r-axSpA if both readers independently recorded the presence of definite radiographic sacroiliitis, defined as at least grade 2 bilaterally or at least grade 3 unilaterally. Otherwise, patients were classified as nr-axSpA.

Statistical analysis

For the analysis, the sacroiliitis sum score (0–8) was calculated as a sum of grades for the left and right SI joints for each patient. An average of scores of both readers was calculated for each patient at each time point. We assessed intra- and inter-reader variability of the assessment using the intraclass correlation coefficients (ICCs) for both SI joints and for the sacroiliitis sum score and the weighted Cohen's κ coefficient for the classification as nr- or r-axSpA. The interpretation for ICC values was as follows: values $<$0.50 are indicative of poor, 0.50–0.75 moderate, 0.75–0.90 good and $>$0.90 excellent reliability [13]. The values for Cohen's κ coefficient were interpreted as follows: values $\leq$0.20 none to poor, 0.21–0.40 fair, 0.40–0.60 moderate, 0.61–0.80 good and 0.81–1.00 excellent agreement [14]. Additionally, the percentage of absolute agreement on classification was calculated.

For the assessment of radiographic sacroiliitis progression, we used the following definitions: (i) absolute change in the mean sacroiliitis sum score; (ii) progression of at least one grade in at least one SI joint in the opinion of both readers; and (iii) progression from nr-

axSpA to r-axSpA in the opinion of both readers. For definitions (ii) and (iii), corresponding rates of regression were calculated. We analysed the reliability of the detection of progression by the ICC for the absolute change scores and by the absolute agreement in addition to κ statistics for the binary outcomes.

No specific power calculation analysis was performed for this exploratory study.

Statistical analysis was performed using SPSS v.25 (IBM Corp., Armonk, NY, USA).

Results

From the 210 previously described patients [15], 97 patients were excluded upfront owing to the lack of visibility of the SI joints in one or both sides of the AP lumbar radiographs at baseline or year 2. Thus, a total of 452 pelvic and AP lumbar radiographs (226 sets of radiographs) from the 113 patients included in the present study were evaluated by readers. All joints could be assessed according to the grading system described above. Table 1 summarizes the demographic and clinical characteristics of the included patients at baseline, which were similar to the characteristics of 210 patients reported previously [16].

Intra-reader variability of assessment of radiographic sacroiliitis

The intra-reader agreement for the sacroiliitis sum score was good between pelvic and AP lumbar radiographs at baseline (V.R.R.: ICC = 0.85, 95% CI: 0.78, 0.90; and M.L.: ICC = 0.89, 95% CI: 0.84, 0.93) and year 2 (V.R.R.: ICC = 0.77, 95% CI: 0.69, 0.84; and M.L.: ICC = 0.81, 95% CI: 0.73, 0.86). The absolute agreement between both radiographic projections with regard to the presence of the definite radiographic sacroiliitis according to the mNY criteria was 75.2 and 81.4% for V.R.R. (κ = 0.50, 95% CI: 0.28, 0.62; and κ = 0.59, 95% CI: 0.44, 0.75) and 84.1 and 85.4% for M.L. (κ = 0.67, 95% CI: 0.53, 0.81; and κ = 0.70, 95% CI: 0.56, 0.83) at baseline and year 2, respectively. The ICCs at the level of single SI joints are presented in Supplementary Table S1, available at *Rheumatology* online.

Table 1 Baseline demographic and clinical characteristics of patients with axial spondyloarthritis ($n = 113$) from the German Spondyloarthritis Inception Cohort

Variable	Value
Age, mean (S.D.), years	38.1 (11.5)
Symptom duration, mean (S.D.), years	3.9 (2.7)
Duration since diagnosis, mean (S.D.), years	1.2 (1.5)
Male sex, *n* (%)	53 (46.9)
HLA-B27 positive, *n* (%)	87 (7.0)
Peripheral arthritis, *n* (%)	21 (18.6)
Enthesitis[a], *n* (%)	24 (21.2)
Uveitis, ever, *n* (%)	22 (19.5)
Psoriasis, ever, *n* (%)	14 (12.4)
Inflammatory bowel disease, ever, *n* (%)	3 (2.7)
Family history for SpA, *n* (%)	26 (23)
BASDAI, mean (S.D.), 0–10	3.9 (2.2)
BASFI, mean (S.D.), 0–10	2.7 (2.2)
Treatment with NSAIDs, *n* (%)	76 (67.3)
Treatment with csDMARDs, *n* (%)	32 (28.3)
Treatment with systemic CSs, *n* (%)	9 (8)
Treatment with a TNF-α blocker, *n* (%)	1 (0.9)
Smoking, current, *n* (%)	30 (26.5)
CRP, mean (S.D.), mg/l	8.9 (13.6)

[a]Twelve enthesitis sites of the lower limbs plus optional symptomatic sites elsewhere were assessed. csDMARDs: conventional synthetic DMARDs; SpA: spondyloarthritis.

Inter-reader variability of radiographic sacroiliitis assessment

For the sacroiliitis sum sore, the inter-reader agreement was good for both radiographic views assessed at baseline and year 2 (Table 2). There was a moderate to good agreement between the readers on the presence of definite radiographic sacroiliitis according to the mNY criteria for both radiographic views at baseline and year 2 (Table 2). The ICCs at the level of single SI joints are presented in Supplementary Table S2, available at *Rheumatology* online.

Reliability of radiographic sacroiliitis assessment in AP lumbar compared with conventional pelvic radiographs

The agreement on the radiographic sacroiliitis grade (sacroiliitis sum score) between conventional pelvic and AP lumbar radiographs was excellent at baseline and year 2: ICC 0.91 for both time points (Table 3). A total of 62 (54.9%) and 55 (48.7%) patients fulfilled the radiographic criterion of the mNY criteria in the opinion of both readers at baseline, and 65 (57.5%) and 60 (53.1%) patients fulfilled this criterion at year 2 based on evaluation of pelvic and AP lumbar radiographs, respectively. The absolute agreement between both views with regard to the classification was 84.9 and 85.0% at baseline and year 2, respectively, with a κ of 0.70 for both time points (Table 3 and Fig. 1).

Figure 2 presents an example of lumbar AP and conventional pelvic radiographs both depicting radiographic sacroiliitis in a patient with axSpA.

Reliability of assessment of radiographic sacroiliitis progression between conventional pelvic and AP lumbar radiographs

After 2 years of follow-up, the absolute change in sacroiliitis sum score showed a rather low progression, with a mean (S.D.) of 0.07 (0.81) for the conventional pelvic radiographs and 0.13 (0.66) for the AP lumbar radiographs, with an ICC of 0.36 (95% CI: 0.08, 0.56).

Progression of radiographic sacroiliitis by at least one grade in the opinion of both readers occurred in 12 (10.6%) and 10 (8.9%) patients based on the assessment of conventional pelvic and AP lumbar radiographs,

TABLE 2 Inter-reader variability of radiographic sacroiliitis assessment in conventional pelvic and AP lumbar radiographs ($n = 113$)

	Conventional pelvic radiographs				AP lumbar radiographs			
	Reader: V.R.R.	Reader: M.L.	Absolute agreement, %	ICC/κ^a (95% CI)	Reader: V.R.R.	Reader: M.L.	Absolute agreement, %	ICC/κ^a (95% CI)
Baseline								
Sacroiliitis sum score (0–8), mean (S.D.)	4.12 (2.05)	4.05 (1.95)	N/A	0.89 (0.85, 0.93)	4.01 (2.00)	4.04 (1.89)	N/A	0.84 (0.77, 0.89)
Fulfilment of the radiographic criterion of the mNY criteria, *n* (%)	80 (70.8)	67 (59.3)	79.7	0.56 (0.40, 0.71)	70 (61.9)	65 (57.5)	77.9	0.54 (0.38, 0.70)
Year 2								
Sacroiliitis sum score (0–8) mean (S.D.)	4.19 (2.33)	4.12 (2.08)	N/A	0.87 (0.81, 0.91)	4.04 (2.13)	4.26 (2.03)	N/A	0.88 (0.82, 0.92)
Fulfilment of the radiographic criterion of the mNY criteria, *n* (%)	77 (68.1)	73 (64.6)	82.3	0.60 (0.45, 0.76)	70 (61.9)	69 (61.1)	83.2	0.66 (0.50, 0.79)

[a]ICC for the sacroiliitis sum score and κ for the fulfilment of the radiographic criterion of the mNY criteria. AP: anteroposterior; ICC: intraclass correlation coefficient; mNY criteria: modified New York criteria; N/A: not applicable.

respectively. At the same time, there was regression of radiographic sacroiliitis by at least one grade in the opinion of both readers in nine (8.0%) and three (2.7%) patients for conventional pelvic and AP lumbar radiographs, respectively. The absolute agreement between the assessments of both radiographic views for progression/regression by at least one grade was 72.6% (Table 4).

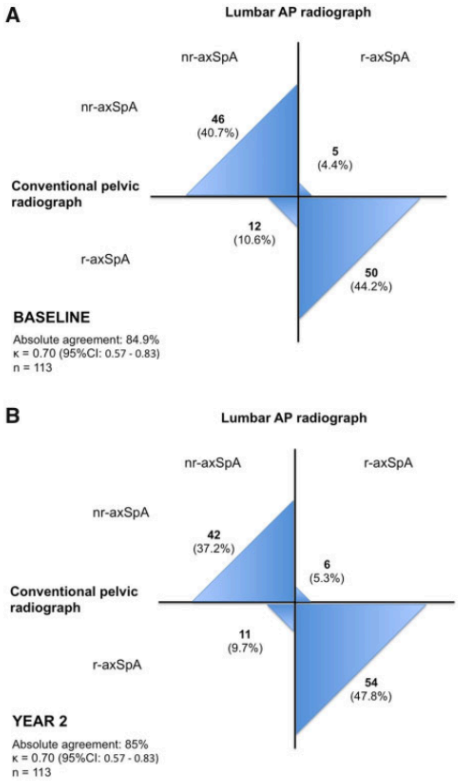
Progression from nr-axSpA to r-axSpA by fulfilment of the radiographic criterion of the mNY criteria in the opinion of both readers occurred in seven (6.2%) and eight (7.1%) patients based on the assessment of conventional pelvic and AP lumbar radiographs, respectively. At the same time, there was regression to nr-axSpA in four (3.5%) and three (2.7%) patients for conventional pelvic and AP lumbar radiographs, respectively. The net percentage of progression from nr-axSpA to r-axSpA, understood as the difference in the number of patients who experienced worsening and improvement divided by the total number in the study population [17, 18], was 2.7 and 4.4% for conventional pelvic and AP lumbar radiographs, respectively. The absolute agreement between the assessments of both radiographic views for progression was 84.1% (Table 4).

Discussion

Radiographic sacroiliitis is usually assessed on conventional pelvic radiographs. Given the complex anatomy of the SI joints, several dedicated techniques, such as the Ferguson view and oblique views of each SI joint, have been proposed to improve the reliability and validity of radiographic assessment of sacroiliitis. Despite some theoretic advantages, none of the dedicated views could show a significant improvement in the detection of sacroiliitis over the conventional pelvic radiographs [10]. At the same time, SI joints are often available for assessment of sacroiliitis on AP lumbar radiographs, which are frequently performed routinely in patients with unclear back pain. In the present study, we compared radiographic assessment of sacroiliitis on conventional pelvic radiographs and AP lumbar radiographs in patients with axSpA. Our findings indicated good agreement overall between both radiograph techniques (in 85% of the cases, patients received the same classification as nr-axSpA or r-axSpA at baseline and year 2, and in ∼84% of the cases the same progression status over 2 years was recorded), with very similar inter-reader variability.

One of the frequent concerns related to radiographs is radiation exposure. In our case, both modalities have a similar effective dose of radiation of ∼0.7 mSv [19, 20]. In daily clinical practice, an AP lumbar radiograph is often obtained together with the lumbar lateral view to evaluate damage of the lumbar spine. Thus, one could avoid unnecessary exposure to radiation if SI joints could be assessed on the AP lumbar radiograph. However, a conventional pelvic radiograph remains the method of choice as first-line imaging in the case of

FIG. 1 Classification as non-radiographic or radiographic spondyloarthritis by fulfilment of modified New York radiographic criteria in the opinion of both readers



suspicion of axial SpA and should not be substituted automatically by a lumbar radiograph.

Obviously, hip joints, which may be involved in SpA [21], cannot be assessed on AP lumbar radiographs in contrast to conventional pelvic radiographs. For patients at risk of hip involvement (e.g. patients with suggestive symptoms), it could be more convenient to perform the pelvic radiograph instead or in addition to the AP lumbar one.

Our study has several limitations. Firstly, not all patients from GESPIC could be included in the present study as a result of the (un)availability of the appropriate radiographs. Indeed, in 97 of 210 patients, SI joints were partly or completely missing on lumbar AP radiographs, which resulted in exclusion of these patients from the analysis. This point has an important practical implication, meaning that in daily clinical practice the SI joints cannot be assessed on lumbar radiographs in ~50% of cases. This indicates that in a new patient with suspicion of axial SpA, conventional pelvic radiography should remain the method of choice for the first-line imaging assessment of SI joints, whereas a lumbar AP radiograph can be used for assessment of the SI joint only if already available and only if the SI joints are well depicted.

Secondly, we used a cohort of patients already diagnosed with axSpA. Although only about half of the patients had definite radiographic sacroiliitis, it is possible that the performance of AP lumbar radiographs would be different if used for the primary diagnostic purpose in patients with back pain and suspicion of axSp.A. However, for the classification (nr-axSpA or r-axSpA) and for the radiographic assessment of sacroiliitis progression in patients with known axSpA, the AP lumbar radiographs have performed reasonably well.

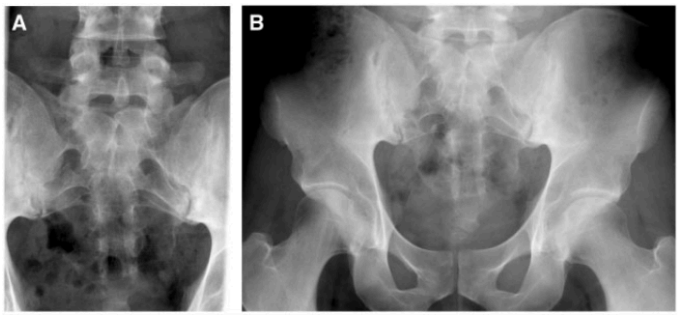
Finally, we used conventional pelvic radiographs, a method known to have poor reliability, as a reference method. CT is currently considered to be the gold-standard technique for the detection of structural

TABLE 3 Reliability of assessment of radiographic sacroiliitis on AP lumbar compared with conventional pelvic radiographs ($n = 113$)

	Conventional pelvic radiographs	AP lumbar radiographs	Absolute agreement, %	ICC/κ[a] (95% CI)
Baseline				
Mean sacroiliitis sum score (0–8), mean (S.D.)	4.09 (1.90)	4.02 (1.81)	N/A	0.91 (0.87, 0.94)
Fulfilment of the radiographic criterion of the mNY criteria in the opinion of both readers, *n* (%)	62 (54.9)	55 (48.7)	84.9	0.70 (0.57, 0.83)
Year 2				
Mean sacroiliitis sum score (0–8), mean (S.D.)	4.15 (2.07)	4.15 (1.96)	N/A	0.91 (0.88, 0.94)
Fulfilment of the radiographic criterion of the mNY criteria in the opinion of both readers, *n* (%)	65 (57.5)	60 (53.1)	85.0	0.70 (0.56, 0.83)

[a]ICC for the sacroiliitis sum score and κ for the fulfilment of the radiographic criterion of the mNY criteria. AP: anteroposterior; ICC: intraclass correlation coefficient; mNY criteria: modified New York criteria.

FIG. 2 An example of radiographic sacroiliitis in two different views of the same patient



(**A**) Anteroposterior lumbar radiograph. (**B**) Conventional pelvic radiograph. Both radiographs show definite subchondral sclerosis, erosive changes and narrowing of the joint space in both SI joints, scored as bilateral sacroiliitis of grade 3.

TABLE 4 Progression and regression of radiographic sacroiliitis after 2 years, in the opinion of both readers ($n = 113$)

		AP lumbar radiograph		
		Progression, *n* (%)	**No change, *n* (%)**	**Regression, *n* (%)**
Progression by at least one grade in one SI joint				
Conventional pelvic radiograph	Progression	**1 (0.9)**	10 (8.9)	1 (0.9)
	No change	9 (8.0)	**81 (71.7)**	2 (1.8)
	Regression	0 (0)	9 (8.0)	**0 (0)**
Fulfilment of the radiographic criterion of the modified New York criteria				
Conventional pelvic radiograph	Progression	**2 (1.8)**	5 (4.4)	0 (0)
	No change	6 (5.3)	**93 (82.3)**	3 (2.7)
	Regression	0 (0)	4 (3.5)	**0 (0)**

AP: anteroposterior.

damage in the SI joint (radiographic sacroiliitis), although it is rarely used as the primary diagnostic method because of the lower feasibility in clinical practice and higher radiation exposure [6]. In recent years, low-dose CT, which has a radiation exposure similar to conventional radiography, has been established for the assessment of structural damage in the SI joints [5, 22]. Furthermore, MRI of the SI joints is currently being evaluated for the detection and scoring not only of bone marrow oedema but also for structural lesions, although not yet with a final agreement on thresholds [5, 8]. Nonetheless, conventional radiography of SI joints still often serves as the first imaging method in the case of suspicion of axSpA owing to its wider availability and lower costs compared with CT and MRI [1, 23]. Therefore, it was reasonable to compare the performance of AP lumbar radiographs with the current standard, conventional pelvic radiographs, even in the absence of the external reference.

In conclusion, the results presented here indicate that radiographic sacroiliitis can be assessed in a lumbar AP radiograph with a similar reliability and validity as in conventional pelvic radiograph in patients with axSpA if SI joints are well depicted.

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Supplementary data

Supplementary data are available at *Rheumatology* online.

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SUPPLEMENTARY DATA

Table S1. Inter-method ICCs of the radiographic sacroiliitis grades for the left and right sacroiliac joints as assessed by VRR and ML at baseline and year 2.

Joint, timepoint	***ICC (95% CI)***
Reader 1 (VRR)	
Left sacroiliac joint, baseline	0.68 (0.56-0.77)
Right sacroiliac joint, baseline	0.63 (0.50-0.73)
Left sacroiliac joint, year 2	0.78 (0.70-0.84)
Right sacroiliac joint, year 2	0.71 (0.61-0.79)
Reader 2 (ML)	
Left sacroiliac joint, baseline	0.78 (0.69-0.84)
Right sacroiliac joint, baseline	0.74 (0.64-0.81)
Left sacroiliac joint, year 2	0.80 (0.73-0.86)
Right sacroiliac joint, year 2	0.77 (0.68-0.83)

Table S2. Inter-reader ICCs of the radiographic sacroiliitis grades for the left and right sacroiliac joints at baseline and year 2 on pelvic and lumbar AP radiographs.

Joint, timepoint	**ICC (95% CI)**
Conventional pelvic radiographs	
Left sacroiliac joint, baseline	0.75 (0.65-0.82)
Right sacroiliac joint, baseline	0.79 (0.71-0.85)
Left sacroiliac joint, year 2	0.76 (0.68-0.83)
Right sacroiliac joint, year 2	0.77 (0.69-0.84)
Lumbar AP radiographs	
Left sacroiliac joint, baseline	0.68 (0.57-0.77)
Right sacroiliac joint, baseline	0.69 (0.58-0.77)
Left sacroiliac joint, year 2	0.67 (0.56-0.76)
Right sacroiliac joint, year 2	0.79 (0.71-0.85)

Chapter 7

Summary and General Discussion

DISCUSSION

In the present work we aim to confirm our hypothesis which states that AP lumbar radiograph has added value for the assessment of structural damage progression in axSpA patients. To answer this question, we conducted two studies: the first focused on radiographic assessment of structural progression of the spine and the second looked at assessing structural progression on SIJs. In both studies, patients with axSpA from the GErman SPondyloarthritis Inception Cohort (GESPIC) were included, based on the availability of clinical data and radiographs at baseline and year 2. Patients included in GESPIC had a definite clinical diagnosis of axSpA according to the treating rheumatologist with symptom duration of up to 5 years for the non-radiographic form and up to 10 years for the radiographic form of axSpA. The final classification as nr-axSpA or r-axSpA was performed based on the central reading of the radiographs.

A major concern in the SpA field is the development of new bone formation in the spine due to its contribution to disease severity and to determine whether drugs are effective in inhibiting structural progression (9). Therefore, to evaluate the structural damage remains crucial.

New data suggest that inflammatory changes are followed by the replacement of subchondral bone marrow by repairing tissue which then stimulates osteoblasts, leading to new bone formation (10). Furthermore, large data of axSpA cohorts support that spinal radiographic progression is strongly dependent on the presence of: syndesmophytes at baseline, elevated acute-phase reactants (CRP and/or ESR), smoking, and high disease activity as measured by Ankylosing Spondylitis Disease Activity Score (ASDAS) (11). The association between the presence of radiographic

damage in the spine and the reduction of spinal mobility and functional status are well known in patents with axSpA, and recently this association seems to be also found when structural damage of the SIJs is present, independently of structural damage in the spine (13).

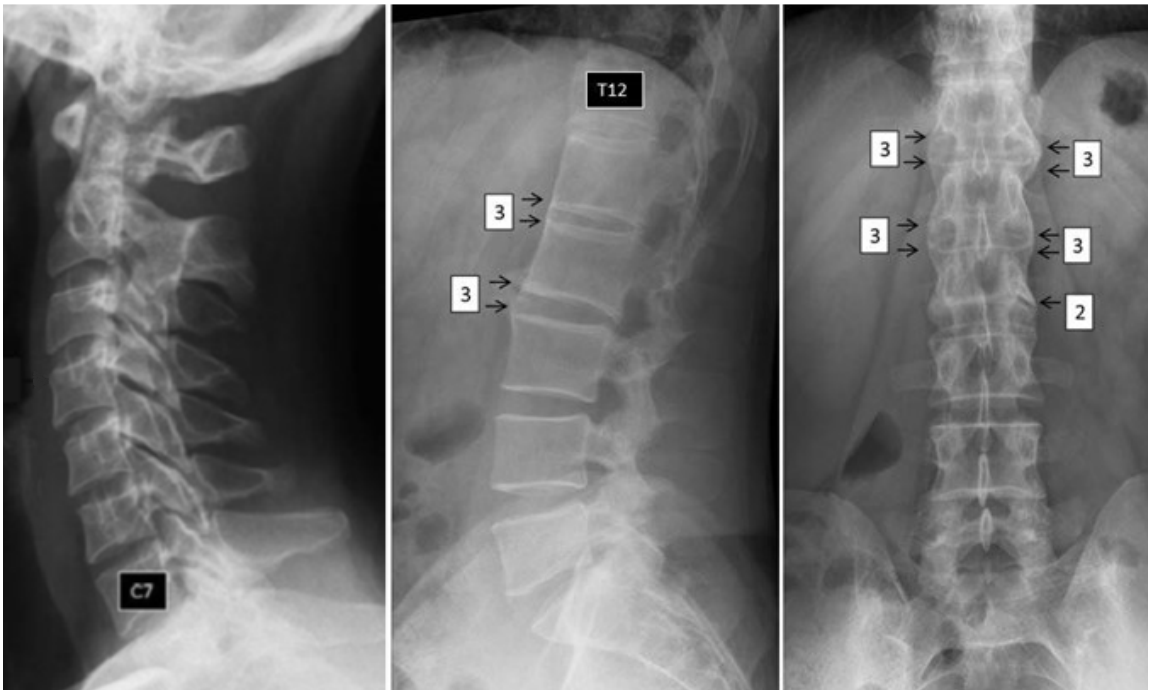
Several studies in r-axSpA have focused on the radiographic progression of the spine. The gold standard for the imaging assessment of radiographic spinal progression is conventional spine radiography (cervical and lumbar). ASAS/EULAR recommends performing radiographs after at least 2 years of follow-up (54). Currently, the modified Stoke Ankylosing Spondylitis Spine Score (mSASSS) is the method most frequently used to score structural damage of the spine, due to its better reliability and sensitivity to change (15) in comparison with the Bath Ankylosing Spondylitis Radiology Index (BASRI) (16) and the SASSS (17). mSASSS captures anterior vertebral corners of the cervical and lumbar spine on lateral radiograph projections and assesses the presence of erosions, sclerosis, squaring, syndesmophytes and bridges with a total score of 72 (18).

BASRI (BASRI-spine) is a combined score of the cervical spine, lumbar spine and SIJs. BASRI uses the combination of AP and lateral views to score the lumbar spine; then cervical and lumbar spine are scored separately on a scale from 0 to 4. SIJs are scored according to the modified New York (mNY) criteria. The final BASRI score results from the sum of the mean score for the right and left SIJs plus the scores for the lumbar and cervical spine (18).

To explore other scores, in the first study, we aimed to evaluate the applicability of the extended mSASSS as a tool to measure radiographic spinal progression. The extended mSASSS is a new proposed tool which incorporates AP lumbar radiography into the

mSASSS, the current gold standard tool for assessing structural damage of the spine in axSpA (18). The extended mSASSS also assesses the presence of erosions, sclerosis, squaring, non-bridging syndesmophytes, and bony bridges affecting the anterior vertebral corners of the cervical spine on radiographs in lateral views and lumbar spine in lateral and AP views with a total score of 144 (figure 1).

Figure 1. Extended mSASSS (modified Stoke Ankylosing Spondylitis Spine Score) range 0-144



Previous studies suggest that AP views of the lumbar spine, which are often performed routinely, can provide additional information on the presence of structural damage in the spine (15, 16). However, the added value of AP lumbar radiography when assessing radiographic spinal progression in axSpA as compared with lateral views is unknown.

To assess the applicability of the extended mSASSS as a tool for the measurement of radiographic spinal progression, the score was compared with the conventional mSASSS

according to the three aspects of the Outcome Measures in Rheumatology (OMERACT) filter: feasibility, discrimination and truth.

In the feasibility aspect, all patients had available AP lumbar radiographs as it was required for the inclusion of the study. Although AP lumbar radiograph is a routine projection in the clinical practice, it increases the costs of the radiographic investigation of the spine by approximately 50% and the time required for the reading according to the extended mSASSS by 50–100% (since additional 24 vertebral corners should be assessed) as compared to conventional mSASSS. Furthermore, AP lumbar radiographs are associated with additional radiation exposure, increasing the overall exposure associated with the assessment by approximately 60–70%.

There was excellent inter-reader agreement on the status scores with intraclass correlation coefficient (ICC) of 0.93 (95% CI 0.91–0.94) and 0.93 (95% CI 0.90–0.94) at baseline and 0.93 (95% CI 0.91–0.95) and 0.92 (95% CI 0.90–0.94) at year 2 for the extended and conventional mSASSS scores, respectively. Agreement on the change score was moderate, with ICCs of 0.45 (95% CI 0.33, 0.55) and 0.43 (95% CI 0.31, 0.53) for the extended and conventional mSASSS scores, respectively. For outcome progression of ≥ 2 points after 2 years, there was fair agreement for both methods, with Cohen's kappa of 0.20 (95% CI 0.06, 0.34) and 0.21 (95% CI 0.06, 0.36) for the extended and conventional mSASSS scores, respectively. Agreement on the development of new syndesmophytes was moderate with Cohen's kappa of 0.39 (95% CI 0.28, 0.57) and 0.43 (95% CI 0.28, 0.57) for the extended and conventional mSASSS scores, respectively. Agreement was also moderate for the outcome development of new syndesmophytes or growth of existing syndesmophytes with Cohen's kappa of 0.44 (95% CI 0.29, 0.58)

and 0.42 (95% CI 0.29, 0.55) for the extended and conventional mSASSS scores, respectively. An analysis of the score components revealed comparable variability for the scores obtained in the cervical spine and in both planes of the lumbar spine.

The change score between baseline and year 2 was 0.73 ± 2.34 and 1.19 ± 3.73 for the mSASSS and extended mSASSS scores, respectively. The smallest detectable change of the extended mSASSS was, however, higher than of the conventional score, while the standardized response mean was equal for both scores. With the extended mSASSS, new syndesmophytes after 2 years were detected in 4 additional patients, new syndesmophytes or growth of existing syndesmophytes in 5 additional patients, and progression by ≥ 2 points in the total score in 14 additional patients that yielded an increase of 25%, 28% and 46% in the proportion of patients with progression according to the respective definition as compared with the conventional score. These proportions were even higher in patients with r-axSpA; hence, in more advanced disease, the added value of the lumbar AP assessment might be greater than in early disease.

The univariable and multivariable regression analyses of both scores showed a significant association with spinal mobility (BASMI) and function (BASFI) that confirms the construct validity of both scores as parameters truly reflecting structural damage in the spine in axSpA.

Therefore, extended mSASSS can be considered as supplementary to conventional mSASSS, as it adds information from the AP lumbar spine view. Nonetheless, the information obtained from the AP lumbar radiograph may also be somewhat redundant, as the same structural damage (same syndesmophyte) can be visible on both lateral and

AP views. This fact explains, for instance, a larger difference in status scores (the extended mSASSS was twice as high as the conventional score) than in percentages of patients with syndesmophytes (30.5% with extended mSASSS vs. 22.9% with conventional mSASSS at baseline).

To conclude, we show that the extended mSASSS offered good reliability and provided some improvement in the detection of radiographic spinal progression in patients with axSpA as compared with the conventional mSASSS. However, this should be weighed against additional costs, additional radiation exposure (although AP lumbar radiographs are often performed routinely), and the additional time investment associated with reading an additional 24 vertebral corners.

The study has several limitations. Structural damage in the spine may not be entirely captured by the radiographs performed. Syndesmophytes with posterior localization or in the lateral aspects of the cervical spine, as well as involvement of posterior structures (i.e., facet joints) are not captured by the extended mSASSS, as in the case of the conventional mSASSS. In most cases, however, structural damage develops more or less simultaneously in different aspects of the spinal column, making it possible to assume that the mSASSS/extended mSASSS may be a proxy for overall structural damage in the spine. Similarly, damage present in the thoracic spine is not depicted due to anatomical overlap with another thoracic structure. However, active inflammatory (23) and structural changes (24) seem to occur here at least as frequently as in other spine regions. For this reason, another modification of the mSASSS was proposed by Baraliakos et al: the Radiographic AS Spinal Score (RASSS), which adds the score of the lower thoracic vertebrae (T10–T12) to the mSASSS, under the hypothesis that

progression occurs mostly in these segments and that new bone formation quantification is superior to the conventional mSASSS. Furthermore, low-dose CT has the potential to become the primary method used to detect radiographic spinal progression in axSpA in the future, as it has been proven to detect more progression in the form of new and growing syndesmophytes in patients with r-axSpA (24).

Therefore, with the first study we support our hypothesis that the incorporation of AP radiography of the lumbar spine in the assessment of structural damage in the spine improves detection of radiographic spinal progression in axSpA. However, this affirmation should be confirmed in further larger studies and using low-dose CT as a reference.

Conversely, assessment of the radiographic progression of the SIJs has been studied less extensively. Early studies reported that approximately 5% to 12% of patients with nr-axSpA developed radiographic sacroiliitis damage within 2 years (19, 20). The conventional method for assessing SIJ structural damage on radiography is the mNY grading system, consisting of a semiquantitative scale from 0 (normal) to 4 (total ankylosis). This method considers three types of structural changes: sclerosis, erosions and joint space narrowing/ankylosis (4). According to the mNY criteria, definite radiographic sacroiliitis is defined as grade ≥ 2 bilaterally or grade ≥ 3 unilaterally. The mNY criteria method was created as a classification tool and until now it has not been validated for the assessment of structural progression in SIJs. More sensitive tools to detect radiographic progression seem to be the change in total SIJ score over time and percentage of patients with a change of at least one grade in at least one SIJ, among other methods (20, 118). According to the EULAR recommendations, the SIJ radiograph

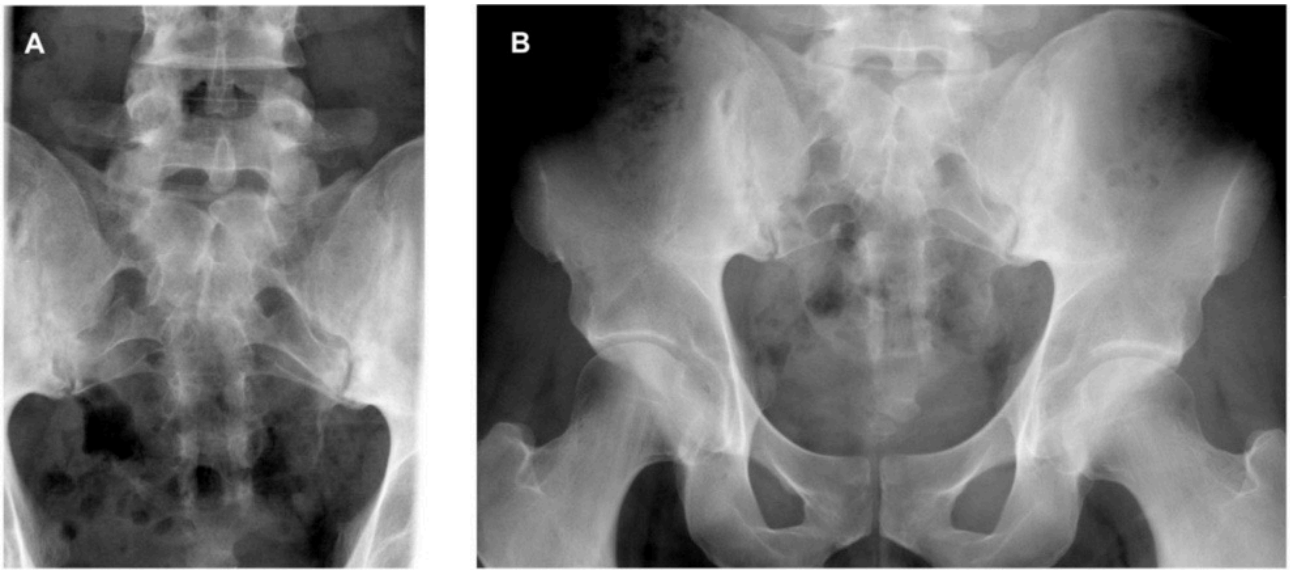
is still the first imaging method recommended when axSpA is suspected (22). The most common routine method of radiographic SIJ examination is conventional AP pelvic radiograph, although SIJs can also be captured by AP lumbar radiography, often performed as part of the diagnostic procedure or for the assessment of the structural damage in the spine. However, it is not known if radiographic sacroiliitis can be reliably assessed on lumbar radiography.

Therefore, in the second study, we compared radiographic sacroiliitis assessment on conventional pelvic radiographs and AP lumbar radiographs in patients with axSpA. As mentioned before, the evaluation of SIJs on radiographs remains essential for the diagnosis and classification of axial axSpA however which is the optimal view to asses structural damage on SIJs remains unclear.

Given the complex anatomy of SIJs, several dedicated techniques such as the Ferguson view (a modified AP pelvic radiograph with the central rays angled 30° caudally) and oblique views of each SIJ have been proposed to improve the reliability and validity of radiographic sacroiliitis assessment. However, despite some theoretic advantages, none of the dedicated views were able to show significant improvement in sacroiliitis detection over conventional pelvic radiographs in previous studies (26, 27). Therefore, the intra- and inter-reader reliability of radiographic sacroiliitis assessment remains poor (123), and large variations with no improvement are seen even when readers have received targeted training (124). Moreover, it seems particularly challenging to score early lesions in SIJs, specifically grades 1 or 2 according to the mNY criteria. Likewise, SIJs are often available for sacroiliitis assessment on AP lumbar radiographs, which are often performed routinely in patients with unclear back pain; however, it is not known

whether the assessment of radiographic sacroiliitis on AP lumbar radiographs have a good reliability and validity (figure 2).

Figure 2. An example of radiographic sacroiliitis in two different views of the same patient:



(A) AP lumbar radiograph, and (B) conventional pelvic radiograph. Both radiographs show definite subchondral sclerosis, erosive changes and narrowing of the joint space in both sacroiliac joints that has been scored as bilateral sacroiliitis of grade 3.

Our findings indicate an overall good agreement between both radiograph techniques, in 85% of cases, patients received the same classification as nr-axSpA or r-axSpA at baseline and year 2. The agreement on the radiographic sacroiliitis grade (sacroiliitis sum score) between conventional pelvic and AP lumbar radiographs was excellent at baseline and year 2: ICC 0.91 for both time-points. A total of 62 (54.9%) and 55 (48.7%) patients fulfilled the radiographic criterion of the mNY criteria in the opinion of both readers at baseline and 65 (57.5%) and 60 (53.1%) patients fulfilled this criterion at year 2 based on evaluation of pelvic and AP lumbar radiographs, respectively. Additionally, inter-reader agreement was moderate to good on the presence of definite radiographic

sacroiliitis. Progression from nr-axSpA to r-axSpA by fulfilling the radiographic criterion of the mNY criteria in the opinion of both readers occurred in 7 (6.2%) and 8 (7.1%) patients based on the assessment of conventional pelvic and AP lumbar radiographs, respectively. There was also regression to nr-axSpA in 4 (3.5%) and 3 (2.7%) patients for conventional pelvic and AP lumbar radiographs, respectively. The net percentage of progression from nr-axSpA to r-axSpA, understood as the difference of the number of patients who experienced worsening and improvement, divided by the total study population (21, 125), was 2.7% and 4.4% for conventional pelvic and AP lumbar radiographs, respectively. The absolute agreement between the assessments of both radiographic views for progression was 84.1%.

One of the most common concerns regarding radiographs is radiation exposure. In our case, both modalities have a similar effective dose of approximately 0.7 mSv (28, 29). In daily clinical practice, AP lumbar radiograph is often performed together with the lumbar lateral view to evaluate the damage of the lumbar spine. Thus, one could avoid unnecessary radiation exposure if SIJs could be assessed on AP lumbar radiograph. However, conventional pelvic radiograph remains the method of choice as first-line imaging when axSpA is suspected, if AP lumbar radiograph are not first available or if SIJ are not well depicted on AP lumbar radiograph. Obviously, hip joints, which may be involved in SpA (30), cannot be assessed on AP lumbar radiographs in contrast to conventional pelvic radiographs. For patients at risk of hip involvement (e.g., patients with suggestive symptoms), it may be more appropriate to perform the pelvic radiograph instead or in addition to AP lumbar radiography.

Our study had several limitations. First, not all patients from GESPIC could be included in the current study as a result due to the unavailability of suitable radiographs. In fact, in 97 of 210 patients, SIJs were partially or completely missing on lumbar AP radiographs, resulting in exclusion of these patients from the analysis. This point has an important practical implication, as SIJs cannot be assessed on lumbar radiography in about 50% of cases in daily clinical practice. Consequently, in a new patient with suspected axSpA, conventional pelvic radiography should remain the method of choice for the first-line imaging assessment of SIJs, while lumbar AP radiograph can be used for the sacroiliac joint assessment only if it is already available and only if SIJs are clearly depicted. Secondly, we used a cohort of patients already diagnosed with axSpA. Although only about half the patients had definite radiographic sacroiliitis, AP lumbar radiography might have been performed differently if the technique was used for primary diagnostic purpose in patients with back pain and suspicion of axSpA. However, for the classification (nr-axSpA or r-axSpA) and for the radiographic sacroiliitis progression assessment in patients with known axSpA, AP lumbar radiography has performed reasonably well.

Finally, we used conventional pelvic radiographs – a method with known poor reliability – as a reference method. To date, CT is considered the gold standard for detecting structural damage in SIJs (radiographic sacroiliitis) but is rarely used as the primary diagnostic method because of its lower feasibility in clinical practice and higher radiation exposure (31). In recent years, low-dose CT, which has a radiation exposure similar to conventional radiography, has been established for the assessment of structural damage in the SIJs (25, 32). Furthermore, MRI of SIJs is currently being evaluated for the

detection and scoring not only of bone marrow oedema but also for structural lesions, however with no final agreement on thresholds as of yet (25, 57). Nonetheless, conventional radiography of SIJs is still often used as the first imaging method when axSpA is suspected, due to broader availability and lower costs compared to CT and MRI (22, 34). Therefore, it was reasonable to compare the performance of AP lumbar radiographs with the current standard (conventional pelvic radiographs), even in the absence of any external reference. With the present study, we confirm our first hypothesis that structural changes in SIJs can be reliably assessed on AP lumbar radiographs using conventional pelvic radiographs as a reference. Therefore, if the patient has already undergone AP lumbar radiography when he or she is first assessed, no additional pelvic radiographs needs to be performed to assess SIJs in the diagnostic work-up of patients with suspected axSpA.

With the combination of the two studies we confirm our principal hypothesis, proving that AP lumbar radiographs have added value for the assessment of structural damage progression in axSpA patients. Thus, the AP lumbar radiograph is useful for the diagnostic work-up and follow-up of these patients.

Through my work on these studies, I gained expertise in the field of radiographic assessment of structural damage progression in axSpA. To achieve this experience, during my stay in the Charité department (center of reference in the research area on SpA) I have performed specific training including teaching sessions and consensus scoring of test cases as well as learning several methods of radiographic scoring (mSASS and mNY criteria). Consistent with this research area, I conducted a study with a Spanish cohort to evaluate radiographic progression in axSpA patients receiving treatment with

TNFis. The study “Radiographic progression in patients with axial spondyloarthritis under treatment with TNF inhibitors. Data from REGISPONSERBIO (Spanish Register of Biological Therapy in Spondyloarthritides)” has been accepted as an oral report at the 2020 Congress of Rheumatology of the Spanish Society of Rheumatology (SER) and as an abstract at the 2020 EULAR and ACR Congress. The manuscript of the study is currently being written for submission to a relevant journal in the field of rheumatic diseases.

Chapter 8

Conclusions

CONCLUSIONS

- The incorporation of AP radiography of the lumbar spine in the assessment of structural damage in the spine improves detection of radiographic spinal progression in axSpA.

- Radiographic sacroiliitis can be assessed by lumbar AP radiography with a similar reliability and validity as conventional pelvic radiography in patients with axSpA if SIJs are well depicted.

- AP lumbar radiography adds value to the assessment of structural damage progression in axSpA patients; therefore, it is useful for the diagnostic work-up and follow-up of these patients.

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Appendices

Curriculum Vitae

List of publications

Abstract

CURRICULUM VITAE

Maria Llop Vilaltella llicenciada en Medicina i Cirurgia en la Universitat Autònoma de Barcelona l'any 2012. Especialista en Reumatologia en l'Hospital Universitari Ramón y Cajal l'any 2017. Activitat de recerca centrada des de l'any 2016 en el camp de les Espondiloartirtis amb diverses publicacions recents en revistes indexades. Rotació externa en l'Hospital Charité - Campus Benjamin Franklin de Berlín, centre de referència a nivell mundial en el camp de les Espondiloartropaties, amb el finançament d'una beca de la Sociedad Española de Reumatología (SER) l'any 2016 i un posterior Felowship en el mateix centre, Charité - Campus Benjamin Franklin, amb el finçament de dues beques (EULAR scientifical training bursary i beca d'ampliació d'estudis en el estranger de la SER) l'any 2017. Membre actiu de la societat investigadora internacional ASAS- Assessment of SpondyloArthritis International Society i young ASAS així com de la societat investigadora GRESSER- Grupo para el estudio de la Espondiloartritis de la Sociedad Española de Reumatología. Des de febrer de 2020, facultatiu especialista en Reumatologia en l'Hospital Universitari Parc Taulí on realitza activitat assistencial e investigadora en el camp de les Espondiloartritis. Actualment, cursant el màster en Bioinformàtica i Bioestadística de la Universitat Oberta de Catalunya amb la coolaboració de la Universitat de Barcelona.

LIST OF PUBLICATIONS

1. Rodriguez VR; **Llop M**; Protopopov M; Sieper J; Haibel H; Proft F; Rudwaleit M; Poddubnyy D. Assessment of radiographic sacroiliitis in anteroposterior lumbar vs conventional pelvic radiographs in axialspondyloarthritis.Rheumatology (Oxford, England). 2020. ISSN 1462-0324

2. Poddubnyy D, Weineck H, Diekhoff T, Redeker I, Gobejishvili N, **Llop M,** Rodriguez VR, Proft F, Protopopov M, Haibel H, Sieper J, Hermann KGA. Clinical and imaging characteristics of osteitis condensans ilii as compared with axial spondyloarthritis. Rheumatology (Oxford). 2020 May 23:keaa175. doi: 10.1093/rheumatology/keaa175. Epub ahead of print. PMID: 32447391.

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4. Mireia Moreno; Jordi Gratacós; Vicenç Torrente Segarra; Raimon Sanmarti; Rosa Morlà; Caridad Pontes; **Maria Llop**; Xavier Juanola. Withdrawal of infliximab therapy in ankylosing spondylitis in persistent clinical remission,results from the REMINEA study.Arthritis research & therapy. 21 - 1, pp. 88. 05/04/2019. ISSN 1478-6362

5. Valeria Rios Rodriguez; **Maria Llop**; Denis Poddubnyy. Hematopoietic and mesenchymal stem cells: a promisingnew therapy for spondyloarthritis?. Immunotherapy. 9 - 11, pp. 899 - 911. 09/2017. ISSN 1750-7448

6. **Maria Llop**; W A Sifuentes; S Bañón; C Macia Villa; M J Perez Elías; M Rosillo; S Moreno; M Vázquez; J LCasado. Increased prevalence of asymptomatic vertebral fractures in HIV-infected patients over 50 years ofage.Archives of osteoporosis. 13 - 1, pp. 56. 08/05/2018. ISSN 1862-3514

7. **Maria Llop Vilaltella**; Valentina Maldonado Romero; Carlos Guillén Astete; Carlos de la Puente Bujidos; Celia deCasanova Peña. Sacroiliitis and gluteal abscess secondary to Staphylococcus aureus infection.Reumatologiaclinica. 11 - 6, pp. 398 - 400. (Spain): 26/05/2015. ISSN 1885-1398

ABSTRACT

TITLE: Radiographic progression in patients with axial spondyloarthritis under treatment with TNF inhibitors. Data from REGISPONSERBIO (Spanish Register of Biological Therapy in Spondyloarthritides)

M. Llop[1], M. Moreno[1], J. Gratacós[1], V. Navarro-Compán[2], E. de Miguel[2], P. Font[3], T. Clavaguera[4], L.F. Linares[5], B. Joven[6], X. Juanola[7] and the Regisponserbio group.

BACKGROUND: Clinical efficacy of TNF inhibitors (TNFi) in axial spondyloarthritis (axSpA) has been widely probed in randomized control trials. In clinical practice, some studies suggested that long-term treatment with TNFi (more than 4 years) could slow down radiographic progression in axSpA. Furthermore, it is thought that the effect of TNFi on radiographic progression may be mediated by reducing disease activity (9).

OBJECTIVE: To evaluate the association between disease activity and radiographic progression in axSpA patients treated with TNFi.

METHODS: Of the initial 204 patients a total of 101 patients with axSpA, 31 starting TNFi and 75 previously treated with TNFi, from the Spanish Register of Biological Therapy in Spondyloarthritides (REGISPONSERBIO) were included in the analysis based on the availability spinal radiographs (cervical and lumbar spine lateral views) at two time points and clinical data. Paired cervical and lumbar spine radiographs were available on all patients at a minimum interval of 2 years (mean 3.45±0.978 years; range 2 to 5 years). Two trained readers, independently and with known chronological order, scored lateral cervical and lumbar spine images according to the mSASSS system (0-72). Disease activity was reported with ASDAS-CRP every 6 months in a 3-year period. Following definitions for progression were used: change of the absolute scores, change of ≥2 points, development of new syndesmophytes, and development of new syndesmophytes or growth of the existing syndesmophytes. ASDAS differences between patients groups at each time point were assessed using a linear mixed-effect model that included progression status at end of follow-up, treatment of > 4 years at recruitment and the interaction of these two parameters. As adjusting factors, the model also included the total time of follow-up and the following patients' characteristics collected at the

time of recruitment: gender, age, smoking habit, radiological diagnosis of axial spondyloarthritis, MSASSS average, HLA-B27 and time from symptomatology onset. ASDAS adjusted values, group means and their corresponding standard errors provided by the model were graphically represented in stripcharts for each time point separately. Statistical significance was assessed using Wald tests. All analyses were carried out using R [M1].

RESULTS: Baseline characteristics of patients at first radiograph are presented in Table 1. Reliability of both readers was excellent with intraclass correlation coefficients (ICCs) of 0.986 (0.979-0.990) at inclusion and 0.981 (0.972-0.987) at follow-up. The mean±SD score at inclusion was 16.46±20.92, the change score between inclusion and follow-up was 1.98±0.83 and the smallest detectable change of progression was of 2.26 mSASSS units. Change of ≥2 points was deteced in 30 patients (29.7%), development of new syndesmophytes was present in 20 patients (15.2%) and growth of the existing syndesmophytes or new syndesmosphytes was present in 22 (21.8%). Figure 1, shows the association between disease activity measured by ASDAS every 6 months with radiographic progression defined as an increase in the mSASSS score at ≥2 points.

CONCLUSIONS: Patients with persitent high disease activity (ASDAS ≥ 2.1) despite long-term treatment with TNFi have radiographic progression.

Table 1. Baseline characteristics at first radiograph of 101 patients

Baselines characteristics at first radiograph		N	Median (IQR) N (%)
Age, years		101	46.00 (16.00)
Male, sex %		101	82 (81.2%)
HLA-B27 positive, %		99	86 (86.9%)
AS, %		101	86 (85.1%)
BMI		95	26.02 (4.63)
BMI > 30%		95	11 (11.6%)
Current smokers, %		101	31 (30.7%)
Symptom duration, years		97	15 (18.00)
CRP (mg/L)		94	3.35 (8.10)
Elevated CRP, %		94	41 (40.6%)
BASDAI		97	3.2 (3.10)
ASDAS-PCR		96	2.06 (1.54)
Inactive disease (ASDAS <1.3)		96	23 (24%)
Low disease (ASDAS < 2.1)		96	50 (52.1%)
BASFI		98	3.85 (4.45)
BASMI		82	2.87 (2.44)
mSASSS		101	5.00 (23.00)
Syndesmophytes present, %		101	51 (50.5%)
On NSAID treatment, %		99	57 (57.6%)
On TNFi treatment, %		101	75 (75%)
Number of previous TNFi	0	101	75 (74.3%)
	1	101	20 (19.8%)
	2	101	6 (5.9%)
Months of TNFi treatment in treated patients		101	37.50 (70.00)
At least 4 years of TNFi use		101	49 (48.5%)
Uveitis		101	22 (21.8%)
Psoriasis		99	7 (7.1%)
IBD		99	7 (7.1%)

ASDAS, Anklyosing Spondylitis Disease Activity Score; AS, Ankylosing spondylitis; HLA-B27, human leucocyte antigen B27; NSAID, non-steroidal anti-inflammatory drug; BMI, body mass index; CRP, c-reactive protein, TNFi, tumor necrosis factor inhibitor: IBD, inflammatory bowel disease; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; BASMI, Bath Ankylosing Spondylitis Metrology Index; mSASSS, modified Stoke Ankylosing Spondylitis Spine Score.

Figure 1. Association between disease activity measured by ASDAS every 6 months with radiographic progression defined as an increase in the mSASSS score at ≥2 points.