

The role of obesity on inflammation and damage in spondyloarthritis: a systematic literature review on body mass index and imaging

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ABSTRACT

Objective. The objective of this systematic literature review was to evaluate the effect of obesity and/or body mass index (BMI) on radiographic findings of spondyloarthritis (SpA) for both axial and peripheral inflammation and damage.

Methods. Medline, Embase and Cochrane databases were screened on February 13, 2017. The titles and the abstracts were independently screened by two investigators. Articles that have evaluated the link between BMI and plain radiography, ultrasound (US) and magnetic resonance imaging (MRI) in SpA were investigated.

Results. The literature search resulted in 613 articles, 5 of which met the inclusion criteria for the final analysis. Studies mostly investigated the effect of BMI on axial disease and mostly in ankylosing spondylitis. The major finding was that a higher BMI was closely related with new bone formation including syndesmophytes, enthesophytes and also a higher modified Stoke Ankylosing Spondylitis Spinal Score.

Fewer studies looked at the effect of BMI on the peripheral enthesitis which found a moderately positive correlation between the Madrid Sonographic Enthesitis Index for enthesitis on US and BMI. Gender was a significant factor to influence this link with one study correlated US enthesophyte scores with BMI in males but not in females. No studies on MRI met the inclusion criteria to be included.

Conclusion. BMI is linked to both axial and peripheral new bone formation and enthesal inflammation by imaging, as supported by the limited number of studies in the literature. Its effect on the sacroiliac joint and spinal inflammation is not clear as MRI studies are lacking.

Introduction

The spondyloarthropathies (SpA) are heterogeneous diseases that can affect the spine, sacroiliac joints, entheses, ligaments and peripheral joints (1, 2, 3). The pathogenesis of SpA is not completely understood due to complex interaction between genetic risk factors and environmental triggers that leads to immune activation (4, 5). The studies have reported that SpA has a multifactorial aetiology with genetic risk factors (predominantly HLA-B27), microbiota and biomechanical stress models shaping the disease-related features (6-9). One of the factors that have been considered in SpA pathogenesis is obesity (9, 10). Obesity predicts the development of psoriatic arthritis (PsA) among psoriasis patients (10). In addition to being more frequent in SpA, increased body mass index (BMI) has been demonstrated to be associated with greater burden of symptoms, poorer function, and decreased response rates to treatments and weight reduction by gastric bypass surgery has been shown to be an effective way to reduce the risk of developing PsA (9-13).

Obesity may lead to longstanding biomechanical stress over the joints and enthesitis, which has been demonstrated to be an important risk factor for developing SpA in animal models (14). In this systematic literature review (SLR), we aimed to investigate the association of obesity and/or BMI on inflammation and damage in SpA, both for the axial and peripheral joints as well as the enthesitis, using imaging modalities.

Methods

Search and selection strategy

The literature search was performed from Medline, Embase and Cochrane databases between 1947 and February

13, 2017, by a medical librarian with the keywords or medical subject headings of “Psoriatic arthritis”, “spondyloarthritis”, “spondylitis”, “spondyloarthropathy”, “ankylosing spondylitis”, “seronegative arthritis”, “axial spondyloarthritis”, “body mass”, “obesity”, “body weight”, “body mass index” and “overweight”. The inclusion criteria were diagnosis of SpA, adult population (age ≥ 18), presence of BMI data, and using imaging modalities (eg plain radiography, ultrasound (US), magnetic resonance imaging (MRI)). Only studies that have investigated the link between obesity and/or BMI with any of the imaging methods were included. Articles that were reviews, letters, case reports, comments and abstracts from scientific conferences, meta-analysis, SLRs, duplications, consensus reports and those in languages other than English were excluded. The study protocol was registered at PROSPERO (CRD42017067094).

General data extraction and data analysis

The titles and the abstracts were independently screened according to the selection criteria by two investigators (SB, JD). The disagreements were discussed with a 3rd investigator (SZA) and a decision was made according to consensus. Articles not fulfilling all the selection criteria were excluded and the reason for exclusion was recorded.

All selected articles were evaluated for the aims of the studies, demographic data, imaging modalities and results of the study relating to BMI during the full text review, extracting the following: study population, sample size, site of interest (peripheral or axial), age, BMI, gender, disease duration by same investigators (SB, JD). Imaging modality types that were used (plain radiography, US, MRI), indices, elementary lesions in the imaging tool, pathology (inflammation or damage) as well as the objectives and the results of studies relating to the BMI were recorded. As all studies included in the manuscript were observational cohorts and cross-sectional studies and we had not found any RCTs, the National Heart, Lung, and Blood Institute of the National In-

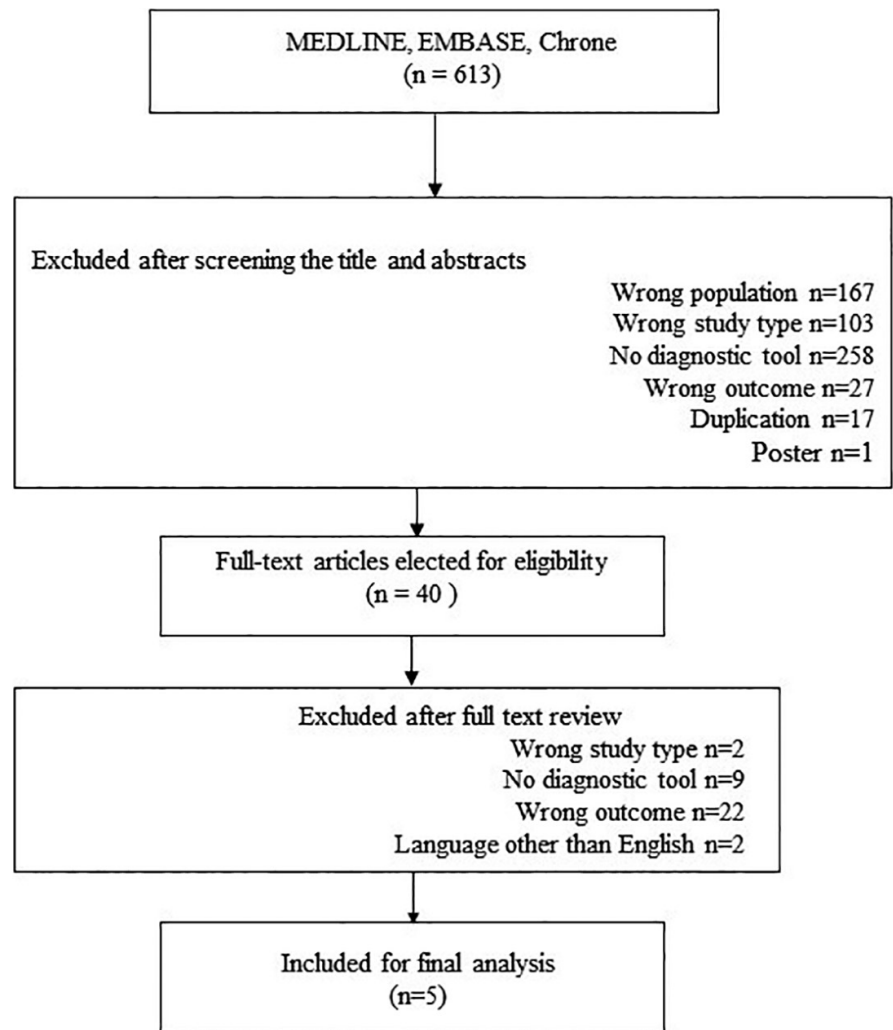


Fig. 1. Flowchart for selection and exclusion of the abstracts and articles.

stitutes of Health (NIH) for quality assessment of Observational Cohort and Cross-Sectional Studies and Controlled Intervention Studies were used to assess the quality of included studies (15). Due to the heterogeneity of the data, inconsistency of the imaging methods and patient groups, a meta-analysis could not be conducted and results were presented as descriptive.

Results

Six-hundred and thirteen articles were retrieved by the literature search (Fig. 1). Among these, 573 articles were excluded due to wrong disease population, wrong study format/design or not using imaging modalities and/or the outcomes that were investigated in this SLR. After the first selection, 40 articles were identified for full text review. Only 5 studies (16–20) met the

inclusion criteria after full text review (Table I).

The demographic data

Three of the publications were on ankylosing spondylitis (AS) (17–19), one on SpA (16) and one on PsA (20). The mean (SD) age in the disease arms was ranged between 35.1–53.2 (1.1–12.5), the mean (SD) BMIs were between 23.3–30.9 (3.5–6.6) and the mean (SD) disease duration was between 5.0–14.2 (6.0–12.1) years. Two studies assessed both axial and peripheral involvement (16, 19), 2 assessed just axial involvement (17–18) and one study evaluated peripheral involvement only (20) (Supplementary file, Table I).

The imaging modalities and indices used in studies

Three out of five studies used plain

Table I. The objectives and the radiological data of studies.

First author / year of publication	Aim of the study	Study population / sample size	Pathology	Site of interest Peripheral / axial	Which sites evaluated in detail	Imagine modalities	Indices	Results
Kim SK <i>et al.</i> 2017 ¹⁶	To determine the direct effect of BMI on the presence of syndesmophytes on radiographs in patients with axSpA	Axial SpA (n=789) Subgroups: a-AS (n=720) b-SpA without sacroiliitis* (n=69)	Damage	Axial	Cervical, thoracic and lumbar spine, sacroiliac joint, peripheral joints.	PR	Sacroiliitis *, presence of any syndesmophyte	Overweight/obese patients were older and had more syndesmophytes. The multivariate analysis showed that BMI was an independent risk factor for the presence of syndesmophytes [OR=1.086, 95% CI (1.031–1.143), <i>p</i> =0.002].
Maas F <i>et al.</i> 2015 ¹⁷	To evaluate spinal radiographic damage over time and to explore the associations of radiographic progression with patient characteristics and clinical assessments including disease activity in AS patients treated with TNF- α blocking therapy in daily clinical practice.	AS n=176	Damage	Axial	Cervical and lumbar spine	PR	mSASSS	For the <i>baseline assessment</i> , higher BMI was linked to the presence of syndesmophytes in addition to other risk factors such as gender, age, disease duration, smoking and disease activity [for BMI 27.2 (4.1) vs. 25.2 (3.7), <i>p</i> =0.004]. <i>During the follow up period</i> where patients were on TNF inhibitors BMI was not linked to radiographic progression.
Kim K <i>et al.</i> 2012 ¹⁸	To investigate whether Leptin/BMI ratio is associated with the presence of syndesmophytes in male patients with AS	AS n=72 HC n=20	Damage	Axial	Cervical, thoracic and lumbar spine	PR	mSASSS	Patients with syndesmophytes had higher BMI [(25.4 (0.7)] than patients without syndesmophytes [23.8 (0.4), <i>p</i> =0.038].
Aydin SZ <i>et al.</i> 2016 ¹⁹	To investigate the link between axial new bone formation on radiographs and peripheral new bone formation on US and the effect of BMI on these	AS n= 225 HC n= 95	Damage	Axial, peripheral	Cervical and lumbar spine, Achilles tendon.	PR for cervical and lumbar spine. US for Achilles tendon.	mSASSS using radiography, Semiquantitative scoring for enthesophytes using US.	Both mSASSS and the number of syndesmophytes were found to be correlated with the enthesophyte scores linking the new bone formation at the peripheral and axial sites. Correlation analysis showed that BMI had an impact on both the spine (with mSASSS <i>r</i> =0.452; <i>p</i> <0.001) and the peripheral sites (US enthesophyte scores <i>r</i> =0.382; <i>p</i> <0.001) in <i>males</i> whereas there was a weaker correlation with BMI and mSASSS in <i>females</i> (<i>r</i> =0.269; <i>p</i> <0.001) but no correlation with enthesophyte scores (<i>r</i> =0.141; <i>p</i> =NS).
Eder L <i>et al.</i> 2014 ²⁰	To compare the enthesal abnormalities in PsA, psoriasis alone and healthy controls and in subgroups stratified by age and BMI.	PsA n=50 PsO n=66 HC n=60	Damage, inflammation	Peripheral	5 lower limb and 1 upper limb entheses #	US	MASEI global score (MASEI-inflammatory, MASEI-damage)	A moderately positive correlation was found between MASEI scores for enthesitis and BMI (<i>r</i> =0.47; <i>p</i> <0.001). In patients with a BMI <25 and BMI 25-30 MASEI scores were higher in PsA patients than psoriasis, which was also higher than healthy subjects (<i>p</i> =0.02, <i>p</i> =0.006, respectively). No significant differences in MASEI scores across patients with a BMI>30 (<i>p</i> =0.18). <i>Multivariate analysis</i> showed a significant link between BMI and MASEI index [OR=1.14, 95% CI (1.07–1.12), <i>p</i> <0.0001].

AS: ankylosing spondylitis; BMI: body mass index; HC: healthy control; mSASSS: modified Stoke Ankylosing Spondylitis Spinal Score; MASEI: Madrid Sonographic Enthesitis Index; NS: non-significant; PsA: psoriatic arthritis; PR: plain radiography; SpA: spondyloarthritis TNF: tumour necrosis factor; US: ultrasound.

*fulfilling the Modified New York Criteria #Lower limb: insertions of the quadriceps femoris tendon, patellar tendon origin and insertion, Achilles tendon and plantar fascia insertions on the calcaneus; Upper limb: triceps tendon insertion to the olecranon process.

radiography (16–18), one study used US only (20) and one had both plain radiography and US (19). Most of the studies on plain radiography evaluated spine, mostly for damage using modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS), which included syndesmophytes, erosions, sclerosis and/or squaring (17–19).

In one of the two studies where US was used, the target site was the Achilles enthesis site for damage, more specifically for enthesophytes (19). The other study evaluated both inflammation (hypoechogenicity, PDUS, thickening and bursitis) and damage (calcifications and erosions) using the Madrid Sonographic Enthesitis Index (MASEI) as a scoring system (20). There were no studies using MRI that met the inclusion criteria.

The results of the studies

• *The link between BMI and spine*

Four studies have found that there was a strong link between BMI and the presence of syndesmophytes (16–19). Kim *et al.* analysed the direct effect of BMI on the presence of syndesmophytes on radiographs (16). They demonstrated that overweight/obese patients were older and had more syndesmophytes (16). In that study, the multivariate analysis showed that BMI was an independent risk factor for the presence of syndesmophytes [OR=1.085, 95% CI (1.031–1.143)] (16).

Another study investigated the clinical and laboratory characteristics of male AS patients according to the presence of syndesmophytes (18). This group found that patients with syndesmophytes had higher BMI than patients without syndesmophytes [25.4(0.7) vs. 23.8(0.4), $p=0.038$] (18).

Aydin *et al.* assessed the link between BMI and axial new bone formation on radiographs and peripheral new bone formation on US, which showed both mSASSS and the number of syndesmophytes correlated with the enthesophyte scores linking new bone formation at the peripheral and axial sites (19). Also a difference between genders was seen as the correlation was only observed in males but not in females. Correlation analysis showed that BMI had an im-

pact on both the spine (with mSASSS $r=0.452$; $p<0.001$) and the peripheral sites (US enthesophyte scores $r=0.382$; $p<0.001$) in males whereas there was a weaker correlation with BMI and mSASSS in females ($r=0.269$; $p<0.001$) but no correlation with the enthesophyte scores ($r=0.141$; $p=NS$) (19). Similarly, the differences according to gender could also be seen in multivariate analysis: Age and BMI was significantly associated with syndesmophytes in males and an increase of 1 unit of BMI was associated with 19% higher probability of having syndesmophytes. This association was not observed in females (19).

Maas *et al.* made a prospective study on the Groningen Leeuwarden AS (GLAS) cohort and performed an analysis on 176 AS patients with active disease. The risk factors for having syndesmophytes at baseline were investigated, BMI being one of the potential variables, and also the risk factors for progression after a mean (SD) of 3.8 (1.8) years of follow-up were searched. For the baseline assessment, higher BMI was linked to the presence of syndesmophytes [27.2 (4.1) vs. 25.2 (3.7), $p=0.004$]. During the follow-up period during which patients were on TNF inhibitors, BMI was not linked to radiographic progression (17).

• *The link between BMI and enthesopathies*

The study by Eder *et al.* investigated the MASEI by US to differentiate PsA from psoriasis alone and healthy controls by stratifying for BMI and also had investigated the link between BMI and the enthesitis scores on US (20). A moderately positive correlation was found in this study between MASEI scores for enthesitis and BMI ($r=0.47$; $p<0.001$). When patients were divided into categories, in patients with a BMI <25 and BMI 25–30, MASEI scores were higher in PsA patients than psoriasis, which was also higher than healthy subjects ($p=0.02$, $p=0.006$, respectively). However, there were no significant differences in MASEI scores across patients with a BMI >30 ($p=0.18$) (20). Multivariate analysis showed a significant link between BMI and MASEI

index [OR=1.14, 95% CI (1.07–1.12), $p<0.0001$].

Another study highlighted that gender differences as being important for the effect of BMI on enthesophytes using US (19). In this study, BMI was correlated with US enthesophyte scores in males ($r=0.382$, $p<0.0001$), whereas there was no significant relationship between BMI and US enthesophyte scores in females ($r=0.141$, $p=NS$). The same study also had 95 age- and BMI-matched healthy controls showing a similar result: male healthy controls had higher enthesophyte scores with increasing BMI ($r=0.421$; $p=0.006$), whereas females did not have the same link ($r=0.186$; $p=NS$). All the data of these studies are summarised in Table I and Supplementary Table I.

• *Quality assessment*

All included studies were rated as “good” according to the United States National Institute of Health (NIH) National Heart, Lung and Blood Institute (NHLBI) Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies (Suppl. Table II).

Discussion

To the best of our knowledge, this is the first SLR to investigate the effect of obesity or BMI on radiological outcomes of disease-related findings in patients with SpA. All the articles that met the inclusion criteria were published after 2012, probably due to the increased recognition of the importance of BMI and biomechanical stress in the pathogenesis of SpA. The major finding of this SLR was the higher BMI being closely related to existing new bone formation including syndesmophytes and enthesophytes as well as higher mSASSS scores on radiographs, which could explain the effect of BMI on clinical outcomes (16–19). The association between obesity and new bone formation highlights the importance of biomechanical factors in patients with SpA. Biomechanical factors can be considered the trigger of an inflammatory process, so the response of healing at these sites can be associated with new bone formation (14, 21).

There are some limitations of this SLR.

Only 5 studies were available for assessment, which emphasises the need for more and larger trials. Furthermore, while these 5 studies provided generalised insight into the correlation to imaging modalities, it is difficult to cross-compare results between the 5 studies given the differences in the imaging modalities that were used. There is no standardisation or conversion coefficient among these tools and it is difficult to compare the result and the outcomes of studies with different assessment tools.

No studies met the inclusion criteria to be included in the SLR on MRI of the spine or the peripheral entheses. For that reason, we were only able to retract on the impact of BMI on either damage on the spine (by plain radiographs) or inflammation/damage of the peripheral entheses (US and/or plain radiographs), but not for the inflammation on the spine which could be detected with MRI. The lack of MRI studies makes it impossible to extrapolate the effect of MRI bone oedema, a surrogate for osteitis or bone inflammation and relationship to BMI. So it remains unclear whether the magnitude of initial spinal inflammation impacts on new bone formation.

This SLR confirms the effects of obesity or higher BMI and their related radiological outcomes of the entheses, joint and axial involvement of SpA patients. Its effect on the sacroiliac joint and spinal inflammation is not clear because of the lack of MRI studies as well as prospective studies to understand the causative effect. These findings sup-

port the concept that weight reduction may be an important component for the optimal therapy of SpA.

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