Review

Juvenile Versus Adult-onset Ankylosing Spondylitis — Clinical, Radiographic, and Social Outcomes. A Systematic Review

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ABSTRACT. Ankylosing spondylitis (AS) has 2 main modes of onset: juvenile-onset AS (JoAS) and adult-onset AS (AoAS). It is not known whether JoAS is a subtype of AS, or AS modulated by early age of onset and longer disease duration. We performed a systematic review of the literature, identifying 12 articles and 1 abstract directly comparing JoAS and AoAS cohorts, with observational study design. Patients with JoAS appear to have more peripheral joint involvement both clinically and radiographically (especially knees and ankles) and more root joint involvement (hips and shoulders); they are more likely to proceed to hip arthroplasty and often initially present with peripheral rather than axial symptoms. Patients with AoAS appear to have more axial symptoms and radiographic disease, particularly in the lumbar spine, and worse axial metrology. In terms of other characteristics, more evidence is needed to confidently state whether JoAS and AoAS are different. (First Release Sept 15 2013; J Rheumatol 2013;40:1797–805; doi:10.3899/jrheum.130542)

Key Indexing Terms:
ANKYLOSING SPONDYLITIS ADOLESCENT ADULT

Symptoms of ankylosing spondylitis (AS) usually start in the third decade of life. However, Wilkinson and Bywaters[1] showed that 18% of cases experience symptoms in their second decade, even as early as age 11 years. AS therefore has 2, possibly 3 main modes of onset. Patients experiencing AS symptoms at ≤ 16 years of age are classified as juvenile-onset AS (JoAS), those with symptoms ≥ 17 years as adult-onset AS (AoAS), and those with symptom onset on or after age 40 years as late-onset ankylosing spondylitis (LoAS)[2].

It is not known whether JoAS is a subtype of AS, or AS modulated by early age of onset and longer disease duration. The common trait is plain radiographic sacroiliitis. But despite having much in common clinically, they are thought to differ in certain ways. Understanding whether JoAS is a separate disease entity with a different pathogenesis to AoAS is of vital importance for several reasons. First, to understand the etiopathogenesis of AS through genetic studies, one must have homogeneous cohorts. Second, being able to stratify patients according to likely prognosis allows for individualized management decisions. Third, AS onset in childhood might affect school performance and social, career, and psychological development, as has been shown in adults[3,4].

Although several observational studies have compared JoAS and AoAS cases in terms of epidemiological, clinical, imaging characteristics, and prognosis, there are no published systematic reviews. This review describes a systematic and critical review of the current literature.

MATERIALS AND METHODS

The inclusion criteria for this systematic review were any articles reporting on research directly comparing JoAS with AoAS cases.

A search was performed on February 1, 2013, of Medline (1950–present), EMBASE (1947–present), CINAHL (Cumulative Index to Nursing and Allied Health Literature, 1984–present), and Cochrane Collaboration databases (1993–present) using the following predefined MeSH (medical subject headings), EMTree or keyword terms as appropriate: "ankylosing spondylitis," "adult," "adolescent," "juvenile," "child," "onset." Cross-sectional or cohort studies meeting the above inclusion criteria were included. Studies not directly comparing JoAS with AoAS were excluded. Publications in abstract-only form were included, while acknowledging their less rigorous peer review process. Case reports, case series, review articles, and studies not directly comparing JoAS with AoAS cases were not included.

Reference lists of included articles were scrutinized to identify articles not captured in the database search. Key investigators were contacted for input on searches.

Two reviewers (DJ, RS) independently assessed articles for inclusion, and extracted data from included articles using a standardized data collection proforma (Figure 1).

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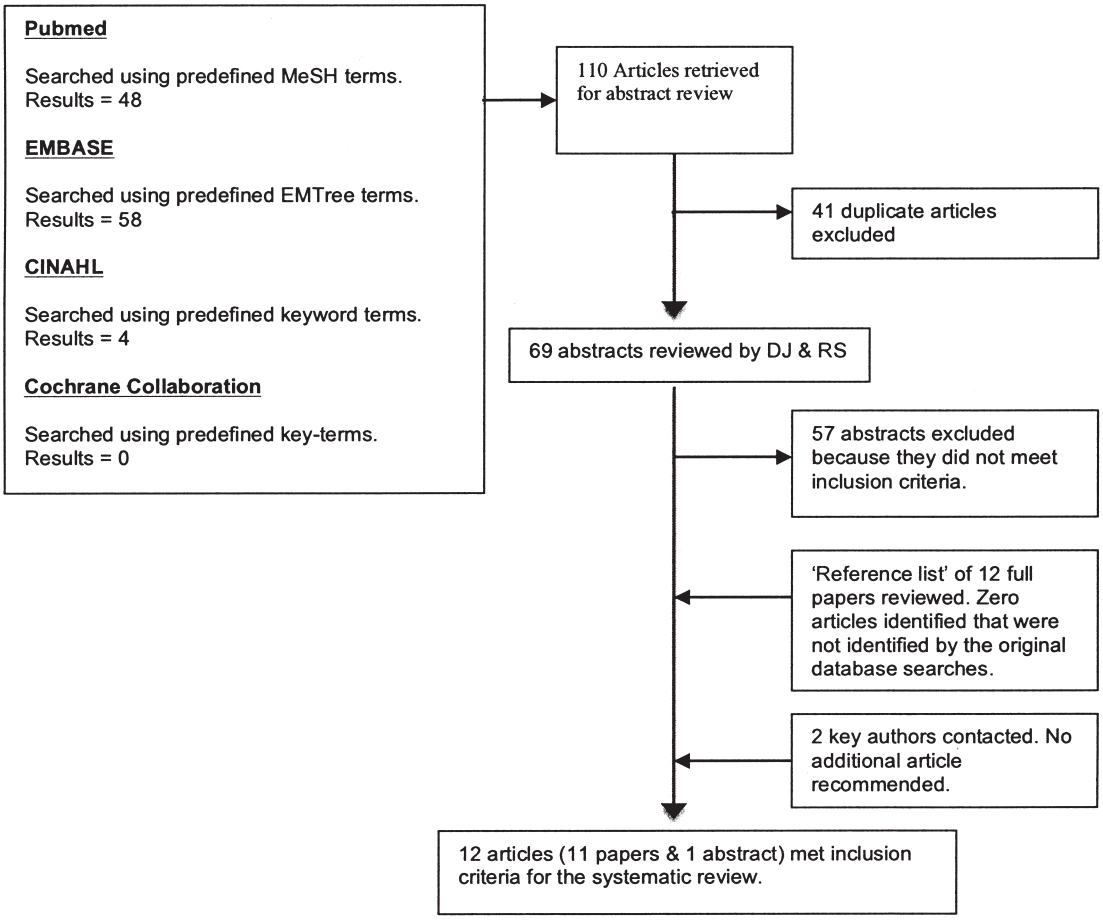

Figure 1. Systematic search tree.

RESULTS

Search results. Searches identified 110 unique articles. Forty-one duplicate articles were excluded. Of 69 remaining unique articles, 57 were excluded because they did not directly compare JoAS and AoAS cohorts. Twelve articles met inclusion criteria (Table 1): 11 full-length articles in peer-reviewed international journals and 1 abstract at the 2012 European League Against Rheumatism Congress.

All 11 full-length articles provided sufficient details of methods to determine that they were of good quality; with appropriate study design, statistical analysis, outcome measures, and results reported in a manner that both acknowledged study limitations and attempted to reduce confounders or bias. Results are summarized in Tables 2–5.

Epidemiology. None of the studies were designed to specifically explore the prevalence of JoAS and AoAS in the general population, nor to investigate the sex distribution in each group. However, 8 studies compared the relative proportions of male and female cases in their JoAS and AoAS cohorts; and were found to be comparable in 6 studies[5,6,7,8,9,10]. All cohorts had a male preponderance of about 3-fold. Chen, *et al* found a larger proportion of males in their JoAS group (89.6%) than in their AoAS group (78.5%; $p = 0.035$)[11].

Chen, *et al* stratified their entire cohort (JoAS, AoAS, and LoAS) by HLA-B27 status[11]. They reported that men had a younger average age at onset than women (22.8 ± 7.3 vs 28.1 ± 7.4 yrs; $p < 0.001$). HLA-B27 positive patients also had a younger age at onset (23.4 ± 7.4 vs 27.6 ± 8.2 yrs; $p < 0.001$). They demonstrated that HLA-B27 positive males had an earlier age at symptom onset than HLA-B27 positive females (exact mean age not stated). In males only, HLA-B27 positive cases had a younger age at symptom onset than HLA-B27 negative cases (exact mean age not stated).

Three[6,12,13] of 4 studies reporting on delay in diagnosis found that patients with JoAS have a greater delay to diagnosis than patients with AoAS. Marks, *et al*[13] reported this as a mean of 8.3 years in JoAS and 5.0 years in AoAS cases.

Patients in both cohorts appear to be similar in terms of patient-reported family history of AS[7,9,12,14], SpA[12], PsA[7], psoriasis[7], uveitis[7], and inflammatory bowel disease (IBD)[7].

Although 2 studies[12,14] suggest that patients with JoAS and AoAS are equally likely to be married, Stone, *et al*[6]

Table 1. Study design, sample size, and demographics of 12 articles meeting inclusion criteria.

Study, Year, Reference	Journal	Article/ Abstract	Country	Design	Meeting NY Criteria for AS, %	JoAS Sample Size	AoAS Sample Size	JoAS Age, mean yrs	AoAS Age, mean yrs	JoAS Disease Duration, mean yrs	AoAS Disease Duration, mean yrs	Comments on Methods
Chen, 2012[11]	J Rheumatol	Article	Taiwan	Pro, single center	100	67	460	26.8	33.9	12.3	9.5	19 LoAS cases
Yacoub, 2012[5]	EULAR	Abstract	Morocco	Pro, single center	NA	37	83	NA	NA	NA	NA	
Ozgocmen, 2009[12]	J Rheumatol	Article	Turkey	Pro, multicenter	100	43	279	29.3	36.1	16.8	10.5	
O'Shea, 2009[7]	Ann Rheum Dis	Article	Canada	Pro database, single center	100	84	183	27.5	42.6	14.7	16.7	
Lin, 2009[16]	J Chinese Med Assoc	Article	Taiwan	Retro, chart review and interviews. Single center	100	47	122	26.9	37.3	14.1	12.5	
Gensler, 2008[14]	Ann Rheum Dis	Article	USA	Retro, cross sectional multicenter	100	79	323	49.8	56.2	35.6	30.9	
Stone, 2005[6]	Arthritis Rheum	Article	USA & Canada	Retro, postal questionnaire study	NA	326	2021	46.5	50.9	18.3	13.4	Diagnosed by rheumatologists in 63%, generalists in 15%, orthopedic surgeons in 13%, ophthalmologists in 5.4%, chiropractors in 4.5%
Baek, 2002[8]	J Rheumatol	Article	S. Korea	Pro, single center	100	41	57	22.0	33.0	10.0	11.2	
Calin, 1988[9]	Br J Rheumatol	Article	UK	Retro, postal questionnaire and case-note review. Single center	NA	135	135	37.3	49.6	24.5	23.5	
Garcia-Morteo 1983[10]	Scand J Rheum	Article	Argentina	Pro, single center	99	24	71	NA	NA	NA	NA	
Marks, 1982[13]	J Rheumatol	Article	USA	Retro, single center	NA	22	22	24.7	40.0	13.0	14.0	
Riley, 1971[15]	Ann Rheum Dis	Article	UK	Retro, 2 centers	NA	28	107	NA	NA	NA	NA	

NA: not available; JoAS: juvenile-onset ankylosing spondylitis; AoAS: adult-onset ankylosing spondylitis; LoAS: late-onset ankylosing spondylitis; EULAR: European League Against Rheumatism; Pro: prospective; Retro: retrospective.

found that patients with AoAS are more likely to be married (74.6 vs 60.4%; $p < 0.001$).

Axial disease. Six studies reported on the occurrence of axial symptoms at presentation. All showed it to be significantly more frequent in AoAS than JoAS cases: 62.6 versus 7.1%[15]; 56 versus 25% ($p < 0.01$)[10]; 80.7 versus 41.5% ($p < 0.01$)[8]; 95 versus 74%[7]; 66.9 versus 4.3% ($p < 0.001$)[16]; 85.2 versus 73.1% ($p = 0.012$)[11], respectively. Chen, *et al* found this to hold true even after adjusting for sex and HLA-B27 status. Similarly, axial disease during the course of disease was more prevalent in AoAS[6,7,13].

A few studies proceeded to analyze by spinal region. Cervical spine pain or stiffness at presentation was equally likely in AoAS and JoAS cases[6]. Two studies reported cervical symptoms during disease course to be equally likely in both cohorts[7,13], while Baek, *et al*[8] found a higher occurrence of cervical spine involvement on examination in AoAS cases (66.7 vs 43.9%; $p = 0.02$).

Lumbar spine pain or stiffness at presentation was shown to be more frequent in AoAS than JoAS cases (71.5 vs 66%; $p = 0.043$) in 1 study[6]. However, 2 studies demonstrated no difference when analyzed by occurrence during the course of disease[7,13].

O'Shea, *et al*[7] reported that sacroiliac joint pain (60.3 vs 33.8%; OR 2.23; $p < 0.05$) and buttock pain (60.6 vs 38.2%; OR 2.43; $p < 0.05$) occur more frequently in AoAS than JoAS.

Table 2. Summary of the clinical presentation of juvenile-onset (JoAS) versus adult-onset ankylosing spondylitis (AoAS).

Domain	Characteristic	JoAS More Likely/ Higher/Worse (Ref. No.)	Equal JoAS & AoAS (Ref. No.)	AoAS More Likely/ Higher/Worse (Ref. No.)
Epidemiology				
	Sex		(5–10)	
	Male	(11)		
	Female	NS (14)		
	Delay in diagnosis	(6, 12, 13)	(5)	
	Family history of AS		(7, 9, 12, 14)	
	Family history of SpA		(12)	
	Family history of PsA		(7)	
	Family history of psoriasis		(7)	
	Family history of uveitis		(7)	
	Family history of IBD		(7)	
	Smoking history		(12, 14)	
	Married		(12, 14)	(6)
Clinical axial disease				
	Axial symptoms at presentation			(7, 8, 10, 11, 15, 16)
	Axial symptoms during disease course			(6, 7, 13)
	C-spine pain/stiffness at presentation		(6)	
	C-spine symptoms during disease course		(7, 13)	
	C-spine involvement on examination			(8)
	L-spine pain/stiffness at presentation			(6)
	L-spine stiffness during disease course		(7, 13)	
	L-spine pain during disease course			(7)
	SIJ/buttock pain			(7)
	Thoracic pain		(7)	
	Sternum pain at presentation	(11)		
	Sternum pain during disease course		(6)	
Clinical root joint disease				
	Root joint involvement at presentation	(15)		
	Hip involvement during disease course	(10)		
	Persistent hip disease		(13)	
	Total hip arthroplasty	(9, 14)		
	Shoulder involvement		(13)	
Clinical peripheral disease				
	Peripheral arthritis at presentation	(6–8, 10–12, 15, 16)		
	Peripheral arthritis during disease course	(10, 12, 13, 16)	(7)	
	Peripheral pain severity	(5)		
	Polyarthritis pattern	(10)		
	Dactylitis of the hand	(13)		
	Knee involvement at presentation	(8)		
	Knee involvement during disease course	(13)		
	Ankle involvement	(13)		
	Mixed onset at presentation (axial & peripheral)	(10)		
	Interval between peripheral arthritis & back pain onset	(13)		
Clinical extraarticular involvement				
	Enthesitis at presentation	(16)	(6, 11)	
	Enthesitis during disease course	(16)		
	Enthesitis score	MASES (5)	BASDAI (12)	
	Achilles involvement		(13)	
	Heel pain	(6)		
	Uveitis at presentation		(6, 11)	
	Uveitis during disease course	(7, 12)	(6, 8–10, 14)	
	Inflammatory bowel disease		(12, 14)	
	Psoriasis		(7, 12)	
	Urethritis		(12)	

NS: not statistically significant; IBD: inflammatory bowel disease; MASES: Maastricht AS Enthesitis Score; PsA: psoriatic arthritis; SpA: spondyloarthritis; SIJ: sacroiliac joint; C-spine: cervical spine; L-spine: lumbar spine; BASDAI: Bath AS Disease Activity Index.

Table 3. Summary of function, disease activity, and metrology in juvenile-onset (JoAS) versus adult-onset ankylosing spondylitis (AoAS).

Domain	Characteristic	JoAS More Likely/ Higher/Worse (Ref. No.)	Equal JoAS & AoAS (Ref. No.)	AoAS More Likely/ Higher/Worse (Ref. No.)
Function				
	BASFI	(5, 6, 11)	(12, 14, 16)	(7)
	BASFI domains	(6)		
	Functional capacity (Steinbrocker)	(10)		
	Functional class (ACR criteria)		(8)	
	ASAQ (including spinal mobility)		(9)	
Disease activity				
	BASDAI	(5) NS (16)	(11, 12)	
Metrology				
	BASMI		(5, 11, 16)	(12)
	Wall to tragus distance			(8)
	Cervical spine rotation			(12)
	Lumbar forward flexion (Schober)			(8)
	Spinal forward flexion (Bruckel deformity score)	NS (6)		
	Lumbar lateral flexion			(12)
	Chest expansion			(8, 12)
	Forced vital capacity			(8)

NS: not statistically significant; ACR: American College of Rheumatology; BASDAI: Bath AS Disease Activity Index; BASFI: Bath AS Function Index; BASG: Bath AS Patient Global; BASMI: Bath AS Metrology Index; ASAQ: Ankylosing Spondylitis Assessment Questionnaire.

Sternum pain at presentation was reported as more common in JoAS than AoAS cases by Chen, *et al*[11], but not corroborated by another study[6].

Root joint disease. Patients with JoAS are more likely than those with AoAS to have root joint (shoulder or hip) involvement at presentation[15], hip involvement at any time during the course of disease (88% of JoAS vs 49% of AoAS affected)[10], and to proceed to total hip arthroplasty[9,14]. However, Marks, *et al*[13] reported comparable rates of persistent root joint involvement in the 2 groups.

Peripheral joint disease. Eight studies have demonstrated significantly more peripheral arthritis at first presentation in patients with JoAS than in those with AoAS: 37.3 versus 21.5% ($p = 0.004$) even after adjusting for sex and HLA-B27 status[11]; 46.6 versus 33.2% ($p < 0.001$)[6]; 37.0 versus 14.0%[16]; 32.6 versus 15.1% ($p < 0.05$)[12]; 26 versus 5%[7]; 73.2 versus 36.8% ($p < 0.01$)[8]; 54 versus 10% ($p < 0.001$)[10]; 64.3 versus 17.8%[15]; respectively.

The same held true for occurrence of peripheral arthritis during the course of disease: 87.5% for JoAS versus 49% for AoAS ($p < 0.01$)[10]; 77% for JoAS versus 27% for AoAS ($p < 0.01$)[13]; and 78.7% for JoAS versus 45.1% for AoAS ($p < 0.001$)[16].

However, O'Shea, *et al*[7] found that using the last clinical assessment, there was no difference between the JoAS and AoAS cases in tender or swollen joint counts. JoAS cases had a mean tender joint count of 1.3 versus 1.1 AoAS cases; JoAS cases had a mean swollen joint count of 0.2 versus 0.2 in AoAS cases. However, comparison of the 2 cohorts by current peripheral arthritis found greater occurrence in JoAS than in AoAS cases; 41.5 versus 26.2% ($p < 0.05$).

Other studies suggest that patients with JoAS are more likely to have persistent arthritis[13], greater pain severity[5], polyarticular pattern, peripheral arthritis (33% JoAS versus 3% AoAS)[10], and to experience dactylitis[13].

While Baek, *et al*[8] showed that patients with JoAS are more likely than patients with AoAS to have knee involvement at presentation, Marks, *et al*[13] showed that this held true over the course of disease. The same study[13] demonstrated greater ankle involvement in JoAS cases.

The mean interval between peripheral arthritis onset and back pain in JoAS cases was 5.5 years in a US study[13], as compared to a mean 3.5 years in patients with AoAS initially having peripheral arthritis.

Extraarticular manifestations. While 2 studies described similar rates of enthesitis at initial presentation in the cohorts[6,11], Lin, *et al*[16] reported more frequent enthesitis both at presentation and during disease course in their patients with JoAS. A Moroccan study found greater enthesitis severity scores using the Maastricht Ankylosing Spondylitis Enthesitis Score in JoAS cases. The 2 subsets of AS have been found to be comparable in terms of Achilles tendon[13] and heel involvement[6].

Only 2 studies have shown an excess burden of uveitis in JoAS versus AoAS cases: 27.7 versus 24.5%, respectively ($p < 0.05$ adjusted for age)[7]; 23.3 versus 10.9%, respectively (age adjusted OR 2.92; $p < 0.05$)[12]. Five studies have shown no difference between the AS subsets either at presentation or during disease course[6,8,9,10,14].

JoAS and AoAS appear to be comparable in terms of the occurrence of IBD[12,14], psoriasis[7,12], and urethritis[12].

Function. As shown in Table 3, several research groups have used the Bath AS Functional Index (BASFI) to compare

Table 4. Summary of radiographic and laboratory outcomes in juvenile-onset (JoAS) versus adult-onset ankylosing spondylitis (AoAS).

Domain	Characteristic	JoAS More Likely/ Higher/Worse (Ref. No.)	Equal JoAS & AoAS (Ref. No.)	AoAS More Likely/ Higher/Worse (Ref. No.)
Radiographic spinal changes				
	BASRI		(5)	(12)
	mSASSS			(12)
	Vertebral squaring, facet joint, or compression fracture		(8)	
	Spinal syndesmophyte frequency			(8)
	Cervical spine radiographic score		mSASSS (11)	BASRI (14)
	C-spine Romanus lesions 10 yrs after disease onset	NS (15)		
	C-spine syndesmophytes frequency (formation & bridging)		(15)	
	C-spine apophyseal joint lesions 10 yrs after disease onset		(15)	
	C-spine apophyseal lesions with minimal syndesmophyte formation	(15)		
	L-spine radiographic score			BASRI (14), mSASSS (11)
	L-spine syndesmophytes frequency (formation & bridging)		(15)	
	L-spine apophyseal joint lesions 10 yrs after disease onset		(15)	
	Sacroiliitis score (New York criteria)	NS (11)		(8)
	Ossification of posterior interspinous ligament		(15)	
Radiographic peripheral changes				
	Radiographic root involvement during disease course	(15)		
	BASRI-hip	(14), NS (11)	(12)	
	Hip radiographic severity	(16)		
	Prevalent hip involvement	(5)		
	Peripheral joint radiographic changes during disease course	(15)	(8)	
	Peripheral enthesis radiographic changes		(8)	
	Heel lesions	(15)		
Genetics				
	HLA-B27 positivity	(11)	(7, 8, 10, 13, 14)	
Serology				
	Rheumatoid factor positivity		(8, 10)	
	Antinuclear antibody positivity		(8)	
Laboratory				
	C-reactive protein	(5, 16)	(11)	
	Erythrocyte sedimentation rate	(16)	(11)	
	Serum immunoglobulin-A	(11)		
	Urinalysis		(8)	
	Electrocardiogram		(8)	

NS: not statistically significant; BASRI: Bath AS Radiology Index; SIJ: sacroiliac joint; mSASSS: modified Stoke AS Spine Score.

function in the 2 AS subsets. Two large studies[6,11] and a smaller study[5] demonstrated poorer mean BASFI scores in JoAS subjects. Chen, *et al*[11] adjusted for multiple covariates including disease duration. Conversely, a prospective database study from Canada found their AoAS cases had a mean 20% poorer function (OR 1.20; 95% CI 1.06–1.35) after adjusting for disease duration[7]. However, 3 sizable studies showed no difference between the 2 AS subsets[12,14,16]. Gensler, *et al* adjusted for duration of AS, sex, current smoking, education level, comorbid conditions, occupational activity, and family history of AS[14].

Other indices of function have been used. Garcia-Morteo, *et al*[10] used the Steinbrocker Functional Capacity score and found JoAS cases fared worse; with 0% of subjects with JoAS retaining full functional capacity after a mean disease duration of 15 years, compared with 20% of subjects with AoAS at 12 years.

Disease activity. The 2 largest studies to report on the Bath AS Disease Activity Index did not demonstrate a difference between the 2 cohorts[11,12].

Metrology. While studies from Taiwan[11,16] and Morocco[5] do not indicate any differences in metrology [using the Bath AS Metrology Index (BASMI)] between the 2 subsets of AS, Ozgocmen, *et al*[12] found BASMI to be worse in AoAS after adjusting for disease duration (OR 0.78; 95% CI 0.66–0.92).

On analysis for BASMI domains, subjects with AoAS were worse in wall to tragus distance[8], cervical spine rotation[12], lumbar forward flexion[8], and lumbar lateral flexion[12].

Chest expansion was more limited in AoAS cases in 2 studies[8,12] and forced vital capacity similarly poorer in AoAS[8].

Spinal radiography. As shown in Table 4, Ozgocmen, *et al*[12] used the Bath AS Radiological Index (BASRI) and modified Stoke Ankylosing Spondylitis Spine Score (mSASSS) to show that spinal radiographic changes are worse in AoAS.

Table 5. Summary of clinical and social outcomes in juvenile-onset (JoAS) versus adult-onset ankylosing spondylitis (AoAS).

Domain	Characteristic	JoAS More Likely/ Higher/Worse (Ref. No.)	Equal JoAS & AoAS (Ref. No.)	AoAS More Likely/ Higher/Worse (Ref. No.)
Treatment				
	NSAID use		(13)	
	Treatments		(5)	
	Medication use		(9, 14)	
Employment				
	Income			Better (6)
	Socioeconomic status		(5)	
	Educational level	Better (6)	(12, 14)	Better (5)
	In school or employment		(13)	
	In full-time employment	(9)		
	Unemployable due to AS		(13)	
	Work disability	(6)	(14)	
Health-related status				
	HAQ		(14)	(7)
	Limitation of lifestyle due to AS		(13)	
	BASG	(11)	(16)	
	PGA	NS (16)		
	Quality of life (SF-36)	(5)		(7)
	ASQoL		(12)	(7)
	Fatigue		BASDAI (12)	FACIT (7)
	Modified Arthritis Impact Measurement Scales (AIMS; includes depression, anxiety, physical activity, pain, impact, social activity)		(9)	
	Social activity domain of AIMS			(9)

NS: not statistically significant; AS: ankylosing spondylitis; ASQoL: AS quality of life index; FACIT: Functional Assessment of Chronic Illness Therapy Fatigue scale; HAQ: Health Assessment Questionnaire; PGA: Patient Global Assessment; SF-36: Medical Outcome Study Short Form-36; AIMS: Modified Arthritis Impact Measurement Scales; NSAID: nonsteroidal antiinflammatory drug; BASG: Bath AS Patient Global Score.

This was not corroborated in another smaller study[5]. Baek, *et al*[8] showed AoAS cases had more vertebral syndesmophyte formation (54.4 vs 17.1%; $p < 0.01$) but similar occurrence of squaring, facet joint disease, atlantoaxial subluxation, and compression fracture.

In the cervical spine, JoAS and AoAS were comparable in terms of radiographic score (mSASSS)[11], Romanus lesions[15], syndesmophyte frequency[15], and apophyseal joint lesions in the 10 years after disease onset[15]. After adjusting for sex and disease duration, Gensler, *et al*[14] reported the BASRI to be poorer in AoAS cases.

In the lumbar spine, after adjusting for sex and disease duration, AoAS cases had worse mSASSS[11] and BASRI[14] scores than JoAS cases.

A large study reported a trend for JoAS cases having higher sacroiliitis scores[11]. However, a smaller study found higher grades of sacroiliitis in AoAS subjects (more often grade 4)[8].

Peripheral radiography. Radiographic root joint changes are consistently reported as being worse in JoAS than in AoAS subjects[5,14,15]. The hip was more frequently affected than the shoulder.

While Baek, *et al*[8] demonstrated comparable peripheral joint radiographic changes in JoAS and AoAS, Riley, *et al*[15] reported worse peripheral joint radiographic changes during disease course in JoAS; especially in the metatarsophalangeal joints, hands, and knees. Riley, *et al*'s findings relating to hand arthritis are somewhat isolated, not reported in other studies, nor consistent with our own clinical experience.

Genetics. Apart from 1 study reporting greater HLA-B27 positivity in JoAS cases[11], 5 studies reported no difference between JoAS and AoAS subjects[7,8,10,13,14].

Laboratory and clinical indices. Two studies show C-reactive protein (CRP)[5,16] and erythrocyte sedimentation rate (ESR)[16] to be higher in JoAS cases, but 1 study does not[11]. Any differences may simply reflect the greater prevalence of peripheral arthritis in JoAS, which is more likely to mount an acute phase response than axial arthritis.

Despite demonstrating no difference in CRP and ESR levels, Chen, *et al* demonstrated higher serum immunoglobulin-A levels in JoAS cases, after adjusting for multiple covariates including disease duration[11].

Treatment. Few studies have directly compared management of JoAS and AoAS patients (Table 5). Of the 5 published studies, no difference was found between the 2 cohorts in terms of nonsteroidal antiinflammatory drugs ("NSAID use": 95% in JoAS, 86% in AoAS)[13], "treatment"[5] or "medication use"[9,14].

Income and employment. Stone, *et al*[6] reported that subjects with AoAS are more likely to be in a self-reported high income category (93.8% vs 88.6%; p = 0.002). However, another study found no difference in socioeconomic status[5], but did not elaborate upon the methodology used to collect or define socioeconomic status. One study found that 74% of patients with JoAS were in full-time employment versus 56% of patients with AoAS ($p < 0.01$)[9].

Four studies have specifically looked at educational attainment. Comparable attainment was demonstrated by 2 studies[12,14] and higher attainment by AoAS subjects in another study, although definitions were not provided[5].

Marks, *et al*[13] reported that after a followup period of 13–14 years, 73% of patients with JoAS and 64% of patients with AoAS were employed or in school. Eighteen percent of patients with JoAS and 14% of patients with AoAS were deemed unemployable because of their disease[13]. Two other studies have explored work disability. Gensler, *et al*[14] found no difference between JoAS and AoAS cases. Using a definition of AS-related work disability as being temporary/permanent work disability due to AS, Stone, *et al*[6] found greater work disability in JoAS than AoAS cases (27.4 vs 20.9%; p = 0.012).

Health-related status. While several studies have evaluated health-related status in both cohorts, direct comparison of studies is difficult because of the variety of indices used.

No difference was found when using the Stanford Health Assessment Questionnaire (HAQ)[14], global evaluation of "limitation of lifestyle due to AS"[13], or Bath Ankylosing Spondylitis Patient Global Score (BASG)[16]. However, Chen, *et al* found the BASG to be higher in JoAS; and O'Shea, *et al*[7] reported the HAQ to be higher in AoAS once adjusted for disease duration.

Quality of life as measured using the Medical Outcomes Study Short Form-36 Survey was worse in AoAS cases in a Canadian study[7], but the converse was demonstrated by a Moroccan study of smaller sample size[5]. Ozgocmen, *et al*[12] found no difference between the cohorts using the AS Quality of Life Scale (ASQoL), even after adjusting for current age and disease duration. However, using the same ASQoL tool, O'Shea, *et al*[7] found poorer outcomes in AoAS.

Prognostic factors. Only 1 study has looked in detail at predictors of prognosis. Using the BASFI as a marker of function, Stone, *et al*[6] demonstrated the following to be associated with a poorer BASFI on multiple regression analysis: age and income status. However, these findings are somewhat confounded by the younger mean age and longer disease duration of JoAS cases at the time of the survey.

DISCUSSION

According to these studies, the phenotype of JoAS, both at presentation and during disease course, is not identical to AoAS, even after adjusting for disease duration. Patients with JoAS appear to have more peripheral joint involvement both clinically and radiographically, especially in the knees and ankles, and more root joint involvement. Patients with AoAS appear to have more axial symptoms and radiographic disease, particularly in the lumbar spine, and worse axial metrology. While a proportion of JoAS cases have dual onset, most have peripheral symptoms followed several years later by axial symptoms. For the other characteristics reported, there is not enough evidence to confidently state whether JoAS and AoAS are different.

Given the spectrum of characteristics addressed, for many themes the studies have reported consistent results. Variability in results can be explained in part by differing study design, study power, the use of patient-reported outcome measures or patient histories that are subject to recall bias and differing interpretation, the choice to analyze by "date of symptom onset" versus "date of formal diagnosis," differing tools to assess outcome, and the need to follow cohorts for decades to capture manifestations.

The reported lag of 4–9 years between symptom onset to formal diagnosis of AS[17] will exacerbate recall bias in retrospective studies of AS. The studies above have been somewhat heterogeneous in their definition of first symptoms, some using onset of inflammatory back pain and others peripheral arthritis. One might argue for disease onset according to occurrence of extraarticular manifestations.

JoAS and AoAS appear to have several clinical and radiographic differences, although there is insufficient evidence yet to state whether they are separate disease entities. Through a better understanding of their natural history and treatment response, clues to pathogenesis and phenotypic differences might be learned, in turn identifying opportunities to modify disease course. Future studies should have conformity of outcome variables to allow for better comparison with the existing literature. Studies in cohorts of different ancestral origin are needed to tease out the influence of genetics on disease manifestations.

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