Evidence-based Correlation Between Anti-Streptolysin O Serum Titer and Sacroiliac Joint Disorder

SHIN-TSU CHANG, CHIH-HUNG KU, and SHIOU-CHI CHERNG

ABSTRACT. ***Objective.*** Poststreptococcal reactive arthritis (PSReA) is a nonsuppurative sequela of antecedent streptococcal infection, and can be investigated when detecting the anti-streptolysin O (ASO) titer. The relationship between ASO titer and involvement of the peripheral synovial joints has been examined in PSRA, but data are sparse for the sacroiliac (SI) joint. Quantitative SI joint scintigraphy has been used clinically to detect active SI joint disorders, but not for PSReA.

Methods. A total of 84 subjects were recruited; mean age at enrollment was 23 years (range 18.0–36.4 yrs). All subjects were examined for ASO titer levels (range 25–520 IU/ml) and SI joint imaging, determined by sacroiliac to sacrum (SI/S) ratio derived from SI scintigraphy.

Results. Most of the subjects with high ASO titer had unclassified or undifferentiated arthritis. Good correlation between the ASO titer and the SI/S ratio was determined statistically using Pearson correlation coefficients. The relationships between ASO titer and SI/S ratio at various locations (laterality: left, right; location of part: upper, middle, lower) were found to be significantly correlated using generalized estimating equations. After adjustment for potential confounders, a highly significant association was determined between ASO titer and SI/S ratio ($p < 0.0001$), with an increase of 1 IU/ml of titer resulting in a significant increase in SI/S ratio by 0.0008 units. Age was significantly associated with SI/S ratio ($p = 0.0022$), with each extra year increasing the ratio by 0.0074.

Conclusion. Our findings demonstrate a high correlation between SI joint involvement and high ASO titers. Subjects with SI joint involvement should be advised to have an ASO titer examination and quantitative SI joint scintigraphy. (First Release July 1 2007; J Rheumatol 2007;34:1746–52)

Key Indexing Terms:
SCINTIGRAPHY BIOLOGICAL MARKERS EVIDENCE-BASED MEDICINE
IMMUNOGLOBULINS ARTHRITIS

The antibody titer of anti-streptolysin O (ASO), detected in clinical practice from blood, is a well established index for suspicion for infection by streptococcus bacteria[1-7]. Primary streptococcal infection in the sacroiliac (SI) joint can invoke a severe pyogenic sacroiliitis, which results in catastrophic incapacitation. Patients have been found to be infected by various types of streptococcal strains, which can be isolated from blood, urine, infected joint spaces, or, preferably, by needle biopsy. Most infected patients have underlying diseases such as chronic joint disease, malignancy, dental manipulation, and severe upper respiratory tract infection, and infection occurs during late pregnancy, after delivery, and postpartum[8-11].

However, poststreptococcal reactive arthritis (PSReA), a disease entity separate from acute rheumatic fever or pyogenic arthritis, is another nonsuppurative sequela of prior streptococcal infection[12]. PSReA appears to be a heterogeneous clinical entity, in a group with spondyloarthropathy traits[13]. PSReA often occurs without obvious contagious sources, and the bacterial pathogen is seldom detected from blood or other tissue, unless investigated for ASO titer while under suspicion. Many investigations of the relationship between ASO titer and involvement of the synovial joints (e.g., elbow, wrist, hip, knee, and ankle) have been conducted[14-20], but data are sparse for the SI joint[19]. Remarkably, none of these studies directly examined the correlation between SI joint and ASO titer. Histologically, the SI joint is about half syndesmotic and half synovial[21]. Since PSReA can affect the peripheral synovial joints, we wished to determine if it can affect the SI joint.

Quantitative SI joint scintigraphy is a procedure that has been used to detect active SI joint disorder for about 3 decades, especially in the early stages of the disease when it cannot be verified by conventional radiology[22-26], although some researchers do not support its investigative efficacy[27]. Its effectiveness/accuracy can reportedly be affected by age[28],

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Supported in part by grants 91-2314-B016096 and 92-2314-B016019 from the National Science Council, Taiwan.

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Accepted for publication April 28, 2007.

drug exposure[29,30], gender[31], and trauma/injury[32,33]. In clinical practice, the application of quantitative SI scintigraphy has largely been confined to investigations of SI joints in patients with hyperparathyroidism, salpingitis, rheumatoid arthritis, systemic lupus erythematosus, and mechanical lower back pain[34], as well as ankylosing spondylitis[35,36], but never for PSReA. Also, most published data describe SI imaging in case reporting, not in statistical research. To our knowledge, there are no studies of the relationship between ASO titer and quantitative SI imaging.

In addition to doubting whether the synovial type of the SI joint might be affected by PSReA, another motivation for our study was a case we encountered that had throat pain with high ASO titer, which was treated with appropriate antibiotics. However, arthritic pain occurred in the SI joint region after 3 months. We doubted there was a relationship between the ASO titer and SJ joints in that patient. Further, the patient's SI joint disorder viewed from a plain pelvis radiograph and computerized tomography (CT) scan did not show obvious erosive change, thus high sensitivity nuclear scintigraphy was our first choice to examine the joint.

The purpose of our study was to investigate the relationship between ASO titer and SI joint disorder based on the hypothesis that a reactive process affects the SI joint, and to determine the significance of the correlation between ASO titer and different locations of SI joint.

MATERIALS AND METHODS

Subjects. All participants underwent ASO titer testing between September 2002 and September 2005, and samples were surveyed at the central laboratory in our hospital. Exclusion criteria were age > 40 or < 17 years, and history of rheumatoid arthritis, ankylosing spondylitis, spondyloarthropathy, urethritis, psoriasis, regional enteritis, inflammatory bowel disease, major trauma or surgery, metastatic disease, metabolic/endocrine disease, positive root tension signs or neuromuscular deficit, peripheral arthritis or swelling/deformity in the small joints, pain associated with early morning stiffness that resolved with exercise, and skeletal malformations such as scoliosis and kyphosis. CT scan or magnetic resonance imaging also excluded subjects with any of the following pathological conditions: congenital anomaly or herniated intervertebral disc in the lumbosacral spine, spondylolysis, and any bony lesion or tumor within the pelvis and spine. Additionally, all subjects were tested for erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), rheumatoid factor (RF), antinuclear antibody (ANA), and HLA-B27, and urinalysis was performed, all with negative results. We measured the ESR and CRP levels twice before and after scintigraphy, and all levels were within normal range. A negative result in ESR, CRP, RF, ANA, and HLA-B27 was our exclusion criterion. At the time of recruitment, body temperature was normal and there was no sign of infection in all subjects. Lower back pain could be traced back with variable duration and intensity in most of the subjects with high ASO titer.

Measurement of ASO titer and SI joint disorder. The ASO test (Bio-Mérieux, Hertogenbosch, The Netherlands) was performed at the central hospital laboratory, and the titers were determined using a Behring nephelometry kit (Behring, Marburg, Germany) and also were estimated using the standard tube dilution method (World Health Organization). The normal range of ASO titer in our hospital is defined as < 116 IU/ml in adults.

Quantitative SI scintigraphy was performed after intravenous injection of 750 MBq ^{99m}Tc methylene diphosphonate. Planar imaging of the spine and SI joints was performed in the anterior and posterior projections 3–4 hours after injection, with image acquisition around the SI joints using a single-head rotating gamma camera (IGE Starcam; GE Medical Systems, Milwaukee, WI, USA) through an elliptical course (360º, 64 projections, 20 s/projection). Data were acquired in a 128 × 128 matrix. Using the region-of-interest (ROI) method, a quantitative SI joint to sacrum ratio, calculated as SI/S ratio, was measured from the ratio between total number of counts for the region derived from the SI joint and an identical region derived from the sacrum. The ratio for the upper, middle, and lower parts of both joints was measured individually.

The equipment for SI joint scintigraphy is available in our Department of Nuclear Medicine, and the reference data have been published[37-39].

All participants provided written informed consent, and the study was approved by the human ethics committee of the local medical center. The research was in compliance with the Helsinki Declaration.

Data analysis and statistics. We recorded the data using an Excel spreadsheet running on a personal computer. Statistical analyses were performed using SAS software (version 9.13; SAS, Cary, NC, USA). Pearson correlation coefficient was used to assess relationships between ASO titer and SI/S ratio for the specified locations. We then applied generalized estimating equations (GEE) to assess the association of interest. With GEE, we adjusted for the correlations due to measurement of the SI/S ratio at left and right sides and at various locations (upper, middle, lower part) and adjusted for potential confounders as well. The analysis was also adjusted for age and sex. A p value ≤ 0.05 was deemed to indicate a statistically significant difference.

RESULTS

A total of 825 subjects from our database for the preceding 3 years were screened; 84 of these met the selection criteria and were enrolled in the study. The average age was 23 years (range 18.0–36.4). A high percentage of subjects, 85.7% (N = 72), reported lower back pain, and declared that back pain was limited to the lumbosacral area, especially in the parasagittal line of sacrum. The quality of pain was characterized as a deep, dull ache that was usually maximal over the SI joint and often radiated to the thigh but rarely below the knees. Data from medical records indicated the duration of back pain ranged from 3 weeks to more than 2 years, the pain behaving with a more gradual onset with no identifiable precipitating factors, such as throat infection. Most subjects did not have a definite diagnosis before testing of ASO titer and nuclear scintigraphy. About half of those patients with backache had posture imbalance, which occurred with prolonged standing still or eyes closed, but rarely happened during sitting. Interestingly, the Patrick test was always positive. Administration of analgesic drugs was partially able to alleviate the subjects' back pain.

All participants completed the SI joint scintigraphic examination as allocated. Nuclear scintigraphy results are shown in subjects with ASO titer 256 IU/ml in Figure 1A, 333 IU/ml in Figure 1B, and 382 IU/ml in Figure 1C.

As shown in Table 1, all data obtained in this descriptive study were expressed as mean, standard deviation (SD), and range (minimum–maximum), with scores indicating good correlation between the ASO titers and SI/S ratios. The means of SI/S ratios for specific locations (upper, middle, lower) in the left side and right side were in the range of 1.21~1.27, and 1.22~1.28, respectively.

The relationships between ASO titer and SI/S ratio for the various locations (left, right; upper, middle, lower) were sig-

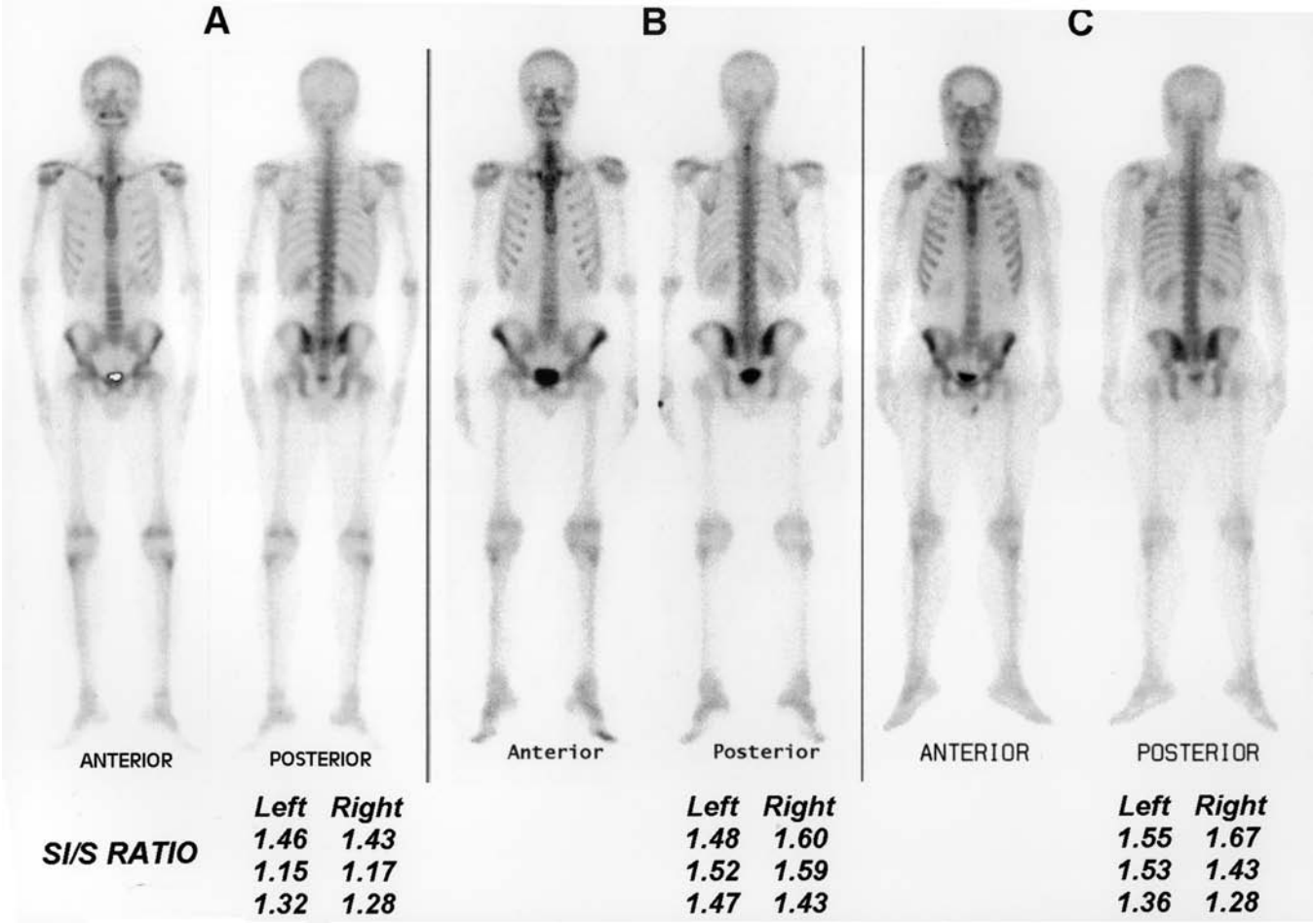

Figure 1. Nuclear scintigraphy in 3 subjects with high anti-streptolysin O (ASO) titer and increased quantitative sacroiliac joint ratio. ASO titers measured in the 3 subjects were (A) 256 IU/ml, (B) 333 IU/ml, and (C) 382 IU/ml.

Table 1. Subjects' characteristics (N = 84).

Variable	Mean	SD	Minimum	Maximum
Age, yrs	23.38	2.69	18.00	36.00
ASO titer	142.55	98.20	25.00	520.00
SI/S ratio				
LU	1.27	0.24	0.87	1.93
LM	1.24	0.18	0.88	1.86
LL	1.21	0.16	0.87	1.90
RU	1.28	0.25	0.84	2.15
RM	1.24	0.17	0.90	1.92
RL	1.22	0.16	0.94	1.71

ASO: anti-streptolysin O. SI/S ratio: the quantitative ratio derived from the counting number of the sacroiliac (SI) joint divided by that of sacrum (S). Region of SI joint inflammation: LU: left upper; LM: left middle; LL: left lower; RU: right upper; RM: right middle; RL: right lower.

nificantly correlated (Table 2). Pearson correlation coefficients for the relationship between ASO titer and SI/S ratio at different locations were 0.25~0.55 and 0.29~0.53 for the left and right sides, respectively.

We designed our statistical model to prevent modifying our associations of interests. Thus, we considered the potential confounders: subject characteristics (age, sex, body weight), laterality (left, right), and location (upper, middle, lower). We then implemented the full model for simultaneous interactions of ASO titer with subject characteristics, laterality, and location.

After adjustment for potential confounders, the association between ASO titer concentration and SI/S ratio was highly significant ($p < 0.0001$; Table 3). An ASO titer increase of 1 IU/ml produced a significant elevation in SI/S ratio by 0.0008 units. Similarly, age was significantly associated with SI/S ratio ($p = 0.0022$), with each extra year increasing the ratio by 0.0074. However, significant differences were not found for sex, body weight, or interaction between ASO titer and laterality, or between ASO titer and location (data not shown). Sex and body weight also were not associated with SI/S ratio. Further, the relationship between ASO titer and SI/S ratio did not vary with laterality or location. With elimination of the influence of ASO titer, the results indicated significant associations between the various locations and SI/S ratio. Compared

Table 2. Pearson correlation coefficients for ASO titer and SI/S ratio at different locations.

	SI/S Ratio					
	LU	LM	LL	RU	RM	RL
ASO titer	0.55	0.46	0.25	0.53	0.42	0.29
	p < 0.0001	p < 0.0001	p = 0.0228	p < 0.0001	p < 0.0001	p = 0.0072
SI/S ratio						
LU	1.00	0.65	0.33	.91	0.59	0.41
		p < 0.0001	p = 0.0019	p < 0.0001	p < 0.0001	p < 0.0001
LM		1.00	0.61	0.65	0.88	0.55
			p < 0.0001	p < 0.0001	p < 0.0001	p < 0.0001
LL			1.00	0.43	0.55	0.85
				p < 0.0001	p < 0.0001	p < 0.0001
RU				1.00	0.64	0.48
					p < 0.0001	p < 0.0001
RM					1.00	0.61953
						p < 0.0001
RL						1.00

SI/S ratio: the quantitative ratio derived from the counting number of the sacroiliac (SI) joint divided by that of sacrum (S). Region of SI joint inflammation: LU: left upper; LM: left middle; LL: left lower; RU: right upper; RM: right middle; RL: right lower. $p < 0.05$ = statistically significant.

Table 3. Generalized estimating equations analysis for association between ASO titer and SI/S ratio at different locations. Model adjusted for sex, body weight, lateralization, and part location using SAS 9.13.

Variable	Estimate	SE	95% CI		Z	p
Intercept	0.9269	0.0456	0.8375	1.0164	20.31	< 0.0001
ASO titer (IU/ml)	0.0008	0.0001	0.0005	0.0011	5.63	< 0.0001
Age (yrs)	0.0074	0.0024	0.0027	0.0121	3.07	0.0022
Lateralization (left vs right)	–0.0062	0.0013	–0.0087	–0.0037	–4.88	< 0.0001
Part (upper vs middle)	0.0331	0.0008	0.0316	0.0347	42.72	< 0.0001
Part (upper vs lower)	0.0609	0.0014	0.0580	0.0637	42.36	< 0.0001
Part (middle vs lower)	0.0275	0.0019	0.0237	0.0312	14.39	< 0.0001

$p < 0.05$ = statistically significant.

to the right side, the SI/S ratio was significantly lower for the left side (0.0062; $p < 0.0001$). The SI/S ratios for the upper locations on both sides were significantly higher compared to the analogous values for the middle and lower locations by 0.0331 and 0.0609 units, respectively ($p < 0.0001$). Similarly, the SI/S ratio for the middle locations was significantly higher compared to the lower locations, by 0.0275 unit ($p < 0.0001$).

DISCUSSION

We emphasize that our study population did not exhibit any clinical criteria associated with PSReA because there was no laboratory evidence suggestive of underlying inflammatory process such as elevated ESR and CRP, and all subjects were HLA-B27-negative. Although symptoms in most patients with PSReA are often subtle, subclinical, or asymptomatic, the presence of only a positive ASO titer or lower back pain cannot confirm the diagnosis of PSReA. At most, identification as unclassified or undifferentiated arthritis would be the most likely[40]. Nonetheless, our main objective was to determine the relationship between ASO titer and degree of SI joint disorder. The ASO titer has been generally utilized as a clinical measure in PSReA assessment and may also serve as an indicator for reactive arthritis. Many reports have addressed the issue of ASO titer levels and their relationship to arthritis/arthritic pain in the peripheral joints (i.e., the elbow, wrist, hip, knee, and ankle), but rarely the SI joint. We speculate that a reactive process possibly derived from antecedent bacterial infection probably affects the SI joint. Based on the demonstrated correlation between ASO titers and SI joint disorder, we strongly confirmed the accuracy of this assumption in our sample population. To our knowledge, this is the first evidence-based investigation to confirm this relationship.

Quantitative SI joint scintigraphy has relatively low specificity, and this has limited its routine clinical application in rheumatology, orthopedics, and rehabilitation. On the other hand, it is generally accepted that SI joint scintigraphy is very sensitive. Increased activity in the region of the SI joint might well be expected because of inflammatory lesions related to sacroiliitis, such as syndesmophyte formation or extraskeletal ligamental calcification[36]. Quantitative SI imaging has proven useful for detection of active sacroiliitis, sometimes even before the radiological detection of SI joint abnormalities. When used in PSReA, it can reveal appropriate detail of the SI

joint easily, as our results show. Our findings suggest that the technique may also be of value for investigating these joints in subjects with high serum ASO titers.

The various correlations with location were somewhat confusing. In order to understand the different locations, anatomy and histology examinations of the SI joint should be instituted. The SI joint is a true diarthrodial joint; however, it does have unique characteristics not typically found in other diarthrodial joints, for example, having fibrocartilage in addition to hyaline cartilage, as well as discontinuity of the posterior capsule[41]. The synovial portion of the SI joint is more anterior in position, and the syndesmotic portion is more posterior; the former consists of the auricular surfaces of the sacrum and ilium and the latter consists of the roughened sacral and ilial tuberosities that attach the interosseous sacroiliac ligaments. The synovial auricular surface is like an auricular "L" shape[42] when viewed from the side, with a broad superior limb oriented posterosuperiorly and an elongated inferior limb oriented posterioinferiorly. The auricular surface on the sacral side is lined by a 3 mm layer of hyaline cartilage, and the auricular surface on the iliac side is lined by a 1 mm layer of fibrocartilage. The chondrocytes between the 2 kinds of cartilage are characterized by distinct size, shape, and cell-column orientation[21]. Interestingly, one report has demonstrated the hyaline cartilage also exists on the iliac side, rather than on the sacral side only. Puhakka, *et al*[43] reported (1) that in the distal third of the joint the margins of the iliac joint facet resemble a synovial joint, and have an inner capsule filled with synovial cells; (2) that the proximal third of the hyaline iliac cartilage and the hyaline sacral cartilage attach strongly to the surrounding stabilizing ligaments, forming wide margins of fibrocartilage; and (3) that on microscopy the dorsal transition between the proximal two-thirds and distal third of the cartilaginous joint is rich in anatomical and histological variants, including osseous clefts, cartilage and subchondral defects, and vascular connective tissue in the bone marrow. This is an important article describing the difference in the upper third and the lower third of the SI joint.

The syndesmotic portion of the SI joint, which is more posteriorly located, contains the interosseous sacroiliac ligaments that consist of short fibers in the deepest part of the joint and are considered the strongest ligament in the body[21]. This would be the second example for considering the difference of location in the SI joint, because the syndesmotic portion only structurally localizes in the upper two-thirds of the joint. In addition to extrinsic ligaments, the SI joint has intrinsic capsular ligaments that consist of the ventral and dorsal sacroiliac ligaments, as well as the Illi's ligament that is located in the uppermost part of the SI joint and is an extension of the interosseous sacroiliac ligaments[21]. This might be the third example of location difference. The fourth example might be considered in view of the biomechanical load on the SI joint, because one of its so-called "self-bracing mechanisms" is the corkscrew appearance of the joint created by the different wedge angles in transverse cross-sections at the cranial and caudal ends of the joint, which provide resistance to sliding[21]. Our study showed that the ASO titer had stronger correlations with both upper parts (0.55 and 0.53) than with the middle (0.46 and 0.42) and lower parts (0.25 and 0.29), even when all the correlations between ASO titer and locations were universally statistically significant.

Based on these observations with respect to varying biology and physiology in specific locations, and on our correlation results, we speculate that the variable locations/parts in the SI joint under the influence of a possible immune-reactive process would show a different uptake in scintigraphic scans. Our statistical data revealed stronger uptake in the upper parts, weaker in middle parts, and weakest uptake in the lower parts. The weakest uptake in the lower third of the SI joint might also respond as speculated by Resnick, "...During degeneration... although the joint space loss may involve the entire articulation, focal areas of abnormality are particularly frequent at the inferior aspect of the joint"[44].

It is difficult to explain the correlation results in the laterality of the SI joint; however, anatomical evidence may shed some light on this. Mior, *et al*[21] demonstrated that the iliac sulcus between the iliac tuberosity and auricular surface and the sacral crest (medial rim of the inferior limb) are structurally interlocking, and the highest point of the iliac tuberosity interlock is with the middle sacral fossa. They noted that, surprisingly, this interlocking disfigured the left-side iliac tuberosity by widening the sulcus, which occurred only on the left side; this feature was present in about 75% of the left iliac tuberosities examined, and it seemed never to occur on the right side[21]. This structural finding might support our results because the iliac tuberosity irregularity might decrease uptake of the radioactive tracer, so the SI/S ratio was significantly lower for the left side than the right side ($p < 0.0001$). This phenomenon needs to be confirmed with more research and elucidation of these mechanisms in detail. Based on these joint biology findings, the measurable different ratios from different parts of the SI joint are explained with quantitative SI scintigraphy because fractional analysis of the upper, middle and lower thirds of the joint is reportedly more sensitive in revealing disorder limited to the lower half of the joint, the location of the synovium[32]. Further, the biology of any one of the 3 parts of the SI joint are measurable, and that is the reason we used the ratios of the 3 parts for statistical analysis.

Considering our results, a critical explanation with respect to the pathophysiology of SI joint disorder is necessary to elucidate the underlying pathology of the joint disorder. Because of the aforementioned characteristics, different joint levels may be affected to different degrees by disorder/inflammation, perhaps by antibody- or immune-mediated reactions. At the same time, we agree with the analysis by Slipman, *et al*[27]; they assumed that SI joint disorder involved synovium with mild irritation only, but as the disorder progressed, adjacent cartilaginous or osseous structures become involved because

of the chronicity of the disorder/inflammatory or immune-mediated response, with acceleration in osteoblast activity. This altered bone metabolism would then be detectable using nuclear imaging.

With respect to the effects of potential confounders, Front, *et al*[45] compared the left and right iliac bones as well as SI regions in 130 healthy subjects; they found no significant laterality differences, but a significant decrease in mean SI/S ratio was found for the older relative to the younger group in their study. In contrast, our statistical findings for the age and laterality factors were not compatible with those of Front, *et al*; we found that the SI/S ratio increased by 0.0074 for every extra year of age, and the SI/S ratio for the left side was significantly lower compared to the right (0.0062) in our population (aged 17 to 40 yrs).

Lin and Wang[46] also studied the influence of age and sex on quantitative SI joint scintigraphy in healthy subjects, observing a significant difference in SI/S ratio change and age irrespective of sex, as well as a trend to decreasing SI/S ratio with increasing age across all age groups. In contrast, our analysis was compatible with their findings for gender, but revealed the opposite relationship in age, with the ratio increasing by 0.0074 with each additional year of age. Further, their results showed no laterality differences in SI/S ratio; but we observed the SI/S ratio for the left side was significantly lower than that for the right (0.0062). These groups also found significant between-sex differences in SI/S ratios for certain age groups, but our results disclosed insignificant differences between sex and SI/S ratios. These differences are probably related to variations in subject selection and sample heterogeneity and size.

We endorse the recommendation of Aviles, *et al*[18], who suggested that PSReA should be included in the differential diagnosis for all adult patients presenting with arthritis. We suggest that subjects with even subtle SI joint involvement should undergo measurement of ASO titer and SI joint imaging study. Our evidence-based results suggest medical staff should use SI imaging and ASO titer to detect the likelihood of unclassified/undifferentiated arthritis in patients with lower back pain. Using well established methods, new insights into PSReA within a broader spectrum of disease were gained.

Our findings demonstrate a high correlation between SI joint involvement by scintigraphy and high ASO titers. The results stress the importance in clinical practice of measurement of ASO titers and quantitative SI joint scan to determine joint involvement when patients present with myalgia or arthritic pain and where there is pain in the SI area.

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