

Research Article

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Relationship of HS CRP and sacroiliac joint inflammation in undifferentiated spondyloarthritis

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Abstract: Objective. Elevation of serum high sensitivity C-reactive protein (hs-CRP) level has been demonstrated as a risk factor for varying diseases, as well as a biomarker for predicting recovery after operation of lumbar disc herniation. Our objective was to investigate the relationship between serum hs-CRP and sacroiliac (SI) joint inflammation in patients with undifferentiated spondyloarthritis (uSpA). Methods. In this retrospective study, we enrolled patients with uSpA who underwent hs-CRP testing between January 2007 and September 2013. Serum hs-CRP was analyzed at our central laboratory. All enrolled patients underwent skeletal scintigraphic scan with quantitative sacroiliac measurement. Results: A total of 29 patients were enrolled with mean age 32.27 years and female:male ratio of 6:23. Pearson's correlation coefficient showed a significant difference between hs-CRP in serum and SI/S ratio in uSpA, particularly the middle part of the sacroiliac joint, either right side or left side. The significantly high concentration of serum hs-CRP might indi-

cate a systemic inflammatory response to flare-up of the SI joint and might be an indicator of SI inflammation in uSpA.

Keywords: High sensitivity C-reactive protein; Sacroiliac joint; Biomarker; Undifferentiated spondyloarthritis; Quantitative sacroiliac scintigraphy

1 Introduction

Elevation of serum high sensitivity C-reactive protein (hs-CRP) level has been demonstrated as a risk factor for heart failure [1], acute stroke [2], infective endocarditis [3], and diabetic nephropathy [4]. Chronic lower back pain is associated with impaired quality of life, loss of productivity and vast expenses of health care [5]. Lumbar disc herniation (LDH) is one of contributing factors for chronic lower back pain [6], and some studies have confirmed the relationship between hs-CRP and LDH. For instance, two studies found that high concentration of hs-CRP measured before intervention for LDH, either operation or injection therapy, strongly indicates poor or less recovery [7,8]. However, a study from Korea did not support the relationship between hs-CRP and many diseases contributing chronic low back pain, including LDH [9].

Undifferentiated spondyloarthritis (uSpA) is a term used to describe symptoms and signs of spondylitis in someone who does not meet the criteria for a definitive diagnosis of AS or related disease. Patients with uSpA often develop chronic lower back pain [10]. The sacroiliac (SI) joint is most frequently involved. We assumed that serum hs-CRP could be a blood biomarker in uSpA. We investigated if serum hs-CRP level correlated with SI joint flare up in uSpA, and further if there was any relationship with varying parts of SI joint(s).

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HSU CS and CHANG ST had equal contribution

2 Materials and methods

2.1 Patients and methods

We retrospectively enrolled patients in a data bank in a medical center, who were confirmed as having a diagnosis of uSpA (codes M4600-M4609, M4680-M4689, M4690-M4699 in the International Classification of Diseases, 10th Revision, Clinical Modification) during the period of January 2007 to December 2013, and those patients underwent testing of erythrocyte sedimentation rate (ESR) and hs-CRP at the central laboratory, as well as musculoskeletal bone scanning and quantitative sacroiliac scintigraphy (QSS). Exclusion criteria included medical history of major surgery, malignant neoplasm, tumor metastasis, metabolic/endocrine disease, and prolonged immobility or cachexia.

2.2 Measurement of ESR, hs-CRP and SI joint inflammation

The ESR and hs-CRP tests were conducted at the central hospital laboratory, and the latter was analyzed by IMMAGE® Immunochemistry Systems (BECKMAN COULTER, USA). The system comprised an infrared particle immunoassay, and the normal range was less than 0.1mg/dL [11].

Table 1: Demographic characteristics of enrolled patients (N = 29; Female = 6, Male = 23)

Variable	Mean	SD	Minimum	Maximum
Age (year)	32.27	13.81	20	78
Serum hs-CRP (mg/dL)	0.21	0.12	0.04	0.41
ESR (mm/hr)	29	18	6	52
SI/S ratio				
RU	1.25	0.35	0.74	2.25
RM	1.31	0.14	0.93	1.98
RL	1.23	0.36	0.84	1.91
LU	1.37	0.54	0.77	2.13
LM	1.34	0.16	0.89	1.96
LL	1.28	0.46	0.77	1.97

SI/S ratio: the quantitative ratio derived from the counting number of the sacroiliac (SI) joint divided by that of sacrum (S)

ESR = erythrocyte sedimentation rate

hs-CRP = high sensitivity C-reactive protein

Region of SI joint inflammation: RU: right upper; RM: right middle;

RL: right lower; LU: left upper; LM: left middle; LL: left lower.

SI joint disorder was measured by QSS, which was performed by using injection of 750 MBq ^{99m}Tc methylene diphosphonate intravenously. Planar imaging of the sacrum and SI joints was performed 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). Using the region-of-interest method, a quantitative SI joint to sacrum ratio (SI/S ratio) was measured from the ratio between total number of counts for the region derived from the SI joint and an identical level region derived from the sacrum. The ratio for the upper, middle, and lower parts of both joints was measured individually (Fig. 1). The equipment for QSS is available in our Department of Nuclear Medicine, and the reference data have been published [12,13].

2.3 Data analysis and statistics

The data were recorded and stored digitally. Statistical analyses were performed using SAS software (version 9.13; SAS, Cary, NC, USA). Pearson correlation coefficient was used to assess relationships among ESR, hs-CRP and SI/S ratio at the left and right sides and at various parts (upper, middle, lower part). A p value ≤ 0.05 was considered to represent statistical significance.

2.4 Ethics statement

The research protocol (TSGHIRB, No. 2-102-05-021) was approved by the Institutional Review Board of Tri-Service General Hospital. The study conformed to the principles of the Declaration of Helsinki. With the approval of the Institutional Review Board, informed consent was waived due to the retrospective nature of the study.

3 Results

A total of 29 patients were enrolled in our study. The number of male patients was approximately 4-fold higher than the number of female patients and the mean age of the study group was around 32 years old. Table 1 shows the demographic characteristics of the enrolled patients. Pearson's correlation coefficient showed no significant relationship between ESR and the varying parts of the SI joints (all p > 0.05; Table 2). However, Pearson's correlation coefficient showed a significant relationship between

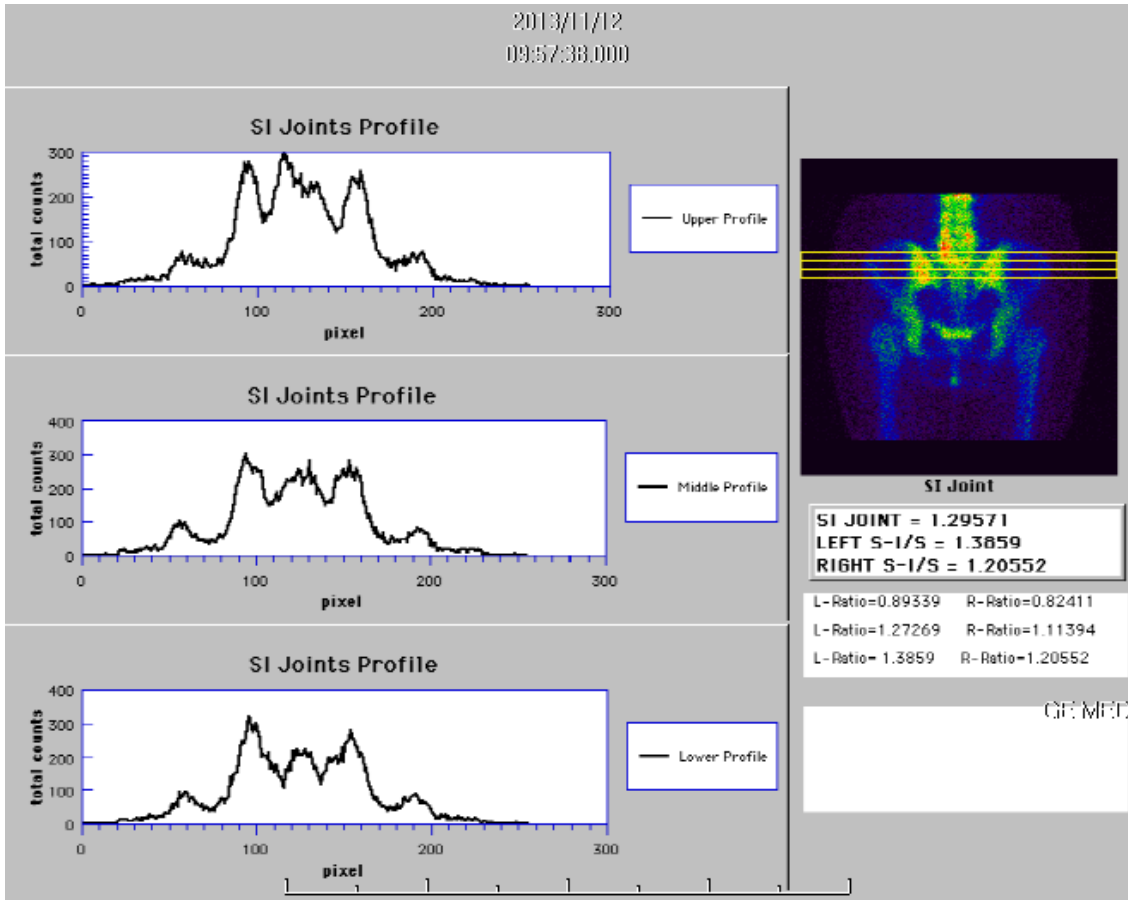


Figure 1: Representative images with sacroiliac joint disorder using quantitative sacroiliac scintigraphy in case 15 (Y.-T.G.) with undifferentiated spondyloarthritis. Measurement of the ratio between total number of counts from the right and left sacroiliac (SI) joints divided by sacrum (S) for each is calculated as SI/S ratio (right panel). The ratio for the upper, middle, and lower parts of both joints was measured separately, showing 0.89339, 1.27269, and 1.3859 in the left-sided joint (mean = 1.3859), and 0.82411, 1.11394, and 1.20552 (mean = 1.20552) in the right-sided joint.

Table 2: Pearson’s correlation coefficient for ESR and SI/S ratio at different parts.

	Pearson’s correlation coefficient	p-value
SI/S ratio of varying parts		
RU	-0.087	0.473
RM	0.623	0.064
RL	0.264	0.372
LU	0.132	0.481
LM	0.548	0.121
LL	0.351	0.176

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

Table 3: Pearson’s correlation coefficient for hs-CRP and SI/S ratio at different parts.

	Pearson’s correlation coefficient	p-value
SI/S ratio of varying parts		
RU	-0.076	0.364
RM	0.519	0.024*
RL	0.107	0.283
LU	0.021	0.350
LM	0.540	0.020*
LL	0.251	0.133

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

hs-CRP and the middle part of the SI joint, either right side or left side (0.519 vs $p=0.024$ and 0.540 vs $p=0.020$, respectively; Table 3).

4 Discussion

Sugimori *et al.* [7] found a positive correlation between the concentration of hs-CRP before operation and the Japanese Orthopaedic Association score after operation, and concluded that a higher concentration of hs-CRP before operation showed a poorer recovery after operation. Ackerman & Zhang [8] examined inflammatory serum markers and pain responses to lumbar epidural steroid injections in patients with LDH, and found that the higher the hs-CRP levels prior to the injection therapy, the less improvement in pain scores seen following the injection therapy. They suggested that elevated hs-CRP level is useful for objectively predicting response to the steroid injection in those patients with LDH with lower extremity radiculitis [8]. Although there is no direct anatomic linkage between LDH and SI joint, our results showed a significant difference between serum level of hs-CRP and the bilateral SI joints. To the best of our knowledge, this is the first study to confirm the relationship between hs-CRP in serum and SI/S ratio in uSpA, particularly in middle part of bilateral SI joints.

The strong correlation between hs-CRP and SI/S ratio may provide some guidance when we face patients with uSpA, particularly tenderness at the middle part of SI joint, (e.g. positive Fortin's finger sign). Serum hs-CRP might indicate some kind of inflammatory condition occurring in the joint. We speculate that the middle part of the SI joint might exert a kind of reaction in response to elevation of serum hs-CRP and vice versa. Back pain is common in the general population and inflammation is an immune or biological reaction most commonly activated by cytokines [14,15]. The serum hs-CRP level might act as a blood biomarker for development of SI joint inflammation in uSpA. The worldwide rheumatologists have accepted the fact that elevated CRP is part of the classification criteria of non-radiographic SpA [16-18].

The term uSpA is used to describe symptoms and signs of spondylitis in someone who does not meet the criteria for a definitive diagnosis of ankylosing spondylitis (AS) or related disease(s). Sometimes a doctor may make an initial diagnosis of spondyloarthropathy or uSpA if certain symptoms are present but are not enough to make a specific diagnosis. Many people with uSpA have been told over the years that they are simply "anxious

and depressed" or received a diagnosis of fibromyalgia, a chronic disorder associated with widespread muscle and soft tissue pain. Over time, some people with uSpA will develop a well-defined form of spondylitis such as AS. Some doctors consider uSpA a "cousin" to AS, psoriatic arthritis, spondylitis associated with inflammatory bowel/Crohn's disease, and reactive arthritis. The presence of concomitant uSpA and sarcoidosis has been reported [19]. The development of uSpA in patients with sarcoidosis should forewarn physicians to the possibility of more than one form of spondyloarthropathy, and a relevant association between these two disorders or their coexistence may cause diagnostic challenges [19].

The etiology of uSpA can be attributed as inflammatory/infectious in origin. HLA-B27 has been shown to be a biomarker of AS [20]. Some authors have conducted DNA analyses on synovial cells collected from patients with sacroiliitis to investigate the link between infection and joint inflammation in patients with sacroiliitis [21,22]. Animal studies have revealed that X gene might be related to the development of sacroiliitis or spondylitis in mice [23]. However, it is hard to say which the etiology would link to uSpA right now due to limited information.

A recent study confirmed that uSpA is a severe and anti-TNF-responsive phenotypic subtype of spondyloarthritis. Patients with uSpA always exhibit a mixed axial (inflammatory back pain in 87.5%) and peripheral (peripheral arthritis in 62.5%) phenotype, with almost half of the patients having low-grade sacroiliitis on conventional plain films. The overall disease activity in uSpA is similar to AS and higher than in psoriatic arthritis. Initiation of TNF blockade significantly decreases disease activity in uSpA, with a similar amplitude to that in AS and psoriatic arthritis [24].

In regards to metabolism, uSpA showed a distinct difference compared with AS. In a study evaluating plasma vitamin D (vit D) level and its association with disease activity in two kinds of patient population, the results showed the plasma vitamin D levels were 18 $\mu\text{g/L}$ (8-38) in the AS group, 20 $\mu\text{g/L}$ (4-92.3) in the uSpA group and 24.3 $\mu\text{g/L}$ (7.2-76.8) in the control group. Surprisingly, the vitamin D levels were inversely related to both ESR and C-reactive protein (CRP) in the AS patients ($p=0.002$, $R=-0.428$; $p<0.001$, $R=-0.592$, respectively); however, the correlation was not observed in the uSpA patients [25].

Articular involvement of inflammation of the SI joint in uSpA is not rare. A case report of a 43-year-old man with uSpA reports that he presented with history of recurrent episodes of anterior uveitis and progressive limping secondary to lower back and buttock pain. Initially he showed only mild tenderness and swelling of the right

midfoot, and the magnetic resonance imaging of the lumbosacral spine was consistent with left sacroiliitis [26].

Involvement of the middle part of the SI joint in relationship with high hs-CRP is of interest. The SI joint is a true but not typical diarthrodial joint and is composed of fibrocartilage in addition to hyaline cartilage [27]. The synovial portion of the SI joint, shaped like an auricular “L”, is more anterior in position and the syndesmotic portion is more posterior [28]. The SI joint acts as “self-bracing mechanisms” because of its corkscrew shape created by the different wedge angles in transverse cross-sections at the cranial and caudal ends of the joint, which provide resistance to sliding [29,30]. We believe that the self-bracing mechanisms can be damaged by inflammation, which occurring in the middle part of the joint was more obvious than in other parts. Furthermore, inflammation at the SI joint occurred simultaneously together with elevation of serum hs-CRP level.

This study has a number of limitations, including its retrospective design, lack of follow-up and small patient numbers. Further study is necessary to explore the relationship between serum hs-CRP and uSpA.

In conclusion, there was an association between hs-CRP in serum and SI/S ratio in uSpA, particularly in middle part of bilateral SI joints. The significantly high concentration of serum hs-CRP might indicate a systemic inflammatory response to flair-up of SI joint and might act as a biomarker to indicate development of SI joint inflammation in uSpA.

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