

Differential mRNA Expression of *COX-2* and Proinflammatory Mediators in Patients with Rotator Cuff Tears and Osteoarthritis of the Hip

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Abstract

Purpose: Bursal inflammation is thought to be a major cause of pain in degenerative rotator cuff tears (RCTs). While the expression of proinflammatory mediators, such as *COX-2*, *TNF- α* , *IL-1 β* , and *IL-6*, is crucial for the pathophysiology of osteoarthritis (OA), their role in degenerative RCTs remains unknown. The aim of this study was to determine the expression of *COX-2* and proinflammatory mediators in the development of RCT-induced pain by comparing their levels in patients with hip OA or RCTs. **Methods:** We included samples obtained from 31 shoulders of 31 patients with RCTs and samples from 30 hips of 27 patients with hip OA. The mRNA levels of *COX-2*, *TNF- α* , *IL-1 β* , and *IL-6* were determined using RT-PCR, and were compared between the subacromial bursa and hip joints. We also analyzed *IL-1 β* -induced *COX-2* expression in the subacromial bursa and synovial blast of the hip. **Results:** *COX-2*, *IL-1 β* , and *IL-6* expression levels were significantly lower in the subacromial bursa of RCTs than in hip OA samples, while no significant difference was observed for *TNF- α* . No significant difference in the fold increase was observed between subacromial bursa and hip OA samples, even though *IL-1 β* -induced *COX-2* expression increased in both samples. **Conclusion:** Our findings suggest that the main mechanism underlying pain development differs between patients with RCTs and those with hip OA.

Keywords

Rotator Cuff Tear, Pain, Hip Osteoarthritis, Tumor Necrosis Factor- α , Interleukin (IL)-1 β , *COX-2*, *IL-6*

1. Introduction

Most patients with rotator cuff tears (RCTs) first come to the hospital because of pain [1]. Inflammation is normally implicated as the source of shoulder pain in patients with rotator cuff impairments [2] [3]. Inflammatory processes occur in the acute phase of RCTs following tendon injury, and bursal inflammation is thought to be a major cause of shoulder pain in degenerative RCTs [2] [3] [4], particularly when compared with inflammation in the glenohumeral (GH) joint [5]. However, the expression of proinflammatory mediators in degenerative RCTs remains largely unknown.

In contrast to RCTs, the origin of pain in osteoarthritis (OA) has been extensively studied. Inflammatory stimuli initiate a cascade of events, including the release of cytokines and other mediators from the cartilage and synovium. These induce metabolic disturbances and enhance catabolism in joint tissues of patients with OA, which promotes joint pain [6]. Proinflammatory mediators, especially tumor necrosis factor- α (TNF- α), interleukin (IL)-1 β , and IL-6, are crucial for the pathophysiology of OA [6]. In addition, anti-inflammatory effects are related to the downregulation of cyclooxygenase-2 (*COX-2*) and reduced proinflammatory mediator expression, regardless of joint [7] [8].

The purpose of this study was to investigate the role of *COX-2* and proinflammatory mediators in the development of pain in patients with degenerative RCTs. To this end, we used real-time polymerase chain reaction (RT-PCR) to compare these mediators' mRNA expression in RCT patients and patients with hip OA-associated pain. We show that *COX-2* and proinflammatory mediator levels were generally lower in patients with RCTs than in those with hip OA-associated pain.

2. Methods

2.1. Patient Selection

The experimental protocol was conducted in accordance with the guidelines of Kitasato University Medical Ethics Organization for Clinical Research (KMEO B13-113). The Institutional Review Board of our institute approved the protocol for this study, and all participants provided written informed consent. Between September 2013 and June 2016, we obtained samples from 31 shoulders of 31 patients undergoing arthroscopic rotator cuff repair for degenerative RCTs, and 30 hips from 27 patients undergoing total hip arthroplasty or arthroscopic hip surgery for hip OA. Inclusion criteria were: onset of joint pain more than one month before surgery and age over 20 years. Patients with traumatic RCTs, shoulder or hip fractures at the time of surgery, a history of previous shoulder or hip operations, a history of rheumatoid arthritis or other collagen diseases, and a history of corticosteroid use, including both injections and oral usage within one month before operation, were excluded from the study.

For all patients, age, sex, and clinical history were recorded. To define the severity of anatomical damage, the size of the RCT was determined by coronal

imaging using Cofield and Deorio classification [9], whereas hip OA grade was assessed using the anteroposterior view of plain radiographs and the Kellgren and Lawrence X-ray grading system [10]. Preoperative clinical assessments of RCTs and hip OA were performed using the Constant score and modified Harris Hip Score, respectively [11] [12]. Cartilage condition was assessed arthroscopically or macroscopically according to the International Cartilage Repair Society (ICRS) classification system [13].

All arthroscopic rotator cuff repair surgeries were performed by a single experienced shoulder surgeon (K.T.). We harvested a synovial membrane sample from the subacromial space of each RCT patient because subacromial bursitis is generally accepted as the main source of pain in degenerative RCTs compared with inflammation in the GH joint [2] [3] [4] [5]. For total hip arthroplasty, every patient was operated using the anterolateral approach in the supine position by two experienced hip surgeons (T.N. and F.K.). We harvested a sample of the synovial membrane from the site of strongest synovitis for further evaluation when capsulectomy was performed.

2.2. Isolation of RNA and Quantitative RT-PCR

Total RNA was extracted from the harvested synovial samples using TRIzol (Invitrogen, Carlsbad, CA, USA) according to the manufacturer's instructions, and was used as template for first-strand cDNA synthesis using SuperScript III RT (Invitrogen). The PCR reaction mixture consisted of 2 μ L of cDNA, specific primer set (0.2 μ M final concentration), and 12.5 μ L SYBR Premix Ex Taq (TaKaRa, Kyoto, Japan) in a final volume of 25 μ L. The sequences of PCR primer pairs are listed in Table 1. Quantitative PCR was performed using the CFX-96 RT-PCR detection system (Bio-Rad, Hercules, CA, USA). PCR cycle parameters were as follows: initial denaturation at 95°C for 1 min, followed by 40 cycles of 95°C for 5 s, and 60°C for 30 s. mRNA expression of target genes was normalized to that of glyceraldehyde 3-phosphate dehydrogenase (*GAPDH*) mRNA using delta-delta method.

Table 1. Sequences of PCR primer pairs.

Primer	Sequence (5'-3')	Product size (bp)
<i>COX-2-F</i> <i>COX-2-R</i>	TGGCTGAGGGAACACAACAG AACAACTGCTCATCACCCCA	74
<i>TNF-α-F</i> <i>TNF-α-R</i>	CTTCTGCCTGCTGCACTTTG GTCACTCGGGGTTGCGAGAAG	118
<i>IL-6-F</i> <i>IL-6-R</i>	GAGGAGACTTGCCTGGTGAAA TGGCATTGTGGTTGGGTCA	199
<i>IL-1β-F</i> <i>IL-1β-R</i>	GTACCTGTCCTGCGTGTTGA GGGAACTGGGCAGACTCAA	153
<i>GAPDH-F</i> <i>GAPDH-R</i>	TGTTGCCATCAATGACCCCTT CTCCACGACGTACTCAGCG	202

The levels of four molecular biomarkers of inflammation in synovial tissue samples were measured: *COX-2*, *TNF- α* , *IL-6*, and *IL-1 β* . We compared these levels between the RCT and OA patient groups, and between the subacromial bursa (SAB) of RCTs and hip joints of hip OA.

2.3. Effect of IL-1 β on COX-2 Expression in the Synovial Fibroblasts of SAB and Hip Synovium

Synovial tissue was excised from the SAB and hip joints for the assessment of molecular biomarker levels, as previously described [2] [3] [14]. However, SAB is pathologically different from joint synovial blast [15], and no reports on the difference in *COX-2* expression between SAB and joint synovial blast are available. Therefore, we analyzed IL-1 β -induced *COX-2* expression in the SAB and synovial blast of the hip. The excised tissue was minced, digested for 2 h at 37°C with type 1 collagenase (0.1%; Sigma-Aldrich, Lakewood, NJ, USA), and passed through a 40- μ m filter (Becton Dickinson, Franklin Lakes, NJ, USA), to yield single-cell suspensions. Cell numbers were determined using a hemocytometer. Nucleated cells isolated from the synovium were seeded at 1×10^4 cells/cm² in 6-well plates containing minimum essential medium (Gibco, Carlsbad, CA, USA) supplemented with 10% fetal bovine serum, 100 U/mL penicillin, and 100 μ g/mL streptomycin, and the cells were incubated at 37°C in an incubator with 5% CO₂ for seven days. After one week, synovial fibroblasts were left untreated or treated with 50 ng/mL of human recombinant IL-1 β (Biolegend, San Diego, CA, USA) for 24 h. Cells were harvested, total RNA was isolated as described, and *COX-2* mRNA in synovial fibroblasts was determined by RT-PCR. The experiment was performed four times.

2.4. Statistical Analysis

Statistical analyses and power analyses were performed using commercial software (JMP Pro version 14.3, SAS Institute Inc., Cary NC, USA). Results are expressed as the mean \pm standard deviation (SD). The chi-square test was used for gender comparisons in RCT and hip OA groups. Mann-Whitney's U-test was used to compare age, and mRNA levels of *COX-2* and proinflammatory mediators between two groups. For all statistical analyses, significance was defined as $P < 0.05$.

3. Results

3.1. Patient Characteristics

Patients' characteristics are presented in **Table 2**. There was no significant difference in age between the groups, whereas significant differences in gender and ICRS classification were observed.

3.2. Proinflammatory Cytokine Levels in Patients with RCTs and Hip OA

Mann-Whitney's U-test revealed a significant difference in *COX-2*, *IL-6*, and

Table 2. Patient characteristics.

	RCT group (31 shoulder samples, 31 patients)	Hip OA group (30 hip samples, 27 patients)	P value
Age (years)	66 (range, 44 - 79)	63 (range, 40 - 86)	0.22
Sex	F, 14; M, 17	F, 23; M, 4	0.002
Side	R, 18; L, 13	R, 18; L, 12	0.88
Anatomical damage*	7:9:5:6:4	0:0:5:25	-
Clinical score*	51.9 (range, 16 - 85)	40.5 (range, 19 - 65)	-
ICRS classification†	18:6:6:1:0	0:0:0:30	<0.0001

RCTs, rotator cuff tears; OA, osteoarthritis; F, female; M, male; R, right; L, left; NSAID, nonsteroidal anti-inflammatory drug. *Severity of RCTs was assessed by Cofield and Deoriot classification [9] (partial tear: small tear; moderate tear; large tear; massive tear). Severity of OA hip joint damage was assessed using plain radiographs [10] (grades 1:2:3:4). †Shoulder damage was assessed by the Constant score [11], whereas hip damage was assessed using a modified Harris Hip Score [12]. †(ICRS grades 0:1:2:3:4) [13].

IL-1 β mRNA levels between RCT and hip OA patients. However, no significant difference in *TNF- α* expression was observed between three synovial fibroblast samples (Figure 1, Table 3).

3.3. Effect of IL-1 β on COX-2 Expression in the Synovial Fibroblasts of SAB and Hip Joint

COX-2 mRNA expression increased in SAB samples of RCT patients and hip OA samples following treatment with IL-1 β . However, no significant difference in fold increase was observed between SAB samples from RCT and hip OA patients (fold change: SAB, 17.7 \pm 5.2; hip OA, 19.5 \pm 12.0; P = 0.76; power, 0.06).

4. Discussion

The present study revealed that *COX-2*, *IL-6*, and *IL-1 β* mRNA levels were significantly lower in patients with RCTs than in those with hip OA, whereas no significant difference in *TNF- α* expression was detected. In addition, both SAB and hip joint synovium showed an increase, albeit non significant, in *COX-2* mRNA expression following treatment with IL-1 β . Hence, our findings suggest that the main mechanism underlying the development of pain in patients with RCTs after the acute phase differs from that underlying the development of pain in patients with hip OA because, with the exception of *TNF- α* , the levels of critical pain mediators involved in the pathophysiology of OA were lower in RCT patients.

Even though they are both ball joints, the shoulder joint differs from the hip joint in that it is a non-weight bearing joint. The destructive response of the synovium, which is induced by cartilage breakdown, plays a major role in the development of OA pain [6]. In contrast to OA, SAB is affected by a torn rotator cuff. Our RCT subjects exhibited a much lower grade of ICRS classification compared with the hip OA group, suggesting that in their case, subacromial bursitis was not affected by cartilage debris as much as it was in hip OA. Accordingly,

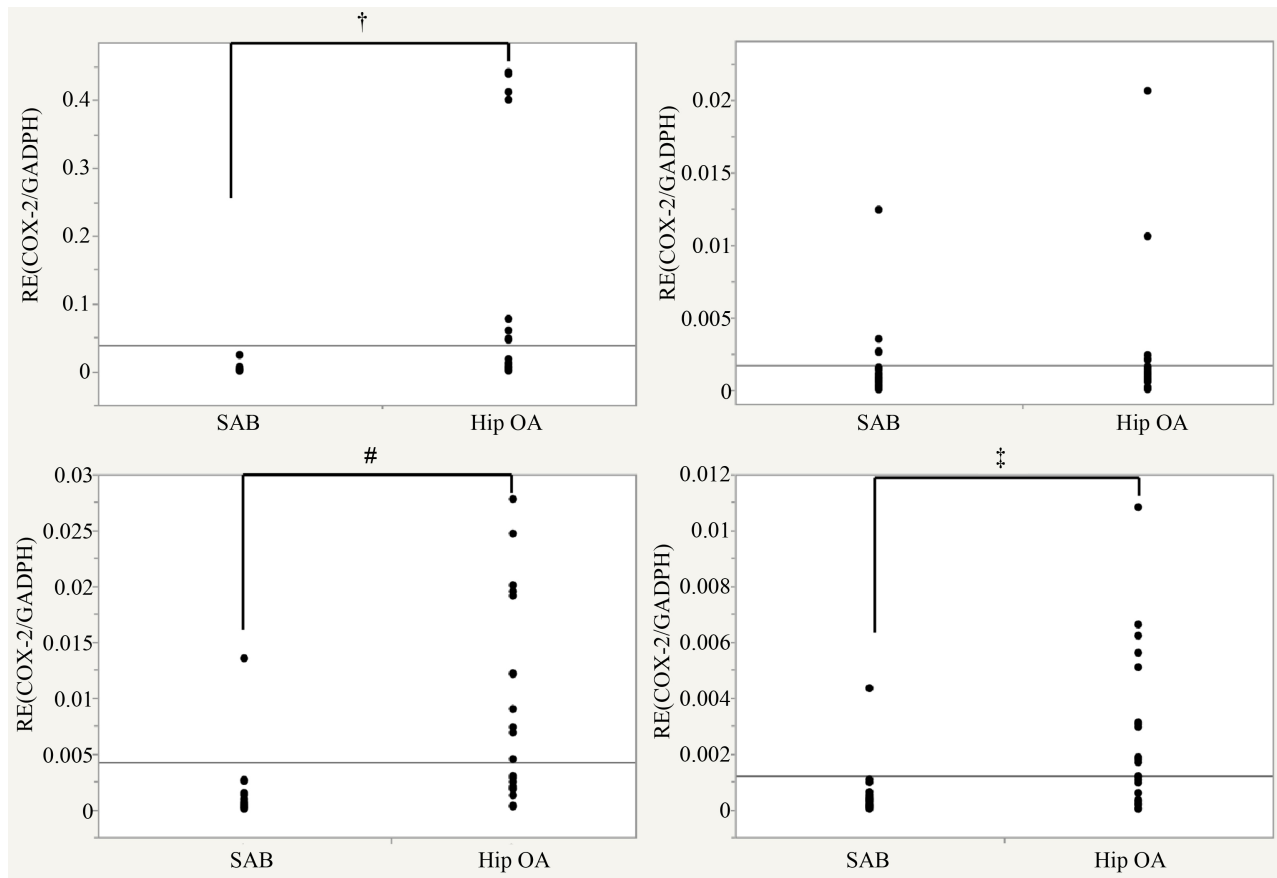


Figure 1. Proinflammatory cytokine levels in patients with RCTs and hip OA. Bars represent significant differences between subacromial bursa (SAB) samples and hip joint samples. †: *COX-2* ($P < 0.0001$); #: *IL-6* ($P < 0.0001$); ‡: *IL-1 β* ($P = 0.021$). RE: relative expression.

Table 3. mRNA levels of proinflammatory cytokines and cyclooxygenase-2 (*COX-2*).

	RCTs	Hip OA	<i>P</i> value (power)
<i>COX-2</i>	0.0024 \pm 0.0044	0.078 \pm 0.15	<0.001 (0.76)
<i>TNF-α</i>	0.0014 \pm 0.0021	0.0021 \pm 0.0042	0.59 (0.13)
<i>IL-6</i>	0.0001 \pm 0.0024	0.0081 \pm 0.0085	<0.001 (0.99)
<i>IL-1β</i>	0.0004 \pm 0.0008	0.0020 \pm 0.0027	0.021 (0.82)

TNF- α , tumor necrosis factor-alpha; IL-6, interleukin-6; IL-1 β , interleukin-1 β .

the significant difference in mRNA expression of *COX-2*, *IL-1 β* , and *IL-6* may be associated with the difference of stimulation for each synovial tissue.

TNF- α is considered the main pain effector in both RCTs and OA [4] [6]. TNF- α correlates strongly with IL-1 or IL-6 in articular or subacromial bursae [3] [4] [6] [16], however, TNF- α can also act independently to initiate or propagate inflammation [6]. In a previous animal study, we confirmed continued TNF- α expression over a period of two weeks, even though *COX-2* and *IL-1 β* were significantly decreased [17]. That result may explain why only TNF- α mRNA levels failed to exhibit any significant difference between RCT and hip OA

groups.

IL-1 β is thought to be associated with pain of both RCTs and OA [2] [4] [6] [18]. The significant increasing of IL-6 expression has been confirmed, however, the relationship between IL-6 and RCTs pain is still controversial [2] [4] [18]. We examined IL-1 β -induced expression of COX-2 in synovial fibroblasts, a treatment that induces considerable COX-2 expression [7] [16] [19] [20]. However, we did not observe any significant differences in COX-2 expression between SAB and hip synovial fibroblasts, suggesting that these cells expressed similar levels of both COX-2 and its downstream effector, prostaglandin E2 (PGE2). COX-2 and IL-1 β mRNA levels decreases with time in rat RCT model [17]. Accordingly, the observed differences in COX-2, IL-1 β , and IL-6 mRNA levels may not reflect differential basal levels of expression between tissues. Instead, they may indicate the difference in inflammation states observed in these diseases.

In spite of their frequent prescription in this context, the effectiveness of non-steroidal anti-inflammatory drugs (NSAIDs) in the management of pain in patients with degenerative RCTs is controversial [21] and not recommended for the conservative treatment and perioperative management of RCTs [22]. In contrast, NSAIDs are strongly recommended for the management of hip OA pain [23] [24], as COX-2 and other inflammation mediators are produced in the synovial tissues of OA joints [14] [25]. The binding of NSAIDs to COX isozymes inhibits the synthesis of prostanoids [26] [27] [28]. PGE2 is the dominant prostanoid produced during inflammation, and inhibition of its synthesis by NSAIDs is believed to be the main mechanism underlying potent analgesic and anti-inflammatory properties of these agents [26] [27] [28]. Moreover, the efficacy with which pain and PGE2 production are inhibited depends on the dose of NSAIDs [25]. Hence, if pain correlates with COX-2 expression, a normal dose of oral NSAIDs can be sufficient to control both OA and RCT pain. Our findings suggest that degenerative RCT-associated pain depends on factors other than COX-2. Thus patients with RCTs, who do not feel any efficacy of taking NSAIDs, may not benefit from their use for pain management. Moreover, discontinuing NSAID treatment would allow such patients to avoid the unwanted side effects caused by these drugs. However, in cases where NSAIDs are efficacious to the patient with RCTs, their use for pain management can be kept in place.

5. Limitations

The major limitation of this study was the impossibility to compare mRNA expression of proinflammatory mediators between RCTs and shoulder OA, as rotator cuff degeneration occurs spontaneously in patients with shoulder OA. The target of pain control medication is to lower the level of pain-related substance rather than that of pain inducers. Our purpose was to compare the mRNA expression patterns of proinflammatory cytokines in synovial tissues between RCTs and hip OA. To this end, our study clearly shows the difference in mRNA

expression of proinflammatory mediators induced by the different forms of stimulation.

Another limitation was our failure to use enzyme-linked immunosorbent assay (ELISA) or western blotting to support RT-PCR data. Assessment of *COX-2* expression by RT-PCR is considered appropriate to determine the activity of this enzyme in synovial tissues, as it is consistent with immunohistochemical data [15]. In addition, the amount of PGE2 measured by ELISA is related to the expression of *COX-2*, *TNF- α* , and *IL-1 β* measured by RT-PCR [7] [8]. Therefore, *COX-2*, *TNF- α* , *IL-6*, and *IL-1 β* levels assessed using RT-PCR are consistent with the detection of these four molecular biomarkers of inflammation by ELISA or western blotting.

A minor limitation is constituted by the significant difference in gender between RCT and hip OA groups due to higher prevalence of hip dysplasia among females [29]. However, we could not detect any difference in mRNA expression levels of *COX-2*, *TNF- α* , *IL-6*, and *IL-1 β* nor in the efficacy of NSAIDs or corticosteroids between genders. Therefore, we believe that the different gender composition between RCT and hip OA groups had no bearing on our results.

6. Conclusion

We compared the mRNA expression of *COX-2* and proinflammatory mediators in patients with degenerative RCTs and hip OA, and demonstrated that *COX-2*, *IL-1 β* , and *IL-6* levels in SAB samples obtained from patients with RCTs were significantly lower than those from patients with hip OA. Our findings suggest that the main mechanism underlying the development of pain in patients with degenerative RCTs differs from that underlying the development of pain in patients with hip OA.

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Conflicts of Interest

The author(s), their immediate families, and any research foundations with which they are affiliated have not received any financial payment or other benefits from any commercial entity related to the subject of this article.

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