Low-Level Laser Therapy Attenuates Arthrogenic Contracture Induced by Anterior Cruciate Ligament Reconstruction Surgery in Rats

Akinori KANEGUCHI[1], Junya OZAWA[1], Kengo MINAMIMOTO[2], Kaoru YAMAOKA[1]

[1]Department of Rehabilitation, Faculty of Rehabilitation, Hiroshima International University, Higashi-Hiroshima, Hiroshima, Japan, [2]Major in Medical Engineering and Technology, Graduate School of Medical Technology and Health Welfare Sciences, Hiroshima International University, Higashi-Hiroshima, Hiroshima, Japan

Received August 28, 2021
Accepted April 25, 2022
Epub Ahead of Print May 26, 2022

Summary

Therapeutic approaches to treat joint contracture after anterior cruciate ligament (ACL) reconstruction have not been established. Arthrofibrosis accompanied by joint inflammation following ACL reconstruction is a major cause of arthrogenic contracture. In this study, we examined whether anti-inflammatory treatment using low-level laser therapy (LLLT) can prevent ACL reconstruction-induced arthrogenic contracture. Rats underwent ACL transection and reconstruction surgery in their right knees. Unoperated left knees were used as controls. After surgery, rats were reared with or without daily LLLT (wavelength: 830 nm; power output: 150 mW; power density: 5 W/cm^2; for 120 s/day). We assessed the passive extension range of motion (ROM) after myotomy at one and two weeks post-surgery; the reduction in ROM represents the severity of arthrogenic contracture. ROM was markedly decreased by ACL reconstruction at both time points; however, LLLT partially attenuated the decrease in ROM. One week after ACL reconstruction, the gene expression of the proinflammatory cytokine interleukin-1β in the joint capsule was significantly upregulated, and this upregulation was significantly attenuated by LLLT. Fibrotic changes in the joint capsule, including upregulation of collagen type I and III genes, shortening of the synovium, and thickening were caused by ACL reconstruction and seen at both time points. LLLT attenuated these fibrotic changes as well. Our results indicate that LLLT after ACL reconstruction could attenuate the formation of arthrogenic contracture through inhibition of inflammation and fibrosis in the joint capsule. Thus, LLLT may become a novel therapeutic approach for ACL reconstruction-induced joint contracture.

Key words

Anterior cruciate ligament reconstruction • Low-level laser therapy • Joint contracture • Inflammation • Arthrofibrosis

Corresponding author

J. Ozawa, Department of Rehabilitation, Faculty of Rehabilitation, Hiroshima International University, Kurose-Gakuendai 555-36, Higashi-Hiroshima, Hiroshima, 739-2695, Japan. E-mail: j-ozawa@hirokoku-u.ac.jp

Introduction

Anterior cruciate ligament (ACL) injury, a major cause of sports-related incidents, induces joint instability [1,2]. The most common treatment for ACL injury is reconstruction surgery [1,2]. Although reconstruction surgery restores joint stability [2], one often-associated complication is joint contracture, which is characterized by reduction in range of motion (ROM) [3,4]. A systematic review by Wang *et al.* showed that reported incidence rates of joint contractures after ACL reconstruction ranged from 0.1 to 71 %, and the overall pooled incidence was 3 % [5]. Joint contracture induced by ACL reconstruction causes knee pain and quadriceps muscle weakness [6,7], which disrupt the return to sports and daily activities [8,9]. Thus, prevention and/or improvement of joint contracture are critical issues in rehabilitation following ACL reconstruction.

In clinical practice, ROM exercises, continuous passive motions, surgical treatments, and manipulations

under anesthesia are performed to treat ACL reconstruction-induced joint contractures. However, it has been reported that ROM exercises and continuous passive motions have limited or no effect on joint contracture [10-13]. Although surgical treatments and manipulations under anesthesia are effective in improving joint contracture, these treatments are linked to complications, such as fractures, heterotrophic ossification, and cartilage damage [14]. Thus, the development of alternative treatment strategies for ACL reconstruction-induced joint contracture is necessary.

Both myogenic and arthrogenic factors contribute to the formation of joint contracture after ACL reconstruction in both human patients [15-17] and rats [18,19]. In 70 % of human patients who underwent surgical treatment for joint contracture after ACL reconstruction, the formation was attributed to arthrofibrosis [20]. Therefore, arthrofibrosis is an important target for joint contracture therapy. Peri-operative inflammation is a major cause of arthrofibrosis [3,4,18-20]; thus, suppression of inflammation may be an effective therapy against arthrofibrosis. Previous studies reported that anti-inflammatory treatments using an interleukin-1 (IL-1) receptor antagonist or corticosteroid improved ROM in patients with arthrofibrosis after ACL reconstruction [21,22]. In clinical practice, however, these treatments are not widely used due to the high cost and/or adverse effects.

To inhibit inflammation, we focused on low-level laser therapy (LLLT). LLLT has anti-inflammatory and anti-fibrotic actions, and is associated with few adverse effects [23-25]. Moreover, it is a low-cost therapy [24], and already widely used for inflammatory and fibrotic diseases, such as arthritis and scarring [26,27]. In this study, therefore, we aimed to examine whether LLLT can prevent ACL reconstruction-induced arthrogenic contracture *via* inhibition of inflammation. To achieve this, we examined the attenuative effects of LLLT on arthrogenic contracture, as well as inflammatory and fibrotic changes, using a rat model of ACL reconstruction.

Materials and Methods

Experimental animals

A schematic diagram of the experiment protocol is illustrated in Figure 1. In this study, twenty-nine 8-week-old male Wistar rats (180-230 g; Japan SCL, Shizuoka, Japan) were used. Rats were randomly divided into ACL reconstruction (ACLR; n=14) and ACL reconstruction plus LLLT (LLLT; n=15) groups. Some data (i.e. ROM, synovial length, and joint capsule area) on the operated (right) side for all rats in the ACLR group were obtained from our previous study [19]. Experimental periods were set for one or two weeks (n=7 or 8 rats/group/time point) post-operation, because inflammatory and fibrotic reactions after ACL reconstruction peak at one week and subside within two weeks [19]. Rats were housed in standard cages under controlled environment conditions (temperature of 20-25 °C, 12 h lighting cycle) with free access to standard rodent chow and water. Experimental procedures were approved by the animal experimentation committee of Hiroshima International University (AE18-018).

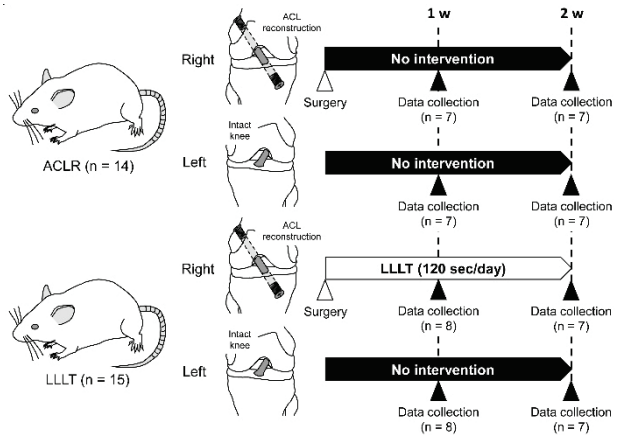

Fig. 1. Experimental protocol. ACLR, anterior cruciate ligament reconstruction; ACL, anterior cruciate ligament; LLLT, low-level laser therapy.

ACL reconstruction surgery

We performed ACL reconstruction surgery on the right knees using previously described methods [18]. Rats were anesthetized with ketamine and xylazine (80 mg/kg and 10 mg/kg, respectively) by an intraperitoneal injection. The knee joint was opened *via* a medial parapatellar approach, and the ACL was transected. Using a 0.8 mm diameter Kirschner wire, bone tunnels were created from the antero-medial side of the proximal tibia to the lateral side of the distal femur. After passing the quadruple-bundle tail tendon autograft through the bone tunnels, both ends of the autograft were fixed to the bones using stainless steel interference screws (diameter of 0.8 mm and length of 2.0 mm, TE-00001; Matsumoto, Chiba, Japan). Finally, the joint capsule and skin were sutured. Unoperated left knees were used as controls. After surgery, the rats could move freely in the cage.

LLLT

After ACL reconstruction, rats in the LLLT group received daily LLLT using semiconductor laser systems (FINE LASER EL-800; Panasonic Healthcare, Tokyo, Japan). Under ether anesthesia, LLLT was performed on the right knee under the conditions as follows: skin contact method, continuous irradiation mode, wavelength 830 nm, power output 150 mW, spot area 0.03 cm^2, power density 5 W/cm^2, attaching areas two points (medial and lateral sides of the knee), and irradiation time 60 s/point (Fig. 2). These irradiation conditions attenuate ACL reconstruction-induced joint swelling in the rat knee [28]. In addition, similar irradiation conditions (i.e. skin contact method, continuous irradiation mode, wavelength 830 nm, power output 100 mW, spot area 0.028 cm^2, power density 3.57 W/cm^2) could decrease inflammatory cytokines (IL-1β, IL-6, and tumor necrosis factor-α) in the articular cartilage in rat osteoarthritis model [29]. LLLT was started immediately after surgery and was performed every day until the day before sacrifice. Rats in the ACLR group did not receive any treatment after surgery.

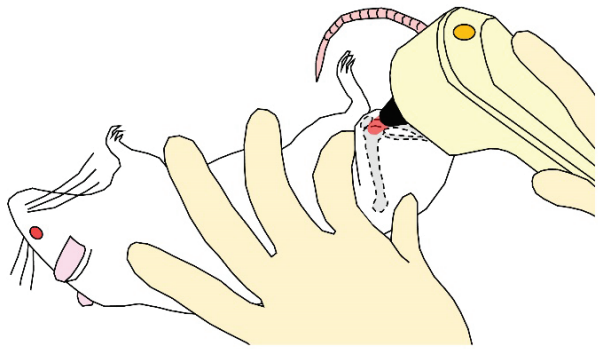

Fig. 2. Image of LLLT. LLLT was applied to the medial and lateral sides of the knee joint. LLLT, low-level laser therapy.

Measurement of ROM

To assess the degree of arthrogenic contracture, we measured ROM after myotomy, which is determined by joint components, as previously described [30,31]. After each rat was sacrificed by exsanguination under ether anesthesia, the skin and knee flexor muscles were removed from the hindlimbs. Subsequently, the trunk and femur of the rat placed in a spine position were fixed manually at a hip flexion of 90°. Then, the knee joint was extended by 14.6 N/mm extension moments, which stretch the rat knee joint close to its physiological limit but does not disrupt the joint components [32,33]. The angle between the femur and fibula was measured using a three-dimensional motion analysis system (Kinema Tracer; Kissei Comtec, Nagano, Japan) as ROM after myotomy. In a pilot study, we confirmed that ROM restriction is induced in the extension direction, but not in the flexion direction in our rat ACL reconstruction model at two weeks post-surgery (unpublished data). In this study, thus, ROM measurement was performed only in the extension direction.

Histological analysis

Tissue preparation

After ROM measurement, the knee joints were sampled and immersion-fixed in 0.1 M phosphate-buffered 4 % paraformaldehyde (pH 7.4) at a flexion of 90° for two days at 4 °C. Next, samples were decalcified using 17.7 % ethylenediaminetetraacetic acid (pH 7.2, Osteosoft; Merck Millipore, Darmstadt, Germany) for one month at room temperature and embedded in paraffin. Sagittal sections (thickness: 4 μm) were obtained from the medial midcondylar level.

Measurements of synovial length and joint capsule area

The posterior region of the knee joint in the sections stained with aldehyde-fuchsin-Masson-Goldner was photographed at 2× magnification. The superior and inferior synovial lengths of the posterior joint capsule were measured according to previously described methods [34] and summed as total synovial length. To assess joint capsule thickening, the posterior joint capsule area was also measured according to previously reported methods [34]. Measurements of synovial length and joint capsule area were performed using ImageJ software (National Institutes of Health, Bethesda, MD, USA). Posterior capsulotomy improves flexion contracture developed after ACL reconstruction in human patients [35], implying that the posterior joint capsule is the structure responsible for flexion contracture. In addition, fibrotic changes in the posterior joint capsule were detected after ACL reconstruction in both human patients [17] and rats [18,19,36]. In this study, thus, we focused on the posterior joint capsule.

Gene expression analysis

Extraction of total RNA from the paraffin sections was performed as previously described [37]. In brief, the posterior joint capsule was isolated from paraffin sections, and total RNA was extracted using the

RNeasy FFPE Kit (Qiagen, Hilden, Germany). Next, cDNA was synthesized using the total RNA and the SuperScript III First-strand synthesis system (Invitrogen, Grand Island, NY, USA).

Using the 7300 Real Time PCR System (Applied Biosystems, Foster City, CA, USA), real-time PCR was performed to quantify gene expression levels. TaqMan primer and probe sets for IL-1β (Rn00580432_m1), type I collagen (COL1A1; Rn01463848_m1), type III collagen (COL3A1; Rn01437681_m1), and S18 (Rn01428913_gH) were obtained from Applied Biosystems. S18 rRNA was used as the internal control. The calibration curve method was used to quantify gene expression levels.

Statistical analysis

The results were expressed as the mean ± standard deviation. Dr. SPSS II for Windows (SPSS Japan Inc., Tokyo, Japan) was used for statistical analyses. Two-way analysis of variance was used to examine the relationship between the intervention and time. If significant main or interaction effects were detected, *post hoc* Bonferroni tests were used to localize the effects. If the interaction between time and intervention and the main effect of time were not significant, an unpaired *t*-test (if the normality assumption had not been rejected by the Shapiro-Wilk test) or a Mann-Whitney test (if the normality assumption had been rejected by the Shapiro-Wilk test) with a Bonferroni adjustment was performed to compare differences between one and two weeks post-surgery. Differences were considered significant at $P<0.05$.

Results

ROM

On the contralateral (left) side, ROM after myotomy was between 160° and 163° (Fig. 3). At one week post-surgery, ROM on the operated (right) side was 131±11° and 150±5° in the ACLR and LLLT groups, respectively. Two-way ANOVA revealed a significant main effect of intervention ($P<0.001$). In both groups, ROM on the operated side was significantly smaller than that recorded on the contralateral side ($P<0.001$). Between the operated sides, ROM was significantly larger in the LLLT group than in the ACLR group ($P<0.001$). Similar results were obtained at two weeks post-surgery. ROM on the operated side was 137±6° and 148±6° in the ACLR and LLLT groups, respectively, and was significantly smaller than that observed on the contralateral side ($P\leq0.003$). ROM on the operated side was significantly larger in the LLLT group than in the ACLR group ($P=0.008$). The interaction between time and intervention ($P=0.156$) and the main effect of time ($P=0.797$) were not significant. There were no significant differences between one and two weeks post-surgery in all groups ($P\geq0.508$, unpaired *t*-test or Mann-Whitney test with a Bonferroni adjustment).

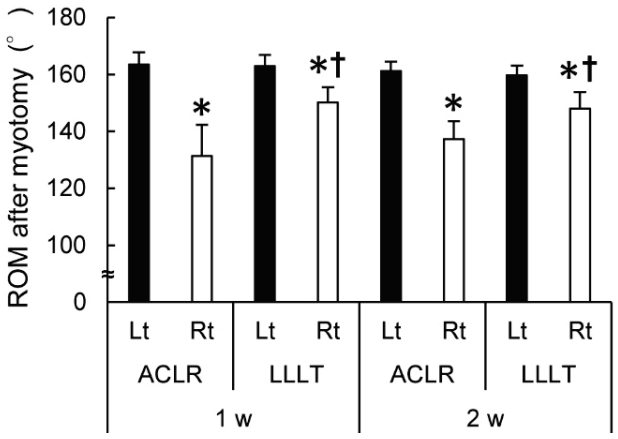

Fig. 3. ROM after myotomy. Values are shown as the mean and standard deviation. *, significant difference compared with the contralateral side ($P<0.05$). †, significant difference compared with the same side in the ACLR group at the same time point ($P<0.05$). ACLR, anterior cruciate ligament reconstruction; LLLT, low-level laser therapy; Lt, left; Rt, right; ROM, range of motion.

Synovial length

On the contralateral (left) side, the postero-superior joint space was blank, and the synovial membrane in the posterior joint capsule was deeply folded at both time points (Fig. 4a-d). At one week post-surgery, the postero-superior joint space was filled with fibrous tissue, and the synovial folds disappeared on the operated (right) side in the ACLR group (Fig. 4e). Two-way ANOVA revealed a significant main effect of intervention ($P<0.001$). In the ACLR group, the total synovial length was significantly shorter on the operated side than on the contralateral side ($P=0.001$) (Fig. 4i). On the operated side in the LLLT group (Fig. 4f), the postero-superior joint space and synovial folds remained largely unchanged, and the total synovial length was similar to that noted on the contralateral side ($P=0.634$). At two weeks post-surgery, in both the ACLR (Fig. 4g) and LLLT (Fig. 4h) groups, the postero-superior joint space was filled with fibrous tissue, and the synovial folds were shallower on the operated side versus the unoperated left side. Consequently, the total synovial

length was significantly shorter on the operated side than on the contralateral side in both groups (P≤0.007). There were no significant differences in total synovial length between the operated sides in the ACLR and LLLT groups at either time point (P≥0.307). The interaction between time and intervention (P=0.592) and the main effect of time (P=0.749) were not significant. There were no significant differences between one and two weeks post-surgery in all groups (P≥0.936, unpaired *t*-test with a Bonferroni adjustment).

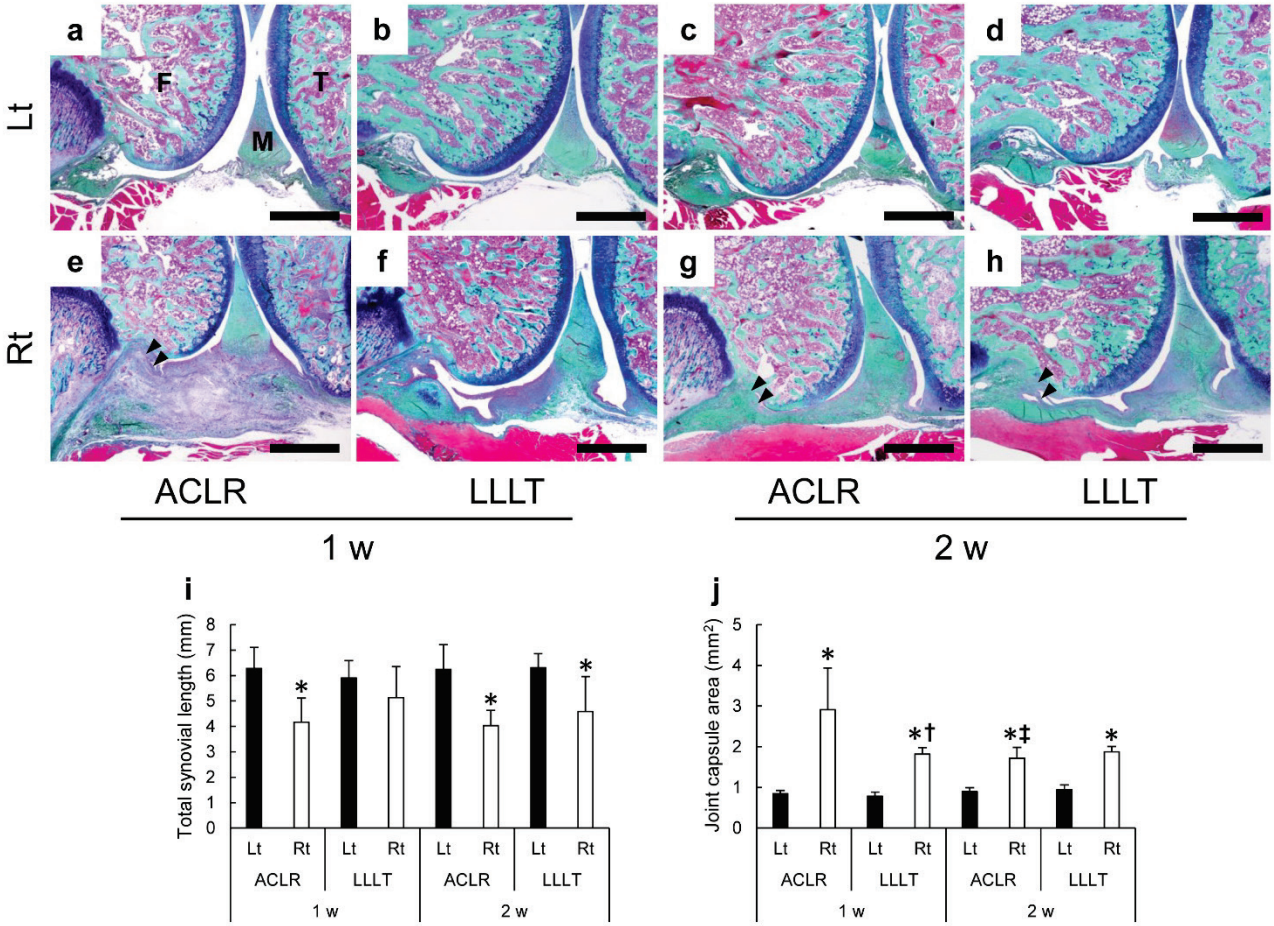

Fig. 4. Histomorphometric changes in the posterior knee joint capsule. Representative images of the aldehyde-fuchsin-Masson-Goldner-stained posterior knee joint in the ACLR group at one week (**a** and **e**), LLLT group at one week (**b** and **f**), ACLR group at two weeks (**c** and **g**), and LLLT group at two weeks (**d** and **h**). (**a-d**) and (**e-h**) show the contralateral (Lt) and operated (Rt) sides, respectively. Arrowheads indicate the postero-superior joint space filled with fibrous tissue. Scale bars = 1 mm. (**i**) Total synovial length. (**j**) Joint capsule area. Values are shown as the mean and standard deviation. *, significant difference compared with the contralateral side (P<0.05). †, significant difference compared with the same side in the ACLR group at the same time point (P<0.05). ‡, significant difference compared with the same group at one week (P<0.05). ACLR, anterior cruciate ligament reconstruction; LLLT, low-level laser therapy; Lt, left; Rt, right; F: femur, T: tibia; M: meniscus.

Joint capsule area

At one week post-surgery, in the ACLR group an apparent thickening of the posterior joint capsule was detected on the operated (right) side (Fig. 4e) compared with the contralateral (left) side (Fig. 4a). Two-way ANOVA revealed significant interaction between time and intervention (P=0.004) and main effect of intervention (P<0.001). The posterior joint capsule area was significantly enlarged compared with the area recorded for the contralateral side (P<0.001) (Fig. 4j). Thickening of the posterior joint capsule was also observed on the operated side in the LLLT group (Fig. 4f). However, this thickening was milder than that noted on the operated side in the ACLR group. The posterior joint capsule area on the operated side in the LLLT group was also significantly larger than that on the contralateral side (P<0.001), but significantly smaller than the area determined for the ACLR group (P<0.001). At two weeks post-surgery, thickening of the posterior joint capsule on the operated side in the ACLR group was

partially attenuated (Fig. 4g). Consequently, the posterior joint capsule area was significantly smaller than that measured at one week post-surgery (P<0.001). However, it remained significantly larger than that observed on the contralateral side (P=0.001). In the LLLT group (Fig. 4h), the posterior joint capsule area was significantly larger on the operated side versus the contralateral side (P<0.001), and comparable to the area recorded for the ACLR group (P=1.000). The main effect of time was not significant (P=0.293).

Gene expression

In the expression of the inflammatory cytokine gene IL-1β, a significant main effect of intervention was detected (P=0.045), and significant simple main effects were detected at only one week post-surgery. At one week post-surgery, the expression of the inflammatory cytokine gene IL-1β in the ACLR group was significantly higher on the operated side than on the contralateral side (P=0.013) (Fig. 5a). The expression of IL-1β on the operated side in the LLLT group was significantly lower than that measured in the ACLR group (P=0.018) and was similar to that recorded for the contralateral side (P=1.000). At two weeks post-surgery, the levels of IL-1β expression on the operated side of the ACLR group returned to the levels observed for the contralateral side (P=1.000). The interaction between time and intervention (P=0.079) and the main effect of time (P=0.162) were not significant. Differences between one and two weeks post-surgery were not significant in all groups (P≥0.068, unpaired *t*-test or Mann-Whitney test with a Bonferroni adjustment).

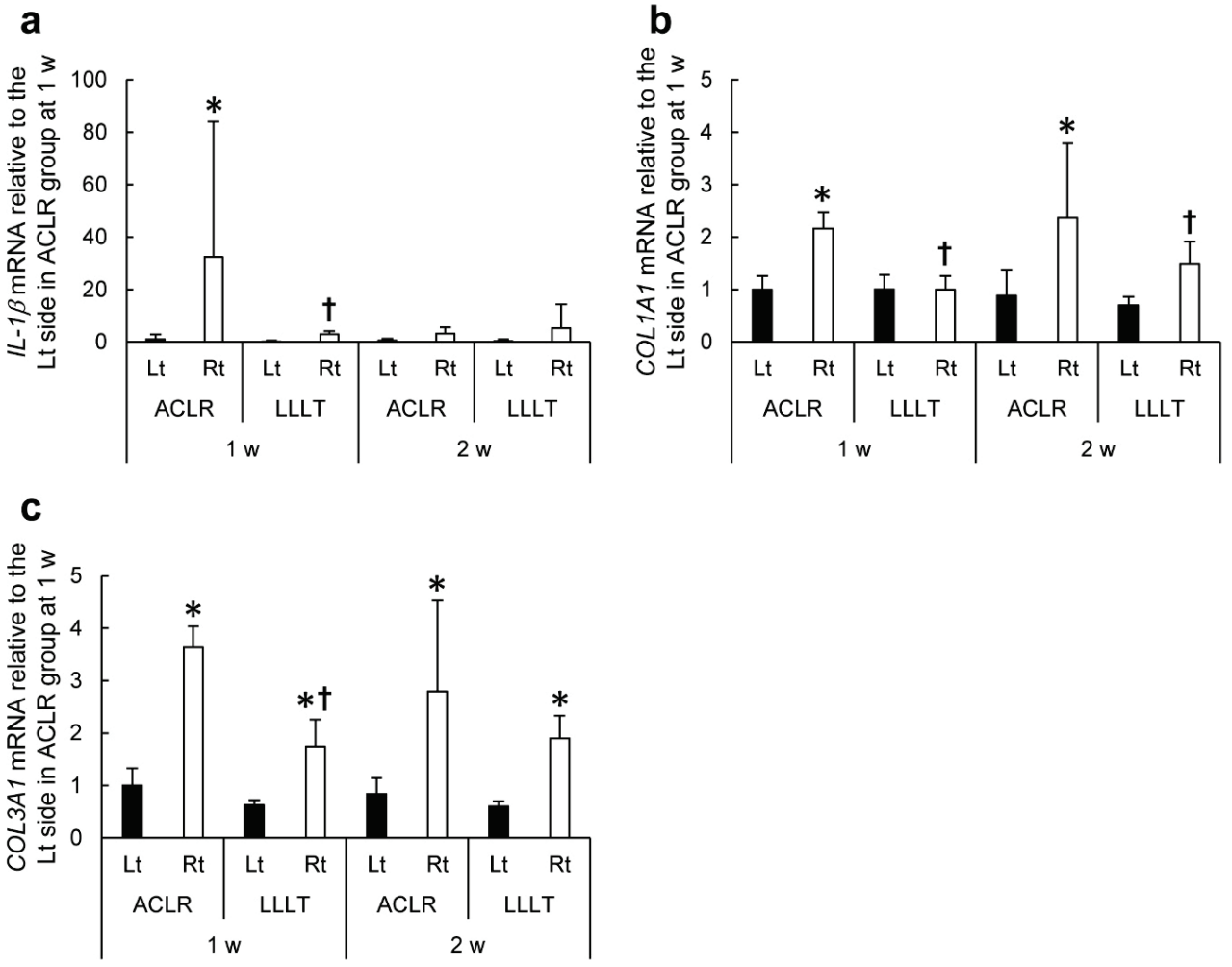

Fig. 5. Gene expression levels in the posterior joint capsule. (**a**) IL-1β, (**b**) COL1A1, and (**c**) COL3A1. Values are shown as the mean and standard deviation. *, significant difference compared with the contralateral side (P<0.05). †, significant difference compared with the same side in the ACLR group at the same time point (P<0.05). ACLR, anterior cruciate ligament reconstruction; LLLT, low-level laser therapy; Lt, left; Rt, right; IL-1β, interleukin-1β; COL1A1, type I collagen; COL3A1, type III collagen.

In the expression of COL1A1, a significant main effect of intervention was detected (P<0.001). At both time points, the expression of COL1A1 in the ACLR group was significantly upregulated on the operated side compared with the contralateral side (P≤0.003) (Fig. 5b). On the operated side in the LLLT group, COL1A1 gene expression was significantly lower than that measured in the ACLR group (P≤0.042), and was not significantly different from that determined for the contralateral side at both time points (P≥0.077). The interaction between time and intervention (P=0.262) and the main effect of time (P=0.662) were not significant. Differences between one and two weeks post-surgery were not significant in all groups (P≥0.064, unpaired *t*-test or Mann-Whitney test with a Bonferroni adjustment).

In the expression of COL3A1, a significant main effect of intervention was detected (P<0.001). At both time points, the expression of COL3A1 on the operated side was significantly higher than that recorded on the contralateral side in both ACLR and LLLT groups (P≤0.011) (Fig. 5c). Between the operated sides of the two groups, COL3A1 gene expression was significantly lower in the LLLT group versus the ACLR group at one week post-surgery (P<0.001); however, it was not significantly different at two weeks post-surgery (P=0.107). The interaction between time and intervention (P=0.222) and the main effect of time (P=0.231) were not significant. There were no significant differences between one and two weeks post-surgery in all groups (P≥0.984, unpaired *t*-test or Mann-Whitney test with a Bonferroni adjustment).

Discussion

In this study, we examined whether LLLT can prevent ACL reconstruction-induced arthrogenic contracture. Our results indicate that LLLT can attenuate arthrogenic contracture *via* inhibition of inflammation and fibrosis in the joint capsule.

Inflammation stimulates the formation of arthrofibrosis, which is the most common cause of ACL reconstruction-induced joint contracture [3,4,18-20]. Thus, anti-inflammatory treatments may become a novel therapeutic strategy for the prevention of joint contracture after ACL reconstruction. In this study, we focused on LLLT as an anti-inflammatory therapy. The anti-inflammatory effects of LLLT have been reported in both human and animal joints [23,25,27]. Our study corroborates these findings, showing that LLLT downregulates the expression of the pro-inflammatory cytokine IL-1β at one week post-surgery. IL-1 plays an important role in the formation of arthrofibrosis. For example, intra-articular injection of the IL-1 antagonist anakinra increases the ROM in patients with arthrofibrosis after ACL reconstruction [22].

LLLT might inhibit inflammation in the posterior knee joint capsule *via* direct and indirect effects. A previous study reported that LLLT for cultured synoviocytes from rheumatoid arthritis patients decreased expression of IL-1β at both the mRNA and protein levels [38]. Thus, LLLT might inhibit inflammation by acting directly on the cells in the posterior joint capsule. In addition, LLLT after injury has been shown to inhibit inflammation and promote repair of the muscle [39] and bone [40], which are damaged during ACL reconstruction surgery. It is considered that injured tissues can lead to secondary damages in adjacent tissues through the release of inflammatory cytokines. For example, exogenous inflammatory cytokines, such as IL-1β and tumor necrosis factor-α, can induce inflammatory reactions in cultured human synoviocytes [41,42]. Thus, the anti-inflammatory effects of LLLT on periarticular tissues other than the posterior joint capsule might indirectly contribute to the inhibition of inflammation in the posterior capsule.

Synovial shortening and joint capsule thickening are characteristic changes in arthrofibrosis, and are considered to be mechanisms of arthrogenic contracture after ACL reconstruction [17-19]. In this study, accordingly, synovial shortening and joint capsule thickening accompanied by upregulation of COL1A1 and COL3A1 expression levels were observed after ACL reconstruction in parallel with formation of arthrogenic contracture. LLLT after ACL reconstruction attenuated both synovial shortening and joint capsule thickening as well as the upregulation of the COL1A1 and COL3A1 genes at one week post-surgery. Therefore, the improvement in arthrogenic contracture as a result of LLLT can be explained, at least in part, by the inhibition of fibrosis in the joint capsule. However, at two weeks post-surgery, there were no differences in synovial length or joint capsule area on the operated side between the ACLR and LLLT groups. Arthrogenic contracture, represented by ROM restriction on the operated side, was significantly milder in the LLLT group versus the ACLR group. Thus, improvement in arthrogenic contracture by LLLT cannot be solely explained by the

inhibition of fibrosis in the joint capsule. Apart from joint capsule fibrosis, osteoarthritis and cyclops syndrome may also contribute to ACL reconstruction-induced joint contracture [20]. Although we did not assess osteoarthritic changes, previous studies reported that LLLT could attenuate ACL transection-induced osteoarthritis [43-45].

The pathways leading joint contracture may be different between joint immobilization and our ACL reconstruction models. Our results suggest that inflammation and fibrosis pathways contributed to the formation of ACL reconstruction-induced arthrogenic contracture. Although inflammation and fibrosis in the joint capsule were also detected in the immobilized knee [46,47], anti-inflammatory treatments, including LLLT [48] and administration of non-steroidal anti-inflammatory drug celecoxib [49], could not attenuated immobilization-induced arthrogenic contracture. Thus, the contribution of inflammation and fibrosis pathways will be larger in joint contracture induced by ACL reconstruction than in that induced by joint immobilization.

The present study has some limitations. Firstly, most ACL reconstruction surgeries in patients are performed arthroscopically [50], but we selected open surgery. Nevertheless, the effect of open surgery on increasing the risk of joint contracture remains controversial [51,52]. Thus, contractures observed in this study may have been overestimated compared with those observed following arthroscopic surgery. However, we previously revealed that arthrotomy (i.e. opening of the joint capsule) alone did not reduce ROM after myotomy under our experimental conditions [36]. Secondly, the follow-up periods were relatively short (up to two weeks). Additional long-term studies are warranted to confirm the favorable effects of LLLT on joint contracture. Thirdly, rats in ACLR group did not undergo daily anesthesia. Between the ACLR and LLLT groups, however, there were no differences in all parameters on the contralateral side. Thus, we consider that effects of anesthesia on contracture formation were negligible. Fourthly, we used young rats (eight-week-old) for the experiment, because ACL reconstruction surgery in pediatric and the adolescent patients has steadily increased [53]. The effect of age on the ACL reconstruction-induced joint contracture remains controversial [54-56], and we cannot exclude the possibility that different results are obtained from older rats.

In conclusion, LLLT after ACL reconstruction could attenuate the formation of arthrogenic contracture through inhibition of inflammation and fibrosis in the joint capsule. Thus, LLLT may be a novel, safe, and effective therapeutic approach for treating ACL reconstruction-induced joint contracture.

Conflict of Interest

There is no conflict of interest.

Acknowledgements

This work was supported by grants from The Japanese Society of Physio Therapeutics and JSPS KAKENHI (Grant Number 20K19400). We acknowledge technical assistance from Mayuki Arataki, Yudai Ishikawa, Yusuke Ueno, Takahiro Uchiyama, Yoshiko Kato, and Kei Takemaru.

References

1. Musahl V, Karlsson J. Anterior cruciate ligament tear. N Engl J Med 2019;380:2341-2348. https://doi.org/10.1056/NEJMcp1805931
2. Boutsiadis A, Panisset JC, Devitt BM, Mauris F, Barthelemy R, Barth J. Anterior laxity at 2 years after anterior cruciate ligament reconstruction is comparable when using adjustable-loop suspensory fixation and interference screw fixation. Am J Sports Med 2018;46:2366-2375. https://doi.org/10.1177/0363546518784005
3. Irrgang JJ, Harner CD. Loss of motion following knee ligament reconstruction. Sports Med 1995;19:150-159. https://doi.org/10.2165/00007256-199519020-00006
4. Millett PJ, Wickiewicz TL, Warren RF. Motion loss after ligament injuries to the knee. Part i: Causes. Am J Sports Med 2001;29:664-675. https://doi.org/10.1177/03635465010290052401
5. Wang B, Zhong JL, Xu XH, Shang J, Lin N, Lu HD. Incidence and risk factors of joint stiffness after anterior cruciate ligament reconstruction. J Orthop Surg Res 2020;15:175. https://doi.org/10.1186/s13018-020-01694-7

6. Eckenrode BJ, Carey JL, Sennett BJ, Zgonis MH. Prevention and management of post-operative complications following ACL reconstruction. Curr Rev Musculoskelet Med 2017;10:315-321. https://doi.org/10.1007/s12178-017-9427-2
7. Grapar Zargi T, Drobnic M, Vauhnik R, Koder J, Kacin A. Factors predicting quadriceps femoris muscle atrophy during the first 12 weeks following anterior cruciate ligament reconstruction. Knee 2017;24:319-328. https://doi.org/10.1016/j.knee.2016.11.003
8. Fisher SE, Shelbourne KD. Arthroscopic treatment of symptomatic extension block complicating anterior cruciate ligament reconstruction. Am J Sports Med 1993;21:558-564. https://doi.org/10.1177/036354659302100413
9. Petersen W, Zantop T. Return to play following ACL reconstruction: Survey among experienced arthroscopic surgeons (AGA instructors). Arch Orthop Trauma Surg 2013;133:969-977. https://doi.org/10.1007/s00402-013-1746-1
10. Wright RW, Haas AK, Anderson J, Calabrese G, Cavanaugh J, Hewett TE, Lorring D, McKenzie C, Preston E, Williams G, Group M. Anterior cruciate ligament reconstruction rehabilitation: Moon guidelines. Sports Health 2015;7:239-243. https://doi.org/10.1177/1941738113517855
11. Henriksson M, Rockborn P, Good L. Range of motion training in brace vs. Plaster immobilization after anterior cruciate ligament reconstruction: A prospective randomized comparison with a 2-year follow-up. Scand J Med Sci Sports 2002;12:73-80. https://doi.org/10.1034/j.1600-0838.2002.120203.x
12. Jaspers T, Taeymans J, Hirschmuller A, Baur H, Hilfiker R, Rogan S. Continuous passive motion does improve range of motion, pain and swelling after acl reconstruction: A systematic review and meta-analysis. Z Orthop Unfall 2019;157:279-291. https://doi.org/10.1055/a-0710-5127
13. D'Amore T, Rao S, Corvi J, Jack RA 2nd, Tjoumakaris FP, Ciccotti MG, Freedman KB. The utility of continuous passive motion after anterior cruciate ligament reconstruction: A systematic review of comparative studies. Orthop J Sports Med 2021;9:23259671211013841. https://doi.org/10.1177/23259671211013841
14. Usher KM, Zhu S, Mavropalias G, Carrino JA, Zhao J, Xu J. Pathological mechanisms and therapeutic outlooks for arthrofibrosis. Bone Res 2019;7:9. https://doi.org/10.1038/s41413-019-0047-x
15. Kuszewski MT, Gnat R, Szlachta G, Kaczynska M, Knapik A. Passive stiffness of the hamstrings and the rectus femoris in persons after an acl reconstruction. Phys Sportsmed 2019;47:91-95. https://doi.org/10.1080/00913847.2018.1527171
16. Pinto FG, Thaunat M, Daggett M, Kajetanek C, Marques T, Guimares T, Quelard B, Sonnery-Cottet B. Hamstring contracture after acl reconstruction is associated with an increased risk of cyclops syndrome. Orthop J Sports Med 2017;5:2325967116684121. https://doi.org/10.1177/2325967116684121
17. Lobenhoffer HP, Bosch U, Gerich TG. Role of posterior capsulotomy for the treatment of extension deficits of the knee. Knee Surg Sports Traumatol Arthrosc 1996;4:237-241. https://doi.org/10.1007/BF01567970
18. Kaneguchi A, Ozawa J, Minamimoto K, Yamaoka K. A rat model of arthrofibrosis developed after anterior cruciate ligament reconstruction without rigid joint immobilization. Connect Tissue Res 2021;62:263-276. https://doi.org/10.1080/03008207.2019.1693548
19. Kaneguchi A, Ozawa J, Minamimoto K, Yamaoka K. Formation process of joint contracture after anterior cruciate ligament reconstruction in rats. J Orthop Res 2021;39:1082-1092. https://doi.org/10.1002/jor.24800
20. Mayr HO, Weig TG, Plitz W. Arthrofibrosis following acl reconstruction--reasons and outcome. Arch Orthop Trauma Surg 2004;124:518-522. https://doi.org/10.1007/s00402-004-0718-x
21. Rue JP, Ferry AT, Lewis PB, Bach BR Jr. Oral corticosteroid use for loss of flexion after primary anterior cruciate ligament reconstruction. Arthroscopy 2008;24:554-559.e1. https://doi.org/10.1016/j.arthro.2007.10.013
22. Magnussen R, Brown C, Lawrence T, Toth A. Intra-articular anakinra for the treatment of persistent inflammation and arthrofibrosis following anterior cruciate ligament reconstruction. Duke Orthopedic J 2011;1:51-56. https://doi.org/10.5005/jp-journals-10017-1008
23. Kaneguchi A, Ozawa J, Minamimoto K, Yamaoka K. Low-level laser therapy prevents treadmill exercise-induced progression of arthrogenic joint contracture via attenuation of inflammation and fibrosis in remobilized rat knees. Inflammation 2019;42:857-873. https://doi.org/10.1007/s10753-018-0941-1
24. Geneva II. Photobiomodulation for the treatment of retinal diseases: a review. Int J Ophthalmol 2016;9:145-152. https://doi.org/10.18240/ijo.2016.01.24

25. Wickenheisser VA, Zywot EM, Rabjohns EM, Lee HH, Lawrence DS, Tarrant TK. Laser light therapy in inflammatory, musculoskeletal, and autoimmune disease. Curr Allergy Asthma Rep 2019;19:37. https://doi.org/10.1007/s11882-019-0869-z
26. Freitas CP, Melo C, Alexandrino AM, Noites A. Efficacy of low-level laser therapy on scar tissue. J Cosmet Laser Ther 2013;15:171-176. https://doi.org/10.3109/14764172.2013.769272
27. Soleimanpour H, Gahramani K, Taheri R, Golzari SE, Safari S, Esfanjani RM, Iranpour A. The effect of low-level laser therapy on knee osteoarthritis: Prospective, descriptive study. Lasers Med Sci 2014;29:1695-1700. https://doi.org/10.1007/s10103-014-1576-6
28. Kaneguchi A, Ozawa J, Minamimoto K. The effects of low-level laser therapy on joint swelling and range of motion restriction after anterior cruciate ligament reconstruction in rat. (In Japanese) Jap J Electrophys Agents 2020;27:73-77.
29. Tomazoni SS, Leal-Junior EC, Pallotta RC, Teixeira S, de Almeida P, Lopes-Martins RA. Effects of photobiomodulation therapy, pharmacological therapy, and physical exercise as single and/or combined treatment on the inflammatory response induced by experimental osteoarthritis. Lasers Med Sci 2017;32:101-108. https://doi.org/10.1007/s10103-016-2091-8
30. Kaneguchi A, Ozawa J, Moriyama H, Yamaoka K. Structures responsible for knee joint contracture secondary to adjuvant-induced arthritis in a rat model. Iryo Kogaku Zassi (J Med Eng) 2015:1-12.
31. Kaneguchi A, Ozawa J, Yamaoka K. Intra-articular injection of mitomycin c prevents progression of immobilization-induced arthrogenic contracture in the remobilized rat knee. Physiol Res 2020;69:145-156. https://doi.org/10.33549/physiolres.934149
32. Moriyama H, Yoshimura O, Sunahori H, Tobimatsu Y. Comparison of muscular and articular factors in the progression of contractures after spinal cord injury in rats. Spinal Cord 2006;44:174-181. https://doi.org/10.1038/sj.sc.3101802
33. Trudel G, Uhthoff HK. Contractures secondary to immobility: Is the restriction articular or muscular? An experimental longitudinal study in the rat knee. Arch Phys Med Rehabil 2000;81:6-13. https://doi.org/10.1016/s0003-9993(00)90213-2
34. Trudel G, Seki M, Uhthoff HK. Synovial adhesions are more important than pannus proliferation in the pathogenesis of knee joint contracture after immobilization: An experimental investigation in the rat. J Rheumatol 2000;27:351-357.
35. Wierer G, Runer A, Gfoller P, Fink C, Hoser C. Extension deficit after anterior cruciate ligament reconstruction: Is arthroscopic posterior release a safe and effective procedure? Knee 2017;24:49-54. https://doi.org/10.1016/j.knee.2016.09.018
36. Kaneguchi A, Ozawa J, Minamimoto K, Yamaoka K. Effects of each phase of anterior cruciate ligament reconstruction surgery on joint contracture in rats. J Invest Surg 2022;35:984-995. https://doi.org/10.1080/08941939.2021.1985193
37. Kaneguchi A, Ozawa J, Kawamata S, Yamaoka K. Development of arthrogenic joint contracture as a result of pathological changes in remobilized rat knees. J Orthop Res 2017;35:1414-1423. https://doi.org/10.1002/jor.23419
38. Yamaura M, Yao M, Yaroslavsky I, Cohen R, Smotrich M, Kochevar IE. Low level light effects on inflammatory cytokine production by rheumatoid arthritis synoviocytes. Lasers Surg Med 2009;41:282-290. https://doi.org/10.1002/lsm.20766
39. Silveira PC, Scheffer Dda L, Glaser V, Remor AP, Pinho RA, Aguiar Junior AS, Latini A. Low-level laser therapy attenuates the acute inflammatory response induced by muscle traumatic injury. Free Radic Res 2016;50:503-513. https://doi.org/10.3109/10715762.2016.1147649
40. Escudero JSB, Perez MGB, de Oliveira Rosso MP, Buchaim DV, Pomini KT, Campos LMG, Audi M, Buchaim RL. Photobiomodulation therapy (pbmt) in bone repair: A systematic review. Injury 2019;50:1853-1867. https://doi.org/10.1016/j.injury.2019.09.031
41. Tohidnezhad M, Bayer A, Rasuo B, Hock JVP, Kweider N, Fragoulis A, Sonmez TT, Jahr H, Pufe T, Lippross S. Platelet-released growth factors modulate the secretion of cytokines in synoviocytes under inflammatory joint disease. Mediators Inflamm 2017;2017:1046438. https://doi.org/10.1155/2017/1046438

42. Chen J, Wu W, Zhang M, Chen C. Taraxasterol suppresses inflammation in il-1beta-induced rheumatoid arthritis fibroblast-like synoviocytes and rheumatoid arthritis progression in mice. Int Immunopharmacol 2019;70:274-283. https://doi.org/10.1016/j.intimp.2019.02.029
43. Assis L, Milares LP, Almeida T, Tim C, Magri A, Fernandes KR, Medalha C, Renno AC. Aerobic exercise training and low-level laser therapy modulate inflammatory response and degenerative process in an experimental model of knee osteoarthritis in rats. Osteoarthritis Cartilage 2016;24:169-177. https://doi.org/10.1016/j.joca.2015.07.020
44. Wang P, Liu C, Yang X, Zhou Y, Wei X, Ji Q, Yang L, He C. Effects of low-level laser therapy on joint pain, synovitis, anabolic, and catabolic factors in a progressive osteoarthritis rabbit model. Lasers Med Sci 2014;29:1875-1885. https://doi.org/10.1007/s10103-014-1600-x
45. Bublitz C, Medalha C, Oliveira P, Assis L, Milares LP, Fernandes KR, Tim CR, Vasilceac FA, Mattiello SM, Renno AC. Low-level laser therapy prevents degenerative morphological changes in an experimental model of anterior cruciate ligament transection in rats. Lasers Med Sci 2014;29:1669-1678. https://doi.org/10.1007/s10103-014-1546-z
46. Yabe Y, Hagiwara Y, Suda H, Ando A, Onoda Y, Tsuchiya M, Hatori K, Itoi E. Joint immobilization induced hypoxic and inflammatory conditions in rat knee joints. Connect Tissue Res 2013;54:210-217. https://doi.org/10.3109/03008207.2013.786056
47. Sasabe R, Sakamoto J, Goto K, Honda Y, Kataoka H, Nakano J, Origuchi T, Endo D, Koji T, Okita M. Effects of joint immobilization on changes in myofibroblasts and collagen in the rat knee contracture model. J Orthop Res 2017;35:1998-2006. https://doi.org/10.1002/jor.23498
48. Usuba M, Akai M, Shirasaki Y. Effect of low-level laser therapy (LLLT) on viscoelasticity of the contracted knee joint: Comparison with whirlpool treatment in rats. Lasers Surg Med 1998;22:81-85. https://doi.org/10.1002/(sici)1096-9101(1998)22:2<81::aid-lsm3>3.0.co;2-s
49. Ozawa J, Kaneguchi A, Tanaka R, Kito N, Moriyama H. Cyclooxygenase-2 inhibitor celecoxib attenuates joint contracture following immobilization in rat knees. BMC Musculoskelet Disord 2016;17:446. https://doi.org/10.1186/s12891-016-1303-5
50. Samuelsson K, Andersson D, Ahlden M, Fu FH, Musahl V, Karlsson J. Trends in surgeon preferences on anterior cruciate ligament reconstructive techniques. Clin Sports Med 2013;32:111-126. https://doi.org/10.1016/j.csm.2012.08.011
51. Raab DJ, Fischer DA, Smith JP, Markman AW, Steubs JA. Comparison of arthroscopic and open reconstruction of the anterior cruciate ligament. Early results. Am J Sports Med 1993;21:680-683; discussion 683-684. https://doi.org/10.1177/036354659302100507
52. Graf BK, Ott JW, Lange RH, Keene JS. Risk factors for restricted motion after anterior cruciate reconstruction. Orthopedics 1994;17:909-912. https://doi.org/10.3928/0147-7447-19941001-07
53. Nogaro MC, Abram SGF, Alvand A, Bottomley N, Jackson WFM, Price A. Paediatric and adolescent anterior cruciate ligament reconstruction surgery. Bone Joint J 2020;102-B:239-245. https://doi.org/10.1302/0301-620X.102B2.BJJ-2019-0420.R2
54. Nwachukwu BU, McFeely ED, Nasreddine A, Udall JH, Finlayson C, Shearer DW, Micheli LJ, Kocher MS. Arthrofibrosis after anterior cruciate ligament reconstruction in children and adolescents. J Pediatr Orthop 2011;31:811-817. https://doi.org/10.1097/BPO.0b013e31822e0291
55. Huleatt J, Gottschalk M, Fraser K, Boden A, Dalwadi P, Xerogeanes J, Hammond K. Risk factors for manipulation under anesthesia and/or lysis of adhesions after anterior cruciate ligament reconstruction. Orthop J Sports Med 2018;6:2325967118794490. https://doi.org/10.1177/2325967118794490
56. Cinque ME, Chahla J, Moatshe G, DePhillipo NN, Kennedy NI, Godin JA, LaPrade RF. Outcomes and complication rates after primary anterior cruciate ligament reconstruction are similar in younger and older patients. Orthop J Sports Med 2017;5:2325967117729659. https://doi.org/10.1177/2325967117729659