Effects of Different Running Intensity on Serum Levels of IL-6 and TNF-α in Patients with Early Knee Osteoarthritis

Zifeng Lin, Tanshu Liu, Zhilong Hu, Wutang Que, Hanming Qiu and Li Chen

Department of Orthopedics, Longyan First Affiliated Hospital of Fujian Medical University, Longyan, Fujian, China

ABSTRACT

Objective: To investigate the effects of different running intensities on interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) in patients with early knee osteoarthritis (KOA).

Study Design: Clinical comparative study.

Place and Duration of Study: Department of Orthopedics, Longyan First Affiliated Hospital of Fujian Medical University, Fujian, China, from January 2019 to January 2021.

Methodology: A total of 131 patients with early KOA admitted to Longyan First Hospital Affiliated to Fujian Medical University from January 2019 to January 2021 were selected and randomly divided into four groups using the random number table method: Group A (static control group, 34 cases), Group B (walking group, 32 cases), Group C (brisk walking group, 32 cases), and Group D (jogging group, 33 cases), and the training duration of the four groups was 6 months. Moreover, the levels of IL-6 and TNF-α, the activity of daily living (ADL), Fugl-Meyer assessment scale (FMA) scores, and adverse events before and after training were compared between the four groups.

Results: No statistical significance was observed in the differences of TNF-α, IL-6, ADL-advanced ability, ADL-basic ability, FMA-upper limb, and FMA-lower limb among the four groups before training ($p>0.05$). After training, the levels of TNF-α and IL-6 of the four groups were decreased, while the scores of FMA and ADL were increased. Group C had the highest FMA-upper limb and FMA-lower limb scores, ADL- advanced ability and ADL-basic ability after training, which were higher than those in groups A, B, and D ($p<0.05$). No statistical significance could be observed in the difference in the adverse event rate among the four groups during training ($X2=3.339$, $p>0.05$).

Conclusion: Exercise training of different intensities, such as slow walking, brisk walking, and jogging, is touted to enhance the overall recovery of patients with early KOA. The exercise intensity of brisk walking training is moderate, and the activity of daily living and exercise ability of patients are significantly improved after training, while the levels of TNF-α and IL-6 are obviously decreased.

Key Words: *Knee osteoarthritis, Interleukin-6, Exercise training, Exercise intensity, Tumor necrosis factor α*.

How to cite this article: Lin Z, Liu T, Hu Z, Que W, Qiu H, Chen L. Effects of Different Running Intensity on Serum Levels of IL-6 and TNF-α in Patients with Early Knee Osteoarthritis. *J Coll Physicians Surg Pak* 2022; **32(07)**:899-903.

INTRODUCTION

Patients suffering from knee osteoarthritis (KOA) often present with symptoms such as persistent knee pain, nocturnal resting pain, joint stiffness, numbness, and limited flexion and extension. The disease can occur at any age, but the age distribution of the affected population is obvious, and it is clinically more common among the middle-aged and elderly population.[1]

Correspondence to: Li Chen, Department of Orthopedics, Longyan First Affiliated Hospital of Fujian Medical University, Longyan, Fujian, China
E-mail: chenli7955@163.com

Received: November 10, 2021; Revised: May 09, 2022; Accepted: May 10, 2022
DOI: https://doi.org/10.29271/jcpsp.2022.07.899

Currently, high tibial osteotomy (HTO) is the preferred treatment for moderate to severe KOA with obvious anatomical changes of the knee, while non-steroidal anti-inflammatory drugs (NSAIDs), local blocking, and other conservative treatments are mainly used for patients with mild KOA in the early stage. After drug treatment, most patients with local pain and swelling symptoms can be effectively ameliorated, but problems such as high recurrence rate, long course of the disease, slow response, and high cost still exist.[2] In recent years, mild rehabilitation training has been clinically proven to accelerate the recovery of knee function in patients with early KOA. Rehabilitation trainings such as slow walking, brisk walking, and jogging have been applied in the treatment and recovery of patients with early KOA, achieving satisfactory outcomes.[3,4]

However, as authoritative guidelines have not been formulated, there is still a lack of a unified clinical view on the intensity of rehabilitation training for early KOA patients, contributing to

certain difficulties in the formulation of treatment and rehabilitation schemes for patients. Based on this, the aim of this study was to determine the effects of different running intensities on interleukin 6 (IL-6), knee function, and tumor necrosis factor α (TNF-α) in patients with early KOA.

METHODOLOGY

The study was approved by the Institutional Ethics Committee of Longyan First Affiliated Hospital of Fujian Medical University, and written informed consent was obtained from all participants. A total of 131 patients with early KOA admitted to Longyan First Hospital Affiliated to Fujian Medical University from January 2019 to January 2021 were selected and randomly divided into four groups using the random number table method as Group A (static control group, 34 cases), Group B (walking group, 32 cases), Group C (brisk walking group, 32 cases), and Group D (jogging group, 33 cases).

Patients who met the KOA diagnostic criteria in the "Guidelines for Osteoarthritis of Knee and Hip"[5] of the American College of Rheumatology; who met the definition of early KOA: mild or no osteochondral structural damage, knee pain symptoms, and obvious aggravation after exercise, symptoms improved or disappeared after absolute rest, and X-ray grade I and II[5]; who underwent physical examination, CT and ultrasonic examination with complete data, receiving treatment for the first time in Longyan First Hospital Affiliated to Fujian Medical University were inducted, patients mandatorily had stable vital signs and conscious mind and volunteered to participate in this study. Exclusion criteria were patients with joint/bone injuries in other parts; acute and chronic infections in other parts, severe circulatory dysfunction, acute and chronic bone marrow disease, severe mental or mental illnesses and poor compliance; and those who have temporarily suspended the study for any reason.

During the treatment period, all the four groups strictly controlled their diet, smoking, alcohol and high-fat, spicy diet, high-sugar and irritant food, and they ate a light diet and avoided staying up late. Group A (static control group) received no exercise training except basic treatment (selective COX-2 inhibitors) and simple daily activities. Group B (walking group) received another routine walking training at a frequency of 5 times/week and 30min/time on the premise of basic treatment, with a walking speed maintained at a daily walking speed of 1.5-2.5 Km/hour. Group C (fast walking group) received another brisk walking training at a frequency of 5 times/week and 30 minutes/-time on the premise of basic treatment, with a walking speed maintained at a brisk walking speed of 4.0-5.5 Km/hour. Group D (jogging group) received another jogging training at a frequency of 5 times/week and 30 minutes/time on the premise of basic treatment, with a running speed maintained at a jogging speed of 6.0-7.5 km/h. The training duration of the four groups was 6 months.

Inflammatory indexes: 3 ml fasting blood samples were collected from the median cubital vein of patients before and after treatment, and IL-6 and TNF-α were detected by enzyme-linked immunosorbent assay (ELISA). The reagents used were produced by Qingdao Hightop Biotech Co., Ltd. Before and after treatment, the Activity of Daily Living Scale (ADL)[6] was utilised to assess the activity of daily living of patients. The scale includes 2 dimensions of basic abilities (7 items with 60 points) and advanced abilities (3 items with 40 points), with a total of 10 scoring items. Scores were given according to the degree of self care of patients. Among the 10 scoring items, 2 items were graded with 0 and 5 points, 2 items were graded with 0, 5, 10, and 15 points, and the remaining 6 items were graded with 0, 5, and 10 points, with a total score of 0-100 points. The higher the score was, the stronger was the patients' self-care ability.

Fugl-Meyer Assessment Scale (FMA)[7] was used to assess the motor function of patients before and after treatment. The scale includes two subscales of upper limb (66 points) and lower limb (34 points), with a total score of 0-100 points. The higher the score, the stronger the motor function. Adverse events such as muscle soreness, joint popping, and fatigue during rehabilitation were compared between the four groups.

The correlation between FMA score (total score) and ADL score, IL-6, and TNF-α levels in patients with KOA was analysed. All data in this study were statistically analysed by SPSS 22.0. The data were tested for normal distribution by Shapiro-Wilk (S-W) method. Normal distribution data were expressed by Skewed distribution data were expressed by median (IQR); Conform to normal distribution used One-Way ANOVA test, non-normal distribution data used Kruskal Wallis test. Disordered outcome classification data (adverse events, gender) were represented by (%) and tested by Chi-square test and rank sum test was used for grade data (KOA X-ray classification). The value $p<0.05$ indicates a statistically significant difference.

RESULT

In comparison of baseline data of the four groups, no statistically significant differences were observed in age ($p=0.228$), course of disease ($p=0.051$), gender ($p=0.984$), and KOA X-ray classification ($p=0.913$) of the four groups, as shown in Table I.

The comparison of inflammatory indexes of four groups before and after training, no statistically significant difference was observed in TNF-α ($p=0.313$) and IL-6 ($p=0.872$) of the four groups before training, and the levels of each index of the four groups decreased after training, with statistically significant differences in TNF-α ($p<0.001$) and IL-6 ($p<0.001$) among the four groups. Moreover, the levels of TNF and IL-6 in Group C were the lowest after training, which were lower than those in groups A, B, and D ($p<0.001$), as shown in Table II.

In comparison of the activity of daily living between four groups before and after training, no statistically significant difference was observed in ADL- advanced ability ($p=0.992$) and ADL- basic ability ($p=0.818$) scores of the four groups before training, and ADL scores of the four groups improved after training, with statistically significant differences in ADL-advanced ability ($p<0.001$) and ADL-basic ability ($p<0.001$) among the four groups. Moreover, Group C had the highest ADL-advanced ability and ADL-basic ability scores after training, which were higher than those of groups A, B, and D ($p<0.001$), as shown in Table II.

Table I: Comparison of baseline data of the four groups.

Group	n	Age (years)	Course of disease (months)	Gender [n,(%)]		Koa X-ray grading [n,(%)]			
				Male	Female	Grade I	Grade II	Grade III	Grade IV
Group A	34	65.38±2.62	16.00(1.00)	18(52.94)	16(47.06)	21(61.76)	13(38.24)	0(0.00)	0(0.00)
Group B	32	64.28±2.20	16.00(1.00)	17(53.13)	15(46.88)	20(62.50)	12(37.50)	0(0.00)	0(0.00)
Group C	32	65.19±2.82	15.00(1.00)	18(56.25)	14(43.75)	19(59.38)	13(40.63)	0(0.00)	0(0.00)
Group D	33	65.52±2.79	16.00(1.50)	17(51.52)	16(48.48)	18(54.55)	15(45.45)	0(0.00)	0(0.00)
$t/x^2/Z$		1.462	7.789	0.155		0.528			
P		0.228*	0.051[*]	0.984[△]		0.913[△]			

*Note: * One-way anova test, [*]kruskal-wallis test, [△]all applied Chi-square test.*

Table II (a): Comparison of inflammation indexes, ADL and FMA scores before and after training in the four groups [median (IQR)].

Group	n	TNF-α(ng/L)		IL-6(ng/ml)	
		Before training	After training	Before training	After training
Group A	34	1251.00(16.50)	632.00(30.00)[*bcd]	6.46 (0.23)	4.98 (0.21)[*bcd]
Group B	32	1241.00(52.25)	524.50(23.50)[*ac]	6.40 (0.36)	3.51 (0.27)[*ac]
Group C	32	1245.00(22.75)	422.50(21.00)[*abd]	6.54 (0.30)	2.60 (0.13)[*abd]
Group D	33	1252.00(57.50)	515.00(15.00)[*ac]	6.45 (0.23)	3.42 (0.24)[*ac]
Chi-Square		3.560	111.598	0.707	110.381
P[△]		0.313	0.000	0.872	0.000

Table II (b): Comparison of inflammation indexes, ADL and FMA scores before and after training in the four groups [median (IQR)].

Advanced ability		Basic ability		FMA-upper limb		FMA-lower limb	
Before training	After training	Before training	After training	Before training	After training	Before training	After training
5.00(2.00)	18.00(2.00)[*bcd]	19.00(2.00)	39.00(2.00)[*bcd]	40.00(2.25)	47.00(2.50)[*bcd]	15.00(1.00)	20.00(3.00)[*bcd]
5.00(1.00)	23.00(1.75)[*ac]	19.00(2.75)	42.00(3.00)[*ac]	41.00(3.00)	52.00(2.75)[*ac]	15.00(2.75)	22.00(2.75)[*ac]
5.00(1.00)	27.00(2.00)[*abd]	19.00(2.75)	48.00(2.75)[*abd]	40.00(3.00)	56.00(2.00)[*abd]	15.00(1.75)	26.00(3.50)[*abd]
5.00(1.50)	23.00(1.75)[*ac]	19.00(3.00)	42.00(3.50)[*ac]	440.00(3.00)	52.00(3.50)[*ac]	16.00(1.00)	23.00(2.50)[*ac]
0.095	107.028	0.931	100.026	0.427	90.404	0.219	75.437
0.992	0.000	0.818	0.000	0.935	0.000	0.974	0.000

*Note: All applied Kruskal-Wallis test.*p <0.05 compared with the same group before training; [a]p <0.05 compared with group A at the same time point, [b]p <0.05 compared with group B after training, [c]p <0.05 compared with group C after training, [d]p <0.05 compared with group D after training.*

In comparison of motor function between the four groups before and after training, no statistically significant difference was observed in the FMA-upper limb (p=0.935) and FMA-lower limb (p=0.974) scores of the four groups before training, and FMA scores of the four groups improved after training, with statistically significant differences in FMA-upper limb (p<0.001) and FMA-lower limb (p<0.001) scores among the four groups. Moreover, Group C had the highest FMA-upper limb and FMA-lower limb scores, which were higher than those of groups A, B and D (p<0.001), as shown in Table II.

Comparison of adverse events between the four groups during training, no statistically significant difference was observed in the rate of adverse events during training among the four groups (x^2=3.339, p=0.342).

DISCUSSION

KOA is a chronic orthopedic disease mainly characterised by the degeneration of articular cartilage. Clinical studies suggest that impaired knee function caused by localised intra-articular inflammation, a disorder of cartilage matrix metabolism, and other factors is the primary cause of KOA.[8-10] The knee joint, as one of the most important weight-bearing joints of the human body, bears most of the weight of the human body. Therefore, the knee joint is prone to joint damage due to joint mechanical damage during daily exercise and walking, and chronic joint injuries caused by overwork and trauma are the main influencing factors of knee degeneration and the main cause of KOA.[11,12] Clinically, the method for the treatment of KOA is comprehensively selected based on patients' conditions. For patients with mild conditions, conservative treatment with medicines is recommended, while for those with moderate and severe conditions, HTO surgery is preferred, which can effectively ameliorate the clinical symptoms of patients and improve their quality of life and prognosis. However, surgery will increase the risk of surgical bleeding and pain in patients, leading to an increase in the probability of postoperative complications and affecting the long-term treatment effect.[13-15] In view of this, conservative therapy is clinically recommended for early KOA patients with mild symptoms and no obvious cartilage plate structural abnormalities. Rehabilitation training is touted to effectively promote the reconstruction of blood circulation and nerve conduction pathways in the knee joints of patients and has a positive effect on improving knee joint inflammation and motor function in patients with KOA.[16] Since there is no unified view of exercise training intensity for patients with KOA in clinical practice, the effect of improving the exercise function of patients with different training intensities and the incidence of adverse events remain unclear, contributing to certain difficulties in the formulation of treatment and rehabilitation schemes for patients with KOA. Based on this, the effects of different running intensities on IL-6, knee function, and TNF-α in patients with early KOA were investigated in this study.

Clinical studies have confirmed that the inflammatory response in the human body is closely related to the

cytokines in the blood. Consequently, the inflammatory response status of the knee of patients with KOA can be assessed by the expression level of inflammatory factors in the blood.[17,18] Among the commonly used indexes, TNF-α is a cytokine with a pro-inflammatory effect. It has a close bearing on the immune regulation of the body and can promote the killing effect of lymphatic T cells on pathogens. In case of intensified human infection, its expression level in the blood will increase. Il-6 plays a role in regulating the immune function of the body and is highly sensitive to the initial inflammatory response of the body. After the occurrence of inflammation, the expression level of IL-6 in the blood will increase significantly in a short period of time, both of which are highly sensitive to the knee inflammatory response of patients with KOA.[19-21] The results showed that the levels of TNF-α and IL-6 in Group A (static control group) were decreased and the ADL and FMA scores were increased after intervention, which was basically similar with Lawford's *et al*.[22] The results also showed that the improvement of TNF-α, IL-6, ADL, and FMA levels in Group B (walking group), Group C (brisk walking group), and Group D (jogging group) was higher than that in Group A after training, and the improvement of TNF-α and IL-6 levels in Group C was the most obvious, but TNF-α and IL-6 levels in Group C were lower than those in groups A, B, and D. Group C had the most obvious improvement effect, and its TNF-α and IL-6 were lower than those of groups A, B, and D, while ADL and FMA were higher than those of groups A, B, and D, indicating that brisk walking had the most obvious improvement effect on motor function, living ability, and local inflammation in early KOA patients, which was similar to the results of Song *et al*.[23] To explain it, on the one hand, brisk walking can improve the vascular endothelial function and reduce the activity of the sympathetic nervous system in patients with KOA, and promote the recovery of patients' motor function. On the other hand, brisk walking has moderate training intensity and avoids the injury of cartilage plate in patients with higher intensity training (jogging), so the prognosis quality of patients is significantly improved.[24,25]

CONCLUSION

The combination of slow walking, brisk walking, jogging, and other different intensities training on the basis of NSAIDs can improve the overall rehabilitation effect of early KOA patients. In particular, fast walking training has moderate exercise intensity, boasting that it can significantly improve patients' life ability and exercise ability after training, and significantly reduce TNF-α and IL-6 levels, which is of high clinical application value.

SOURCE OF FUNDING:
This study is projected by the startup Fund for scientific research, Fujian Medical University (No.2017XQ1192).

ETHICAL APPROVAL:
The study was approved by the Institutional Ethics Committee of Longyan First Affiliated Hospital of Fujian Medical University.

PATIENTS' CONSENT:
Written informed consent is obtained from patients to publish the data concerning this case.

COMPETING INTEREST:
The authors declared no competing interest.

AUTHORS' CONTRIBUTION:
ZL, LC: Designed this study and prepared this manuscript, and are responsible and accountable for the accuracy or integrity of the work.
TL, ZH: Collected and analysed clinical data.
WQ, HQ: Significantly revised this manuscript.
All authors approved the final version of the manuscript to be published.

REFERENCES

1. Chen H, Zheng X, Huang H, Liu C, Wan Q, Shang S. The effects of a home-based exercise intervention on elderly patients with knee osteoarthritis: Aquasi-experimental study. *BMC Musculoskelet Disord* 2019; **20(1)**:160. doi:10.1186/s12891-019-2521-4.
2. Conger A, Gililland J, Anderson L, Pelt CE, Peters C, McCormick ZL. Genicular nerve radiofrequency ablation for the treatment of painful knee osteoarthritis: Current evidence and future directions. *Pain Med* 2021; **22(Suppl 1)**:S20-23. doi:10.1093/pm/pnab129.
3. van Helvoort EM, Hodgins D, Mastbergen SC, Marijnissen AK, Guehring H, Loef M, *et al*. Relationship between motion, using the Gait Smart TM system, and radiographic knee osteoarthritis: An explorative analysis in the IMI-APPROACH cohort. *Rheumatol (Oxford)* 2021; **60(8)**:3588-97. doi:10.1093/rheumatology/keaa809.
4. Yang Y, Wang J, Dong L, Liu AF, Zhang XY, Li CY. The effect of continuous passive motion in patients treated with total knee arthroplasty for osteoarthritis: A systematic review and meta-analysis of randomized controlled trials. *Am J Phys Med Rehabil* 2021; **10**.1097/PHM.0000000000001718. doi:10.1097/PHM.0000000000001718.
5. Swezey RL. Comment on the American College of Rheumatology guidelines for osteoarthritis of the knee and hip. *Arthritis Rheum* 1996; **39(12)**:2083. doi:10.1002/art.1780391224.
6. Almeida Gulart A, de Araujo CLP, Bauer Munari A, Schneider BF, Dal Lago P, Mayer AF. Minimal important difference for London Chest Activity of Daily Living scale in patients with chronic obstructive pulmonary disease. *Physiotherapy* 2020; **107**:28-35. doi:10.1016/j.physio.2019.08.007.
7. Hernández ED, Forero SM, Galeano CP, Barbosa NE, Sunnerhagen KS, Alt Murphy M. Intra- and interrater reliability of fugl-meyer assessment of lower extremity early after stroke. *Braz J Phys Ther* 2021; **25(6)**:709-18. doi:10.1016/j.bjpt.2020.12.002.
8. Monteiro NRO, Pegorari MS, Ohara DG, Ferreira VTK, Matos

AP. The basis of information to guide clinical decision-making in knee osteoarthritis management: A survey with Brazilian physical therapists. *J Eval Clin Pract* 2021; **27(6)**:1216-22. doi:10.1111/jep.13532.

9. Chou SH, Shih CL. Efficacy of different platelet-rich plasma injections in the treatment of mild-moderate knee osteoarthritis: A systematic review and meta-analysis. *Int J Clin Pract* 2021; **75(6)**:e14068. doi:10.1111/ijcp.14068.
10. Gu W, Shi Z, Song G, Zhang H. MicroRNA-199-3p up-regulation enhances chondrocyte proliferation and inhibits apoptosis in knee osteoarthritis *via* DNMT3A repression. *Inflamm Res* 2021; **70(2)**:171-82. doi:10.1007/s00011-020-01430-1.
11. Deng R, Zhang H, Huang L, Xiong X, Fu X. MicroRNA-186 ameliorates Knee osteoarthritis *via* regulation of P2X7-mediated Cathepsin-K/Runx2/ADAMTS5 signalling axis in particular chondrocytes. *Saudi J Biol Sci* 2021; **28(8)**: 4270-5. doi:10.1016/j.sjbs.2021.06.091.
12. Liu SC, Qiao XF, Tang QX. Therapeutic efficacy of extracorporeal shock wave combined with hyaluronic acid on knee osteoarthritis. *Medicine (Baltimore)* 2019; **98(8)**:e14589. doi:10.1097/MD.0000000000014589.
13. Wei B, Zhang Y, Tang L, Ji Y, Yan C, Zhang X. Protective effects of quercetin against inflammation and oxidative stress in a rabbit model of knee osteoarthritis. *Drug Dev Res* 2019; **80(3)**:360-7. doi:10.1002/ddr.21510.
14. Balato G, Ascione T, Iorio P, De Franco C, De Matteo V, D'Addona A, *et al*. Knee septic arthritis caused by α-hemolytic Streptococcus in a patient with a recent history of knee arthroscopy: A case report. *BMC Infect Dis* 2019; **19(1)**:887. doi: 10.1186/s12879-019-4556-4.
15. Ueda K, Takura T, Fujikoshi S, Meyers J, Nagar SP, Enomoto H. Long-term pain management and health care resource use among an employed population in Japan with knee osteoarthritis combined with low back pain. *Pain Med* 2021; **22(12)**:3041-50. doi:10.1093/pm/pnaa424.
16. Iijima H, Yorozu A, Suzuki Y, Eguchi R, Aoyama T, Takahashi M. Hip abductor muscle weakness and slowed turning motion in people with knee osteoarthritis. *J Biomech* 2020; **101**:109652. doi:10.1016/j.jbiomech.2020.109652.
17. Chen Z, Lin CX, Song B, Li CC, Qiu JX, Li SX, *et al*. Spermidine activates RIP1 deubiquitination to inhibit TNF-α-induced NF-κB/p65 signaling pathway in osteoarthritis. *Cell Death Dis* 2020; **11(7)**:503. doi:10.1038/s41419-020-2710-y.
18. Alonso B, Bravo B, Mediavilla L, Gortazar AR, Forriol F, Vaquero J, *et al*. Osteoarthritis-related biomarkers profile in chronic anterior cruciate ligament injured knee. *Knee* 2020; **27(1)**:51-60. doi:10.1016/j.knee.2019.12.007.
19. Nambi G. Does low level laser therapy has effects on inflammatory biomarkers IL-1β, IL-6, TNF-α, and MMP-13 in osteoarthritis of rat models-a systemic review and meta-analysis. *Lasers Med Sci* 2021; **36(3)**:475-84. doi:10.1007/s10103-020-03124-w.
20. Nguyen H, Prasath V, Campbell C. (115) Interleukin-6 is associated with abdominal muscle growth in knee osteoarthritis patients. *J Pain* 2019; **20(4)**:503-5. doi: doi.org/10.1016/j.jpain.2019.01.034.
21. Sun G. Ba CL. Gao R. Liu W. Ii O. Association of IL-6. IL-8. MMP-13 gene polymorphisms with knee osteoarthritis susceptibility in the Chinese Han population. *Biosci Rep* 2019; **39(2)**:BSR20181346. doi:10.1042/BSR20181346.
22. Lawford BJ, Bennell KL, Allison K, Schwartz S, Hinman RS. Challenges with strengthening exercises for people with knee osteoarthritis and comorbid obesity: A qualitative study with patients and physiotherapists. *Arthritis Care Res (Hoboken)* 2020; 10.1002/acr.24439. doi:10.1002/acr.24439.
23. Lee SJ, Ren Y, Chang AH, Press JM, Hochberg MC, Zhang LQ. Plane dependent subject-specific neuromuscular training for knee rehabilitation. *IEEE Trans Neural Syst Rehabil Eng* 2020; **28(8)**:1876-83. doi:10.1109/TNSRE.2020.3005119.
24. Dell'Isola A, Jönsson T, Ranstam J, Dahlberg LE, Ekvall Hansson E. Education, home exercise, and supervised exercise for people with hip and knee osteoarthritis as part of a nationwide implementation program: Data From the better management of patients with osteoarthritis registry. *Arthritis Care Res (Hoboken)* 2020; **72(2)**:201-7. doi:10.1002/acr.24033.
25. Cederström N, Granér S, Nilsson G, Ageberg E. Effect of motor imagery on enjoyment in knee-injury prevention and rehabilitation training: A randomised crossover study. *J Sci Med Sport* 2021; **24(3)**:258-63. doi:10.1016/j.jsams.2020.09.004.