Journal of
Modern Rehabilitation

January 2022, Volume 16, Number 1

Research Paper

Effects of Pulsed Ultrasound on Knee Joint Friction and Inflammation in Non-traumatic Experimental Osteoarthritis

Mahmoud Ahmadi Fakhreh[1], Giti Torkaman[1*], Roya Ravanbod[1]

1. Department of Physiotherapy, Faculty of Medical Sciences, Tarbiat Modares University, Tehran, Iran.

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Citation: Ahmadi Fakhreh M, Torkaman G, Ravanbod R. Effects of Pulsed Ultrasound on Knee Joint Friction and Inflammation in Non-Traumatic Experimental Osteoarthritis. Journal of Modern Rehabilitation. 2022; 16(1):53-60. https://doi.org/10.18502/jmr.v16i1.8562

https://doi.org/10.18502/jmr.v16i1.8562

Article info:
Received: 07 Mar 2021
Accepted: 03 May 2021
Available Online: 01 Jan 2022

Keywords:
Ultrasound, Friction, Inflammation, Knee joint, Osteoarthrosis, Guinea pig

ABSTRACT

Introduction: Knee Osteoarthritis (OA) is one of the most important etiologies of pain and disability among adults. The effects of pulsed Ultrasound (US) on pain reduction and joint function have been proven, but its role on joint friction and inflammatory mediators is still unclear. Therefore, this study was designed to investigate the effects of US on knee joint friction and inflammation in non-traumatic experimental knee OA.

Materials and Methods: Forty-eight guinea pigs were randomly assigned into four groups: OA+US, OA+US sham, 30 days after OA induction (OA30), and normal control (n=12 for each group). OA was induced by intra-articular injection of 3 mg/kg of Mono-Iodoacetate (MIA) in the animal's left knee. Joint circumstance and weight of the animals were measured at baseline, before (i.e., after 30 days of MIA injection), and after US treatment. Joint friction was evaluated by a pendulum friction tester system. Cytokine levels, including Tumor Necrosis Factor (TNF)-α and Interleukin (IL)-1β, were measured by the ELISA method. The Pearson correlation coefficient was calculated to study the relationships between friction and inflammation variables.

Results: Joint circumference was increased in the OA30 group. Joint friction variables, including exponential curve fitting, cycle number, and friction coefficient, were significantly better in the US group ($P<0.05$). TNF-α and IL-1β cytokine levels were significantly lower in the US group. A significant positive correlation was observed between joint friction indices and TNF-α and IL-1β cytokine levels ($P<0.05$).

Conclusion: US was an effective approach for reducing joint friction and inflammation in OA30. Moreover, the relationship between knee joint friction and inflammation could help us better understand the etiology, mechanism, and treatment strategies of this disease.

*** Corresponding Author:**
Giti Torkaman, PhD.
Address: *Department of Physiotherapy, Faculty of Medical Sciences, Tarbiat Modares University, Tehran, Iran.*
Tel: *+98 (21) 82884509*
E-mail: *torkamg@modares.ac.ir*

1. Introduction

Osteoarthritis (OA) is one of the most common forms of joint arthritis and a noticeable cause of pain and disability among adults [1, 2]. The cartilage and other joint structures, including synovial membrane and fluid, subchondral bone, ligaments, and muscles around the joint, are affected by OA [3]. In addition to maintaining stability, the healthy synovial joint has a noticeable ability to perform reciprocal movements with the lowest friction under a wide range of loads and speeds. To evaluate joint friction and lubrication, Coefficient of Friction (COF) could be investigated [4, 5]. The interaction between the superficial layer of the joint cartilage and synovial fluid through the boundary and fluid film lubrication mechanisms provides smooth movement with minimal friction in a synovial joint [6]. Lubrication dysfunction could initiate a cascade of metabolic and structural changes and eventually the degenerative process to induce OA [7]. Inflammation in the synovial membrane leads to the infiltration of inflammatory cells and results in hyperplasia and hypertrophy of this membrane.

The inflammation of the synovial membrane leads to the permeation of immune cells and cytokine secretion with the resultant pain and joint destruction [8]. It has been shown that inflammatory mediators play a crucial role in starting and progression of the OA. Interleukin (IL)-1β can induce the symptoms of OA and cause the expression of Matrix Metalloproteinases (MMPs), including MMP1, MMP 3, and MMP 13. In addition, this cytokine may prevent type II collagen and proteoglycan synthesis in chondrocytes and is one of the leading causes of apoptosis in these cells [9, 10]. Tumor Necrosis Factor-alpha (TNF-α) has similar effects on joint cartilage and acts synergistically with IL-1β [11]. Increasing joint friction could also happen due to inflammation [12]. The impact of inflammatory cytokines on reducing superficial zone protein and hyaluronic acid could compromise joint lubrication [13]. It was also reported that modulating inflammatory mediators could reduce joint friction [12, 13]. Therefore, the relationship between inflammation and articular friction is essential in understanding and interpreting the mechanisms involved in OA.

Therapeutic modalities have been recommended to reduce pain, improve quality of life and movement, and delay OA progression [14]. One of the most common modalities is ultrasound therapy. It was shown that low-intensity pulsed Ultrasound (US) could induce cartilage regeneration [15]. In OA patients, US was also used to transfer hyaluronic acid compounds to the synovial membrane [16]. To the best of our knowledge, the effects of US on both friction and inflammation in OA have not been investigated so far. To prevent damage to the joint integrity, non-traumatic models of OA are superior to surgical methods, such as ligamentous and meniscus injuries. Moreover, the use of guinea pigs is more appropriate as they develop articular cartilage degeneration similar to that seen in human OA [17-19]. Therefore, we aimed to investigate the effects of US on knee joint friction and inflammation in the non-traumatic knee OA in guinea pig model and the relationship between these variables.

2. Materials and Methods

Study subjects

This experimental and interventional study was performed with an animal model and approved by the Medical Ethics Committee of the Tarbiat Modares University (No. 52.3066). Forty-eight male guinea pigs with an average weight of 400 to 500 g (bred in the Razi Vaccine And Serum Research Institute, Karaj, Iran) were transferred to the animal laboratory of Tarbiat Modares University. They were kept in particular cages of transparent polycarbonate materials under the standard condition: temperature 18°C-20°C, humanity 40%-50%, a dark-light cycle of 12-12 h, and free access to water and special food for guinea pigs [20]. In the first week, guinea pigs were allowed to adapt to the living conditions in the lab. In the second week, they were randomly divided into 4 groups: normal control (without any intervention); OA30 (one month after Mono-Iodoacetate [MIA] injection); OA+US (one month after the MIA injection), which received 10 sessions of the US treatment; and OA+US sham (one month after MIA injection), received 10 sessions of sham US treatment. The sample size was determined according to the friction parameter in Teeple et al.'s study, considering alpha error probability of 0.05, power 80%, and effect size of 0.8 [21].

Study intervention

The OA model was performed in the test groups with intra-articular injection of 3 mg/kg of MIA [17]. It was injected into the left knee joint from the lateral side of the patella [22].

The joint perimeter was measured using a digital caliper (Mitutoyo, Tokyo, Japan) in four areas, including suprapatellar pouch side-to-side (5 mm above patella), patellar superior border edges, the greatest part of the joint in a plane parallel to the articular surface line, and

the mid-distance between the inferior pole of the patella and the tibial tuberosity. The mean of these values was considered the knee joint perimeter [22]. Joint perimeter measurements were performed on the first and last days of the study and after 30 days or the beginning of the treatment period. US treatment program began on day 31 for 10 sessions, five consecutive days per week, within 2 weeks. Ultrasound treatment was performed with Sonopuls 434 (Enraf-Nonius, Delft, Netherland) with a duty cycle of 10%, frequency of 1 MHz, and average intensity of 0.3 w/cm2, 8 minutes per session [22, 23]. In the OA+US sham group, all procedures were similar, except for the US device that was switched off.

Measurements of study variables

After 30 days in the OA group and normal control, and after 45 days of MIA injection and the following 10 sessions of the US treatment in the OA+US and OA+US sham groups, the animals in the related groups were anesthetized and sacrificed.

The left knee joint was resected following transection from the middle of the tibia/fibula and femoral shafts. Friction testing was performed immediately after the joint resection using a pendulum friction tester [22, 23]. The exponential curve fitting damping slope of the pendulum oscillations was measured using a designed software (National instrument LABVIEW 7.1 software, Austin, TX, USA). As illustrated in Figure 1, in exponential curve fitting, the software considered and marked peak angles in each pendulum cycle and fitted an exponential curve on all pendulum's peak cycles, and calculated the slope of this curve as the joint friction [22, 23]. Moreover, the mean number of oscillations of the pendulum needed to reach the equilibrium position and the mean pendulum cycle number in each test was recorded by the designed software. The Coefficient of Friction (COF) of the knee joints was calculated by Stanton's equation, in which the amplitude of the oscillation was considered to decay linearly and affected by the joint radius [22, 23]. All friction tester variables were calculated in both flexion and extension movements of the animal joints.

After the joint friction test, the animal's joint was opened, and synovial membrane was extracted for pro-inflammatory cytokine measurements, including TNF-α and IL1β. The synovial membrane was homogenized (Heidolph DIAX 900, Sigma-Aldrich, Darmstadt, Germany) and then centrifuged at 4°C at 14000 rpm for 5 minutes to get prepared for ELISA measurement. The ELISA test was performed with commercial kits (Cusabio Corporation, China) according to the manufacturer's instruction for measuring cytokines levels.

Statistical analysis

SPSS software v. 20 was used for the statistical analysis. The normal distribution of the data was evaluated by the Kolmogorov-Smirnov test. One-way ANOVA and post hoc Tukey test were used to compare the variables in different groups. The Pearson correlation coefficient was used for evaluating the relationship between the joint friction and inflammatory variables. All results are shown as the Mean±SD. The significant level was considered as $P<0.05$.

3. Results

Data obtained from the weight and the circumference of the animal's joint are presented in Table 1. There was no significant difference in the baseline values ($P>0.05$).

Friction tester results in joint extension movement are presented in Table 2. Significant differences of the exponential curve fitting variable in extension mode were

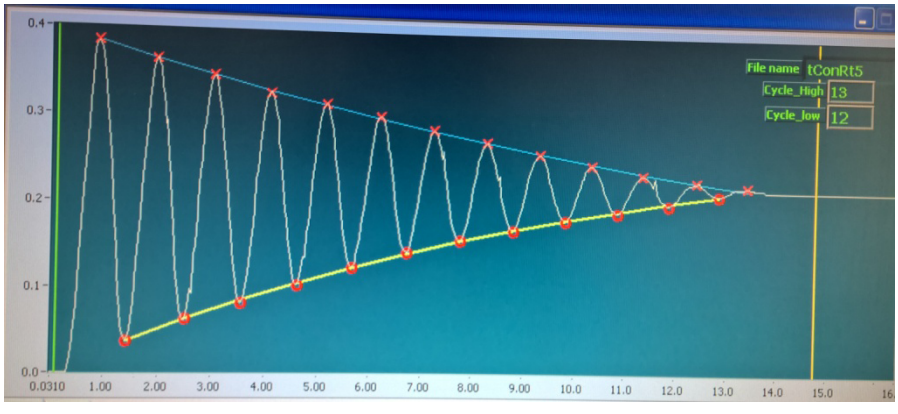

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Figure 1. Exponential curve fitting damping slope on the peak of pendulum Oscillations as the measure of joint friction

observed between groups of OA+US and OA+US sham (P=0.001), OA+US and OA30 (P=0.004), OA+US sham and OA30 (P=0.049), OA+US sham and normal control (P=0.001), and finally OA30 and normal control (P=0.003). Friction tester results in joint flexion movement are presented in Table 3.

Significant differences of exponential curve fitting variable were observed between groups of OA+US and OA+US sham (P=0.001), OA+US and OA(P=0.041), OA+US sham, and OA30 (P=0.025), OA+US sham and normal control (P=0.001), and finally OA30 and normal control (P=0.016).

Cycle number in flexion and extensions modes was the same in a pendulum friction tester device and showed significant differences between groups of OA+US and OA+US sham (P=0.001), OA+US, and OA30 (P=0.001), OA+US sham, and normal control (P=0.001), and finally OA30 and normal control (P=0.001). The friction coefficient showed a significant difference in extensions between OA+US and OA+US sham (P=0.006) groups and between OA+US sham and normal control (P=0.001) groups. The friction coefficient in flexion was significantly different between the OA+US and OA+US sham (P=0.001) groups and between OA+US sham and normal control (P=0.001) groups.

Inflammatory variables are illustrated in Figure 2. TNF-α levels had a significant difference between OA+US and OA+US sham (P=0.001) groups, between OA+US sham and OA (P=0.008) groups, between OA+US sham and normal control (P=0.001) groups, and finally between OA and normal control (P=0.001) groups. Significant differences of the IL-1β were observed between the OA+US and OA+US sham (P=0.001) groups, between OA+US and OA30 (P=0.028) groups, between the OA+US sham and normal control (P=0.001), and finally between OA30 and normal control (P=0.001) groups.

The Pearson correlation coefficient between each friction variable and inflammatory cytokines, including TNF-α and IL-1β, are presented in Table 4.

TNF-α and IL-1β had a positive correlation between friction coefficient and exponential curve fitting (P=0.001) and a significant negative correlation with the cycle number of the friction tester (P=0.001).

Table 1. Animal's weight and knee joint circumference in studied groups

Variables	Groups	Mean±SD		
		Baseline	Before Treatment	After Treatment
Weight (g)	OA+US	449.25±19.54	536.00±21.22	553.33±20.81
	OA+US Sham	453.17±17.26	542.42±13.19	564.42±13.77
	OA30	460.25±21.18	534.17±14.80	-
	Normal Control	455.42±16.32	525.58±17.96	555.42±15.23
Joint circumference (mm)	OA+US	7.65±0.56	10.16±0.28	8.68±0.18
	OA+US Sham	7.53±0.31	10.01±0.24	10.13±0.26
	OA30	8.52±0.56	10.54±0.52	
	Normal Control	7.51±0.25	8.27±0.37	8.65±0.34

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Table 2. Joint friction variables in knee extensions in the research groups

Variables	Mean±SD				P
	OA+US	OA+US Sham	OA30	Normal Control	
Exponential curve fitting	0.067±0.03	0.239±0.11	0.166±0.05	0.064±0.04	<0.001
Cycle number	12.5±1.68	8.08±1.44	8.75±1.22	14.00±2.00	<0.05
Friction coefficient	0.429±0.06	0.572±0.16	0.480±0.08	0.388±0.07	<0.001

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Table 3. Joint friction variables in knee flexions in the research groups

Variable	Mean±SD				P
	OA+US	OA+US Sham	OA30	Normal Control	
Exponential curve fitting	0.060±0.03	0.244±0.15	0.149±0.04	0.048±0.03	<0.001
Cycle number	12.5±1.68	8.08±1.44	8.75±1.22	14.00±2.00	<0.05
Friction coefficient	0.495±0.06	0.633±0.11	0.558±0.09	0.473±0.06	<0.001

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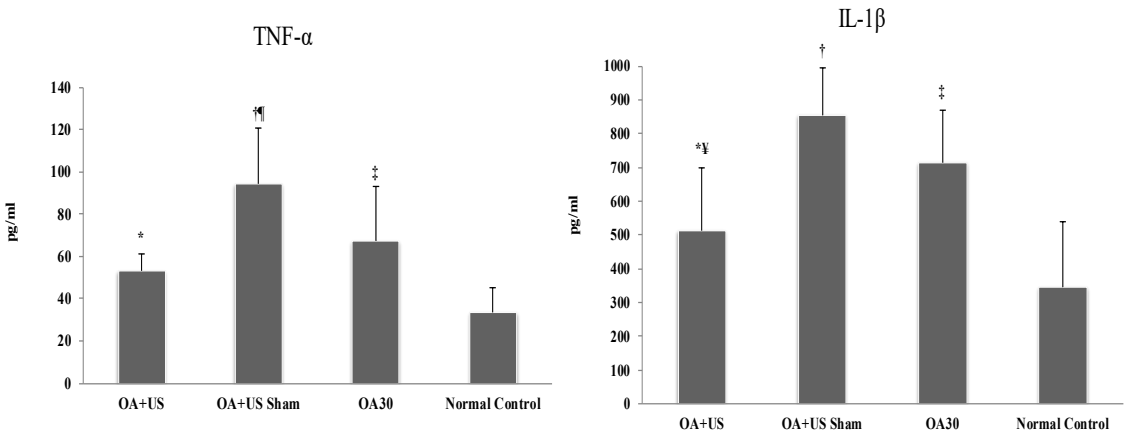

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Figure 2. Tumor Necrosis Factor-Alpha (TNF-α) and Interleukin (IL)-1β inflammatory cytokines in different study groups

* Significant difference between OA+Us and OA+US sham groups.

† Significant difference between OA+US sham and normal control groups.

‡ Significant difference between normal control and OA30 groups.

¥ Significant difference between OA30 and OA+US groups.

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Friction Coefficient	0.495±0.06	0.633±0.11	0.558±0.09	0.473±0.06	<0.001

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Table 4. Correlation between Tumor Necrosis Factor-Alpha (TNF-α) and Interleukin (IL)-1β, and friction parameters

Variables	Exponential Curve Fitting	Cycle Number	Friction Coefficient
TNF-α	0.539*	-0.609*	0.480*
IL-1β	0.634*	-0.732*	0.553*

* P<0.05

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4. Discussion

This research aimed to investigate the effects of US on friction and inflammatory cytokines in experimental OA of the knee joint. One advantage of this study was the use of a non-traumatic model of OA and preserving normal integrity of the joint to provide more similar condition to human OA [17, 18]. We did not find any significant difference between the flexion and extension cycle of the joint's movements. Regarding joint circumference, induction of OA by MIA intra-articular injection caused inflammation within the joint and increased joint diameter, which was significant compared to the normal control group. A significant increase in TNF-α and IL-1β levels confirmed inflammation and the resultant joint circumference increase in the present study.

US treatment caused a significant decrease in joint circumference compared to the OA+US sham and OA30 groups that showed its effective treatment and were comparable with previous studies [24, 25]. By applying micromechanical strains, US waves imply a series of biochemical events that result in the prevention of inflammation and triggering tissue repair [25]. Yang et al. showed that treatment with the US significantly improved joint symptoms and reduced joint inflammation, increased joint movement, and decreased inflammation in OA patients [26]. Chung et al. showed a decrease in circumference and inflammation in OA by the US via reducing and preventing proinflammatory factors [27], consistent with the present study results.

Regarding friction variables, the exponential curve fitting was lower in the US treatment group and no more significant with normal control after OA induction by MIA. This finding reveals that the US could reduce joint friction and might have a repairing capacity as it could lower the friction of an OA joint with high friction towards normal control friction. The higher cycle number in the OA + US group confirms the exponential curve fitting method of calculating joint friction. The cycle number of the pendulum friction tester in a healthy joint with low friction should be higher than that in a destroyed OA joint with surface irregularities and high friction [22, 23].

The friction coefficient is the force needed to start the movement against the compressive force between the two surfaces. Therefore, the smaller coefficient, the less resistance to motion [23]. The friction coefficient in the OA + US group was significantly lower than the OA+US sham group, which indicates a positive effect of US application. A significant difference in the coefficient of friction between OA + US sham with the OA30 group could be attributed to the shorter duration of degeneration in the OA30 group as these animals were killed after 30 days of MIA injection while the OA+US sham group underwent a period of 10 placebo sessions and OA was progressed in this period. In accordance with the result of the present study, Gurkan et al. reported modification of the OA in guinea pigs after the low-intensity US that reduced the severity of the disease and slowed down the progression of the disease. They indicated that US treatment was more effective in the early stages of OA and MMP-3 and MMP-13 as inflammatory cytokines showed significantly lower levels in the US-treated groups comparable to lower TNF-α and IL-1β in the present study [19]. Unlike Gurkan et al., Huang et al. reported that US at early stages of the OA improved cartilage repair and stopped further deteriorative damage in the later stage of induced arthritis in more advanced stages [28]. Joint destruction after MIA injection is a kind of severe destruction [17]; therefore, the present study has also shown that the US could reduce joint friction in advanced OA. According to DuRaine et al., increased articular cartilage surface roughness and increased friction were seen after applying IL-1β [12]. Therefore, it could be assumed that friction reduction in the present study could be attributed to lower TNF-α and IL-1β and probable better cartilage surface condition. Even though we did not assess cartilage histology, moderate to a high correlation between TNF-α and IL-1β and friction parameters in the present study, and according to DuRaine et al.'s study, we can postulate the result [12, 29]. Possible mechanisms to reduce joint friction observed in the OA+US group could improve joint lubrication and control of inflammatory mediators and prevent the above-mentioned further degeneration of the cartilage [7, 12]. Further histological studies are recommended.

5. Conclusion

The current study showed that controlling inflammatory cytokines by US treatment improved joint friction and inflammation in OA. There was a significant positive correlation between IL-1β and TNF-α with exponential curve fitting and friction coefficient and a significant negative correlation with cycle number of the pendulum friction tester. These findings mean that increased levels of the IL-1β and TNF-α in OA increased joint friction. According to the present study results, beyond other beneficial effects of the US modality in OA, it should also be considered in clinical practices that the US could reduce joint friction and inflammation. This study also has some limitations. In addition to inflammatory, anti-inflammatory cytokines could also be measured to provide more information about the beneficial effects of the US modality.

Ethical Considerations

Compliance with ethical guidelines

This study was approved by the Ethics Committee of the Tarbiat Modares University (No. 52.3066).

Funding

This research did not receive any grant from funding agencies in the public, commercial, or non-profit sectors.

Authors contributions

All authors equally contributed to preparing this paper.

Conflict of interest

The authors declared no conflict of interest.

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