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AD-41-25 REV 0

Potential Application of Low-Intensity Focused Ultrasound in Rapidly Relieving Delayed-Onset Muscle Soreness Induced by High-Intensity Exercise

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Supplemental material online at jultrasoundmed.org

Received June 22, 2021, from the State Key Laboratory of Ultrasound in Medicine and Engineering, College of Biomedical Engineering, Chongqing Key Laboratory of Biomedical Engineering, Chongqing Medical University, Chongqing, China (Y.X., J.L., D.W., J.C., F.L., Y.W.); and College of Exercise Medicine, Chongqing Medical University, Chongqing, China (M.S., P.J.). Manuscript accepted for publication November 20, 2021.

This research was supported by Philosophy and Social Science Projects (physical education) of Chongqing Medical University (No. 2018079).

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Abbreviations

CK, creatine kinase; DOMS, delayed-onset muscle soreness; ELISA, enzyme-linked immunosorbent assay; IL-6, interleukin-6; LD, lactic acid; LDH, lactate dehydrogenase; LIFU, low-intensity focused ultrasound; NSAIDs, non-steroidal anti-inflammatory drugs; RPE, rating of perceived exertion; TNF-α, tumor necrosis factor-α; VAS, visual analog scale

doi:10.1002/jum.15904

Objectives—To evaluate the efficacy of low-intensity focused ultrasound (LIFU) treatment on rapid relief of delayed-onset muscle soreness (DOMS) triggered by high-intensity exercise.

Methods—A total of 16 healthy male college students were randomly divided into two groups: the LIFU group ($n = 8$) and the Sham group ($n = 8$). After the exercise protocol, the LIFU group received treatment, which parameters included that the power output was 2.5 W/cm^2, the frequency was 1 MHz, and the treating time was 20 minutes. The Sham group was treated with LIFU without energy output. Visual analog scale was used to evaluate the level of DOMS in every participant. The activities of plasma creatine kinase, lactate dehydrogenase, and the plasma concentration were measured by spectrophotometry. Tumor necrosis factor-α and interleukin-6 of serum were analyzed by enzyme-linked immunosorbent assay.

Results—The visual analog scale of quadriceps femoris and/or calf muscles in the LIFU group decreased significantly at 24 hours ($P < 0.01$) and 48 hours ($P < .01$) after the exercise protocol. Both the accumulation of lactic acid ($P < .01$) in muscle and the activity of lactate dehydrogenase ($P < .01$) reduced immediately after LIFU treatment. The activities of tumor necrosis factor-α and interleukin-6 24 hours lowered in the LIFU group ($P < .01$).

Conclusions—LIFU treatment could relieve muscle soreness rapidly and effectively in the early stages of DOMS. The application of LIFU may provide a potential strategy for clinical treatment for DOMS.

Key Words—delayed-onset muscle soreness; exercise-induced muscle damage; high-intensity exercise; inflammation response; low-intensity focused ultrasound

The delayed-onset muscle soreness (DOMS) in the sports science field usually occurs after unaccustomed or high-intensity physical activity.[1,2] DOMS is characterized by varying degrees of muscle tenderness, stiffness, and pain, which can vary from slight muscle soreness to severe decline in exercise capacity.[3] The discomfort increases rapidly in the first 24 hours after the cessation of exercise, peaks between 24 and 72 hours, then gradually subsides, and disappears 5 to 7 days after exercise.[4]

Although this discomfort is temporary, these and other compensation mechanisms for relieving pain may lead to the decline of athletes' performance.[5] Therefore, the rapid relief of muscle soreness is particularly important for relieving athletes' discomfort without affecting their sports performance and career development.

To reduce the negative effects of DOMS, many interventions have been reported, including cold-water immersion,[6] compression therapy,[7] physical therapy like foam rolling[8] and massage,[9] antioxidant supplementation,[10] nonsteroidal anti-inflammatory drugs[11] and nutritional interventions like branched-chain amino acids.[12] These studies are able to provide promising results or show mixed results. However, these strategies have a limited effect on rapidly relieving muscle soreness or have some side effects.[13] For example, long-term use of nonsteroidal anti-inflammatory drugs is often accompanied by complications, such as gastrointestinal mucosal erosion, ulcers, gastroenteritis, etc.[14] Therefore, we would like to propose a treatment strategy that can rapidly and effectively alleviate DOMS after high-intensity exercise.

The low-intensity ultrasound can effectively relieve pain and swelling and increase the motion range of injured skeletal muscles.[15] However, the clinical efficacy of traditional ultrasound treatment has not been well proved, which may be due to insufficient ultrasound dose in the injured area.[16] Low-intensity focused ultrasound (LIFU) was designed to focus the ultrasonic beams on the target area without damaging the acoustic channels.[17] Previous studies have confirmed that LIFU has a significant pain relief effect on soft tissue injuries.[17] Therefore, we believe LIFU has potential application value in relieving DOMS after high-intensity exercise.

The purpose of this study was to evaluate the therapeutic effect of LIFU on DOMS after high-intensity exercise and to try to propose a rapid and effective treatment strategy for DOMS in clinical practice.

Materials and Methods

Experimental Design

In this study, a randomized controlled trial was conducted to evaluate the effect of LIFU treatment on DOMS after intensive exercise. The LIFU group received the treatment after high-intensity exercise, while the Sham group performed sham treatment (no energy output from transducers). The randomization of these groups was carried out by a volunteer, who did not participate in the experiment. Before the beginning of the experiment, the group assignment of participants was hidden. The design process for this research is shown in Figure 1.

Participants

The college students ($n = 16$, male, healthy) participated in this study. Those who suffered from leg muscle or orthopedic diseases, arthritis, or other chronic inflammatory injuries and could not exercise vigorously during the experiment were excluded. In addition, according to previous reports on gender differences, especially sex hormones can affect muscle damage, inflammation, and oxidative stress after high-intensity exercise. The participants of this study were limited to men.[18] The students' characteristics were as follows (mean $\pm$ standard deviations): age 24.12 $\pm$ 1.03 years old, height 175.56 $\pm$ 2.16 cm, and weight 67.31 $\pm$ 3.24 kg. All participants received explanations of the purpose, contents, and risk of the experiment before participation in this study. In addition, they provided oral and written consent before participating in the research. All procedures described in this study have been approved by the Ethics Committee of the Chongqing Medical University and implemented by Helsinki Declaration.

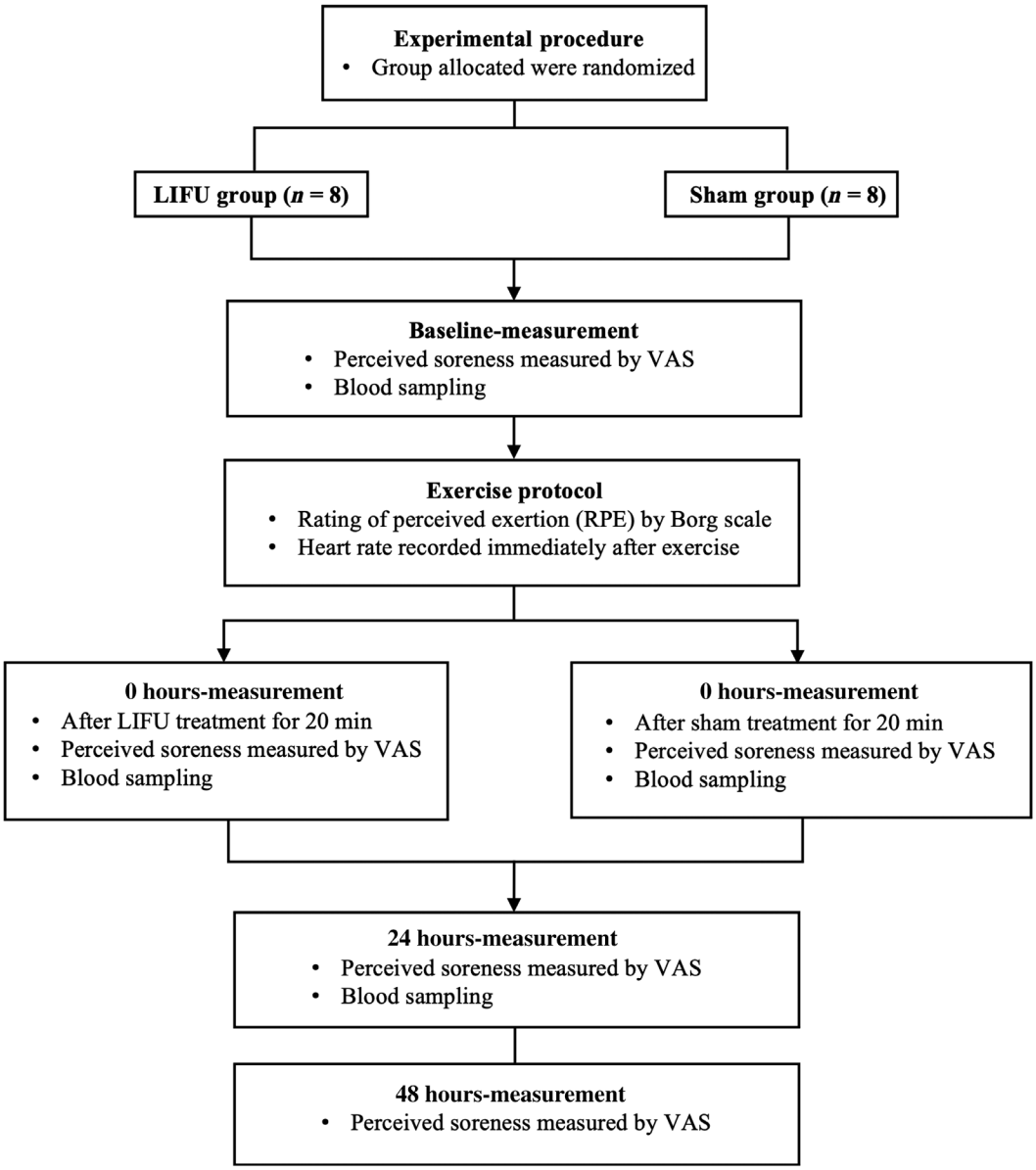
Exercise Protocol

All participants completed the whole exercise program in the following order: (a) standard warm-up of 5 to 10 minutes, including stretching and jogging; (b) run 800 m in 4 minutes; (c) 4 sets of 20 squats with 30 seconds intervals; (d) 50-meter and 100-meter sprints. The experiment was started with the first participant of the LIFU group and the Sham group. After the exercise, the participants received treatment for 20 minutes. During the treatment period, the next participant begins training until all participants have completed the entire exercise protocol and treatment process. In addition, heart rate was measured by an electronic sphygmomanometer (OMRON Co., Ltd., Shanghai, China) immediately after exercise, and the rating of perceived exertion of the Borg scale was recorded to evaluate the exercise intensity during the exercise protocol of two groups.

Low-Intensity Focused Ultrasound Treatment

In the LIFU group, this step was performed with a therapeutic LIFU device (LCA200; Chongqing Haifu Medical Technology Co., Ltd., Chongqing, China; (Figure 2A). The treatment probe was a 41.3 mm focal length focused ultrasound transducer with a 1 MHz output frequency, 2.5 W/cm^2 sound intensity, and a −6 dB focusing area of 0.34 cm × 0.34 cm. The transducer was pressed against the quadriceps femoris and calf muscles through a medical ultrasonic coupling medium (Tianjin Chengxin Medical Auxiliary Materials Factory, Tianjin, China). The transducer with a diameter of 6 cm was placed against the skin. The participants received this treatment through fixed and mobile methods. The transducer (speed was 5–10 mm/second) was moved to find the muscle soreness point. Stay at this point for 15 to 30 seconds according to the thickness of muscles and the

Figure 1. The design process of this research.



individual's bearing capacity (Figure 2B). A total of four sites in the quadriceps and calf muscles were treated for 5 minutes each, with a total treatment time of 20 minutes. After treatment, the coupling agent was wiped off the participants' legs, and the participants were reminded to keep warm.

Visual Analogue Scale

DOMS (quadriceps femoris and calf muscles) of all participants was measured by visual analog scale (VAS). According to previous research,[19] Vaile et al used this approach as a noninvasive way to monitor changes in DOMS after muscle damage protocols. In this study, participants were asked to rate their perception of soreness on a scale from 0 mm ("absence of soreness") to 10 mm ("very severe soreness").

Blood Sampling and Analyses

Blood (3.0 mL each) was collected from the anterior elbow vein and stored in the tube containing coagulant gel (Health Medical Products Co., Ltd., Jiangsu, China) at baseline (before exercise), 0 hours (after LIFU or Sham treatment), and 24 hours. The blood samples were centrifuged at 3000 rpm for 15 minutes, and then the supernatant was extracted and immediately frozen at −80°C until it was analyzed.

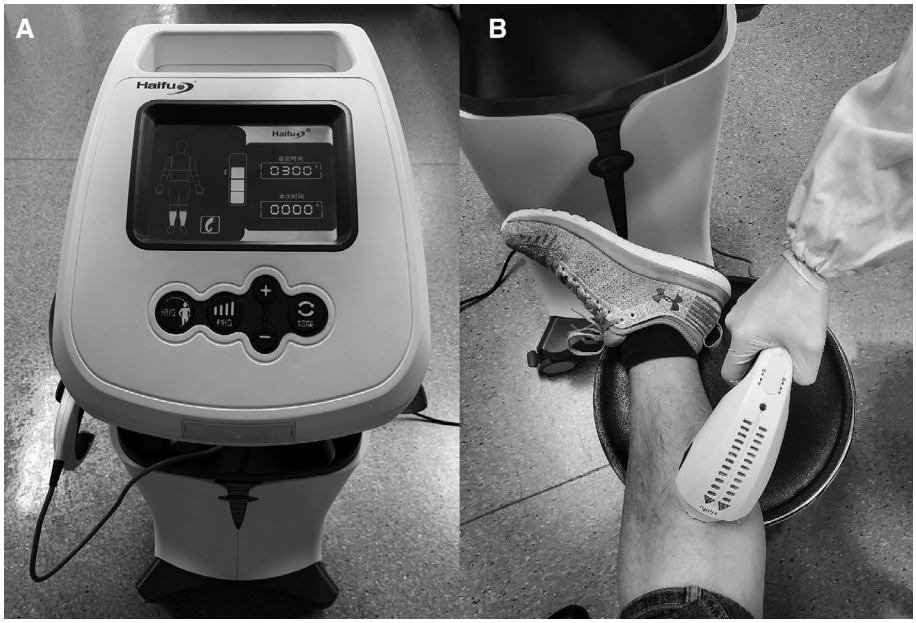
The activities of plasma creatine kinase(CK), lactate dehydrogenase (LDH), and the plasma lactic acid (LD) concentration were measured by spectrophotometry. The activities of CK (U/L) and LDH (U/L) were determined at 37°C using the assay kits (Nanjing Jiancheng Biotech Co., Ltd., Nanjing, China) at 630 and 450 nm, respectively. LD concentration (mmol/l) was measured at 530 nm at 37°C using an assay kit (Hushang Biological Technology Co., Ltd., Shanghai, China).

The activities of plasma tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) were analyzed by enzyme-linked immunosorbent assay (ELISA), using a specific kit (4A Biotechnology Co., Ltd., Beijing, China), at 450 nm at 37°C. The assay was performed in strict accordance with the manufacturer's instructions.

Statistical Analysis

Data were expressed as the mean ± standard deviations and differences between groups were expressed as mean difference (95% confidence interval). GraphPad Prism 8.2.1 (GraphPad, San Diego, CA) was adopted for statistical analysis. An unpaired *t*-test was used to determine the difference in exercise intensity (rating of perceived exertion and heart rate) between the LIFU

Figure 2. A, The therapeutic LIFU device (LCA200; Chongqing Haifu Medical Technology Co, Ltd, Chongqing, China). **B,** Treatment using the LIFU device at the calf muscles. LIFU, low-intensity focused ultrasound.



group and the Sham group. Two-factor analysis of variance (group × time) with Sidak's multiple comparisons test was used for VAS and biochemical data. The *P*-value less than .05 was considered to be statistically significant. The *P*-value less than .01 was regarded as highly statistically significant.

Results

Exercise Intensity after Exercise Protocol

There was no significant difference in exercise intensity between the two groups after exercise, such as rating of perceived exertion value of Borg scale (LIFU group: 15.14 ± 1.07; Sham group: 15.38 ± 1.19, $P = .52$) and heart rate (LIFU group: 151.10 ± 6.44 bpm; Sham group: 153.70 ± 5.47 bpm, $P = .44$). Complications were not reported in any group of participants in this study.

Delayed-Onset Muscle Soreness

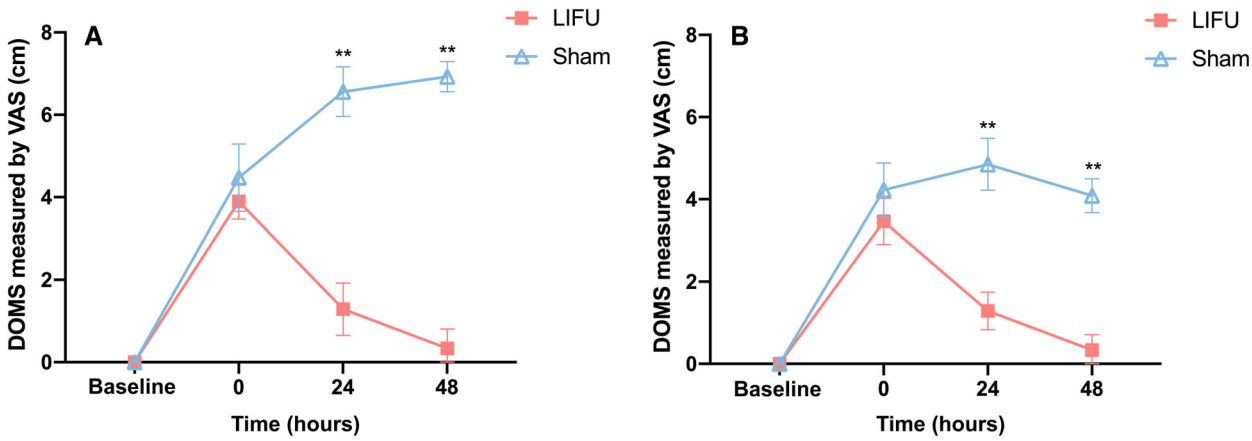
For DOMS, there was a main effect of group × time interaction in the VAS (quadriceps femoris; $F = 211.80$, $P < .01$) and VAS (calf muscles; $F = 100.70$, $P < .01$). In addition, there was a significant difference between the two groups. The LIFU group reported that the VAS

Table 1. The VAS Outcome for Quadriceps and Calf During the Measurement Time Between the LIFU Group and Sham Group

Outcome	Difference Within Groups		Difference Between Groups (95% CI)
	Mean Change Compared to Baseline		
	LIFU Group ($n = 8$)	Sham Group ($n = 8$)	LIFU minus Sham
Visual analogue scale—Quadriceps (cm)			
0 hours	3.90 ± 0.15	4.48 ± 0.81	−0.58 (−1.55 to 0.40)
24 hours	1.40 ± 0.26	6.56 ± 0.60	−5.16 (−6.16 to −4.39)
48 hours	0.34 ± 0.17	6.93 ± 0.37	−6.59 (−7.19 to −5.98)
Visual analogue scale—Calf (cm)			
0 hours	3.46 ± 0.20	4.23 ± 0.65	−0.76 (−1.64 to 0.11)
24 hours	1.29 ± 0.16	4.85 ± 0.63	−3.56 (−4.36 to −2.77)
48 hours	0.36 ± 0.15	4.09 ± 0.41	−3.74 (−4.41 to −3.19)

Difference (mean ± SD) within groups and mean (95% CI) difference between groups.
VAS, visual analog scale; LIFU, low-intensity focused ultrasound; CI, confidence interval.

Figure 3. A, DOMS of quadriceps femoris measured by VAS. **B,** DOMS of calf muscles measured by VAS. Data are presented as the means ± SD of eight participants in each group (LIFU: $n = 8$, Sham: $n = 8$). $^{**}P < .01$. DOMS, delayed-onset muscle soreness; VAS, visual analog scale; LIFU, low-intensity focused ultrasound.



(quadriceps femoris and calf muscles) decreased significantly at 24 hours ($P < .01$) and 48 hours ($P < .01$) after the exercise protocol. However, an increase in DOMS was observed after the exercise, and the VAS scores of quadriceps femoris and calf muscles in the Sham group reached the peak at 48 and 24 hours, respectively (Table 1 and Figure 3). These results indicated that the DOMS could be significantly and rapidly reduced by LIFU treatment.

Muscle Damage Markers

Plasma CK, LDH, and LD concentration were measured as markers of muscle damage. All the biochemical data related to muscle damage showed a significant time effect (all $P < .05$). No group effect was found for CK activity, but there was statistical difference on group × time interaction ($F = 6.58$, $P = .02$; Figure 4A); Post hoc analysis showed that there was no significant difference in CK activity

Figure 4. A, CK activity of all participants during the experiment. **B,** LDH activity of all participants during the experiment. **C,** LD concentration of all participants during the experiment. **D,** TNF-α activity of all participants during the experiment. **E,** IL-6 activity of all participants during the experiment. Data are presented as the means ± SD of eight participants in each group (LIFU: $n = 8$, Sham: $n = 8$). *$P < .05$, **$P < .01$. CK, creatinine kinase; LDH, lactate dehydrogenase; TNF-α, tumor necrosis factor-α; IL-6, interleukin-6.

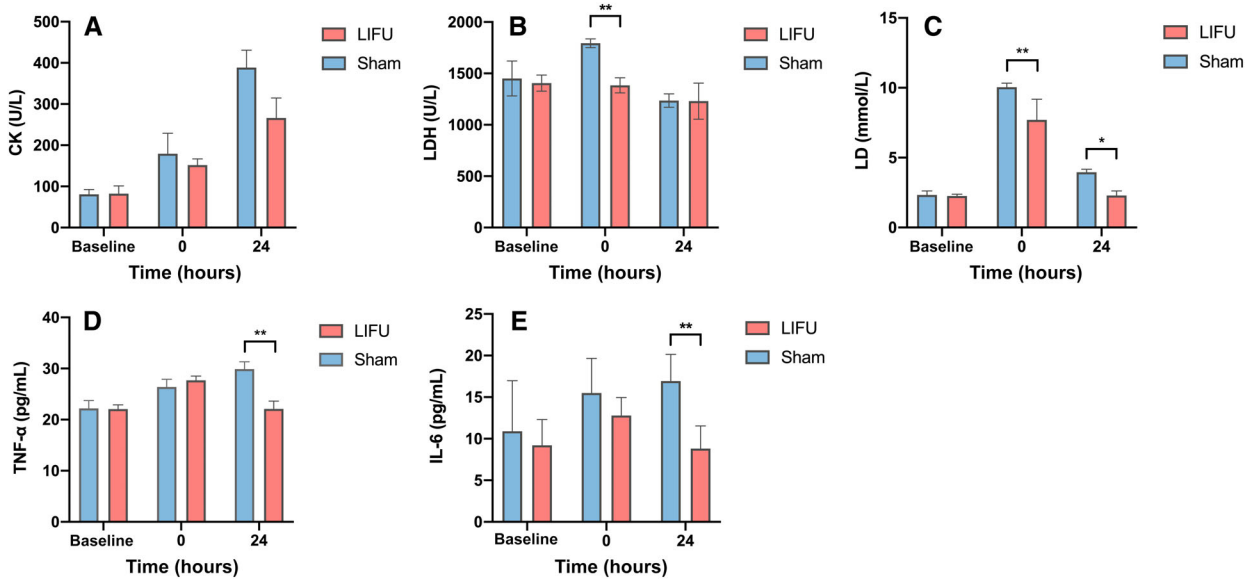
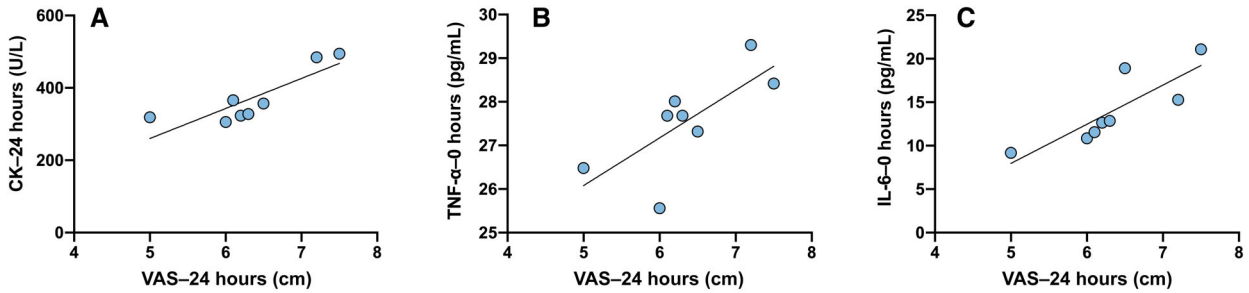


Figure 5. Relationships among DOMS, muscle damage markers, and inflammatory cytokines in LIFU group and Sham group during the experiment (Pearson's correlation coefficient). **A,** The relationships between VAS (quadriceps femoris) at 24 hours and CK activity at 24 hours. **B,** The relationships between VAS (quadriceps femoris) at 24 hours and TNF-α activity at 0 hours. **C,** The relationships between VAS (quadriceps femoris) at 24 hours and IL-6 activity at 0 hours. DOMS, delayed-onset muscle soreness; LIFU, low-intensity focused ultrasound; VAS, visual analog scale; CK, creatinine kinase, VAS, visual analog scale; TNF-α, tumor necrosis factor-α; IL-6, interleukin-6.



between the two groups at baseline ($P = .99$), 0 hour ($P = .82$), and 24 hours ($P = .09$). For LDH (Figure 4B), significant improvement over interaction was observed ($F = 4.94$, $P = .04$). In addition, post hoc analysis revealed that LDH activity was lower in the LIFU group at 0 hour ($P < .01$). There was statistical interaction in LD concentration ($F = 4.67$, $P = .04$), and LD in the LIFU group was lower than that in the Sham group at 0 hour ($P < .01$) and 24 hours ($P = .03$; Figure 4C). These findings indicated that LIFU treatment immediately reduces the accumulation of LD in muscle and decreases the activity of LDH.

Inflammatory Cytokines

Plasma TNF-α and IL-6 were determined as markers of inflammatory reaction. There was significant main effect in the group × time interaction for TNF-α ($F = 56.72$, $P < .01$) and IL-6 ($F = 10.45$, $P < .01$). The activity of TNF-α in the LIFU group decreased significantly at 24 hours ($P < .01$; Figure 4D). At the same time, IL-6 showed a similar trend, and the activity of IL-6 was lower in the LIFU group at 24 hours ($P < .01$; Figure 4E). These results suggested that LIFU treatment could reduce the inflammatory response at 24 hours after high-intensity exercise of the body.

Relationships among DOMS, Muscle Damage Markers and Inflammatory Cytokines

To clarify the relationship among the DOMS, markers of muscle damage, and inflammatory cytokines, we also explored the correlation among them on the basis of the previous research.[20] There was a positive correlation between CK activity at 24 hours and VAS (quadriceps femoris) at 24 hours ($r = 0.85$, $P < .01$; Figure 5A). Inflammatory cytokines IL-6 and TNF-α activities at 0 hour were also significantly correlated with VAS (quadriceps femoris) at 24 hours ($r = 0.84$, $P < .01$ and $r = 0.73$, $P < .05$, respectively; (Figure 5B and C). These results indicated that both muscle damage markers and inflammatory cytokines are associated with DOMS.

Discussion

The aim of our study was to evaluate the efficacy of LIFU treatment on the alleviation of DOMS after high-intensity exercise. Based on these results, the main finding of the current study was that after LIFU treatment, the symptoms of DOMS-related discomfort were significantly and rapidly alleviated in the quadriceps femoris and calf muscles. Since the peak value of DOMS appears in 24 to 72 hours after high-intensity exercise, we focused on the VAS results of the two groups at 24 hours in this study. The results demonstrated that the VAS of the LIFU group decreased significantly at 24 hours, while the VAS of the Sham group increased continuously. Thus, these findings suggested that LIFU treatment could be considered as an immediate effect. In another study,[21] a single focused extracorporeal shock wave therapy was administered to treat DOMS induced by eccentric exercise. Despite descriptive and clinically significant differences, decreases in pain intensity were found to be not significantly different between groups. The focused extracorporeal shock wave therapy might present an option in the mid-term recovery from DOMS (72 hours). In our study, LIFU treatment may increase energy deposition in the sore parts of muscles, resulting in rapid relief of muscle soreness in the early stage of DOMS. In addition, there were no side effects such as skin injury and other adverse reactions during the treatment.

Plasma LD and LDH levels, coupled with the reduction of IL-6 and TNF-α, decreased after LIFU treatment. Perhaps these biochemical indicators were influenced by LIFU treatment, which together quickly relieved DOMS. Many hypotheses have been put forward about the pathogenesis of DOMS, such as LD and muscle damage.[1] LD may cause acute pain associated with fatigue after strenuous exercise.[1] Serum CK and LDH are important enzymes for anaerobic metabolism, the leakage of these enzymes into the plasma is related to muscle damage and DOMS.[22] Potteiger et al[23] reported that CK level increased 24 hours after exercise, which was a sign of muscle damage. In this study, the results showed that muscle damage may be induced in the quadriceps femoris and calf muscles because CK activity in both groups increased significantly 24 hours after the high-intensity exercise. Furthermore, the decrease of LDH activity and LD concentration at 0 hour in the LIFU group enhanced the positive result of treatment. According to Fonseca et al,[7] the lower plasma LDH levels and less DOMS may be related to the rapid recovery of muscle homeostasis.

DOMS caused by high-intensity exercise usually leads to a local inflammatory reaction in an "acute

phase."[24] This inflammatory reaction is related to cytokines released from muscle damage sites, which promotes tissue healing.[24] The majority of cytokines, such as IL-6, are sensitive to inflammatory responses and play an indispensable role in controlling the acute immune response accompanied by exercise-induced muscle damage.[25] In addition, it has been suggested that increased serum IL-6 after strenuous exercise may prolong muscle damage and proteolysis.[26] In our study, the significant decrease of IL-6 at 24 hours in the LIFU group supported the anti-inflammatory effect of LIFU treatment.

TNF-α is a kind of pro-inflammatory cytokine,[27] and it can also inhibit muscle repair after injury.[28] Therefore, TNF-α was selected for analysis in this study. Intense physical activity can induce the inflammatory reaction of TNF-α in skeletal muscle.[29] TNF-α increases moderately with resistance to exercise and plays a role in initiating the decomposition and removal of damaged muscle fragments.[30] The increase of plasma TNF-α after high-intensity exercise in both groups directly provided evidence of muscle damage after exercise. However, our results indicated that plasma TNF-α in the LIFU group was lower than that in the Sham group at 24 hours. This finding indicated that LIFU treatment can alleviate the inflammatory response after high-intensity exercise and suggested that LIFU treatment can relatively reduce the degree of muscle damage.

Low-intensity ultrasound, as a mechanical wave, relies on its prominent mechanical–biological rather than thermal effects when acting on biological tissue.[31,32] The results of experiments by Dallapiazza et al[33] on the neuromodulatory effects of LIFU treatment (1.14 MHz experimental ultrasound transducer and the 650 kHz- and 220- kHz clinical ultrasound transducers) also revealed that there was no histological evidence of tissue heating as well as tissue damage was observed during magnetic resonance thermography. To investigate whether the effects of LIFU treatment in biological tissues are mediated by its mechanical effects, we also constructed simulation experiments based on the MATLAB platform, which found that the maximum temperature rise in the tissue during the entire treatment was within 0.7°C. In addition to the simulation experiments, we also assessed the temperature change in isolated porcine muscle tissue irradiated with the device, which demonstrated a very minimal temperature rise (see supplementary information). As a result, we further infer that the biological effects of LIFU are primarily mediated by mechanical effects rather than thermal effects, while the exact mechanism by which LIFU treatment rapidly relieves DOMS remains unknown.

Study Limitations

In this study, we observed a significant positive correlation among plasma CK activity, IL-6, and DOMS as assessed by VAS. This was consistent with the results of Kawamura's previous research.[34] In addition, we found that there was a significant correlation between TNF-α and DOMS. Although insufficient evidence might be caused by the limitation of sample size due to time constraints and physical requirements of participants in this experiment, it could be considered that muscle damage and inflammatory response were involved in the process of DOMS after high-intensity exercise. Meanwhile, the duration of the experiment should be prolonged to observe more biochemical changes and the degree of DOMS remission. In addition, Dieli-Conwright et al[35] proved that postmenopausal women who did not using hormone (estrogen) therapy experienced greater muscle damage after strenuous exercise, which indicated that estrogen might have a protective effect on exercise-induced muscle damage. Therefore, the effect of LIFU treatment on the relief of DOMS in women was also worthy of study. In the future, more randomized controlled trials should be carried out to determine the clinical significance and long-term efficacy of this treatment.

Conclusions

Our results indicated that LIFU treatment can rapidly and effectively relieve muscle soreness in the early stages of DOMS. At the same time, plasma markers related to muscle damage and inflammatory cytokines decreased, which highlighted its potential protective effect on exercise-induced muscle damage. The use of LIFU treatment provides a potential novel therapeutic strategy for the clinical management of DOMS.

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