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ORIGINAL ARTICLE

Efficacy and safety of far infrared radiation in lymphedema treatment: clinical evaluation and laboratory analysis

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Abstract Swelling is the most common symptom of extremities lymphedema. Clinical evaluation and laboratory analysis were conducted after far infrared radiation (FIR) treatment on the main four components of lymphedema: fluid, fat, protein, and hyaluronan. Far infrared radiation is a kind of hyperthermia therapy with several and additional benefits as well as promoting microcirculation flow and improving collateral lymph circumfluence. Although FIR therapy has been applied for several years on thousands of lymphedema patients, there are still few studies that have reported the biological effects of FIR on lymphatic tissue. In this research, we investigate the effects of far infrared rays on the major components of lymphatic tissue. Then, we explore the effectiveness and safety of FIR as a promising treatment modality of lymphedema. A total of 32 patients affected by lymphedema in stage II and III were treated between January 2015 and January 2016 at our department. After therapy, a significant decrease of limb circumference measurements was noted and improving of quality of life was registered. Laboratory examination showed the treatment can also decrease the deposition of fluid, fat, hyaluronan, and protein, improving the swelling condition. We believe FIR treatment could be considered as both an alternative monotherapy and a useful adjunctive to the conservative or surgical lymphedema procedures. Furthermore, the real and significant biological effects of FIR represent possible future applications in wide range of the medical field.

Keywords Far infrared radiation · Infrared ray · Lymphedema · Lymphatic tissue · Fat · Hyaluronan

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Introduction

The lymphatic system is the second largest circulation system in our bodies. Lymphatic obstruction may lead to an increase of the protein content in the extravascular tissue, with consequent retention of water and swelling of soft tissues. The abnormal buildup of fluid stimulates proliferation of fibroblasts as well as nonpitting edema and the development of swelling, most often in the arms or legs, causing lymphedema. There are two types of lymphedema: primary and secondary, and the prevalence all over the world has reached from 1.3/1000 to 1.5/1000 [1–3]. Primary lymphedema is rare and is caused by congenital dysplasia of lymphatic system, lack of lymph nodes or lymphatic vessels, and incompetence of lymph nodes or lymphatic vessels, whose prevalence is nearly 1.15/100,000. Secondary lymphedema occurs as a result of a

blockage or interruption that alters the lymph flow through the lymphatic system and can develop from an infection, malignancy, surgery, scar tissue formation, trauma, radiation, or other cancer treatment. The prevalence of secondary lymphedema is nearly 1.3/1000 [4–6]. The excess of tissue and fluid causes pain and anxiety, affects the patient's daily activities, decreases function due to heaviness, leads to body image disturbance, and has significant impairment on quality of life [7].

The pathophysiology and mechanism of lymphedema are still poorly understood. The composition of lymph fluid has aroused great interest since in the last century, many researchers investigated the composition of the interstitial fluid from swollen limbs. A biochemical analysis of lymph demonstrated that lymphatic fluid contains several components, such as proteins, lipids, glycosaminoglycans, leukocytes, and electrolytes, with different gradients in different pathological conditions. Among glycosaminoglycans, hyaluronan or hyaluronic acid (HA) is one of the major components of the interstitial tissue [8–14].

Conventional treatment for chronic lymphedema includes complex physical therapy (massages, limb exercises and elevation, and skin scare), manual lymphatic drainage, pneumatic pumps, compression garments, self/partner massage, and oral pharmaceuticals [15]. The conservative treatments are not only the most common method to care lymphedema, especially in the earliest stages, but can also be uncomfortable, restrictive, and time-consuming [9, 16–20]. With the advancement of technologies, novel devices were introduced for lymphedema treatment [21]. Low-level laser therapy is reported to have beneficial effects on cells and tissues promoting lymphatic flow and new lymphatic vessels (lymphangiogenesis), stimulating the immune system and removing the excess fat in tissues [22].

Lasers are classified by the US FDA based on different characteristics to classes 1, 2, 3A, 3B, 4, and 5 respectively from the lowest power in the first laser class (for example, barcode readers and some types of LED), which do not interact with the tissues, to the fourth and fifth laser class that are very high powered and are surgical lasers that can cut tissue. Class 1, 2, and 3 (A and B) lasers do not harm tissue. The main therapeutic lasers are classified as class 3B. Class 3 infrared wavelengths A and B refer to near infrared or short wavelengths (A) and far infrared or long wavelengths (B) [23]. The infrared region of the spectrum lies beyond the red end of the visible range, with wavelengths between 0.01 and 7.5×10^{-5} cm. Infrared rays are further divided in: near infrared, medium infrared, and far infrared. Among the different frequencies composing the infrared spectrum, far infrared rays are the most beneficial for the living beings. FIR treatment has an action similar to hyperthermia, which has three main biological effects: radiation, vibrational (or resonance), and thermal effect [17–20, 24]. Far infrared rays are able to deeply penetrate skin layers and resonate with water and organic molecules of our body. In fact, according to Wien law, which calculates the highest wavelength of radiation emitted by a body at a given temperature [($T \times \lambda = K$) T: temperature, Kelvin scale (Celsius scale + 273) λ: wavelength in microns (μ) K: kostant = 2896] at 35 °C, the highest wavelength of emitted radiation is 9.40 μ. This explains why the human body easily absorbs far infrared rays between 4 and 16 μ [25].

The human body is composed of 60% water in adult males and 55% in adult females. As FIR interacts with water molecules, it causes a thermal reaction which increases tissues temperature. The human body reacts to this phenomenon by dilating blood vessels: In this way, blood circulation is improved and more oxygenized blood reaches the soft tissue region being treated and, at the same time, stimulates the removal of accumulated toxins. That could improve even lymphedema promoting microcirculation flow and improving collateral lymph circumfluence. Although FIR therapy has been applied for several years on thousands of lymphedema patients, there are still few studies that have reported the biological effects of FIR on lymphatic tissue [26, 27]. Furthermore, it is still unclear whether the FIR could affect the other components of lymphedema tissues. In this research, we investigate the effects of far infrared rays on the major components of lymphatic tissue, such as fluid, fat, protein, and hyaluronan. Then, we explore the effectiveness and safety of FIR as a promising treatment modality of lymphedema.

Patients and methods

A consecutive group of 32 patients affected by lymphedema were treated between January 2015 and January 2016 at the Plastic and Reconstructive Surgery Department of Ninth People's Hospital in Shanghai (China). On a total of 32 patients, 11 cases had upper extremity lymphedema and 21 cases had lower extremity lymphedema. The inclusion criteria were as follows: stage II and III International Society of Lymphedema disease (15% greater circumference than the normal limb) with repeated episodes of cellulitis and lympho-scintigraphically confirmed proximal lymphatic obstruction [15], no acute cellulitis or unhealed wounds, no medical or family history of coagulation disorders or on medications affecting coagulation, patients with unilateral limb lymphedema untreated for more than 3 years, and lymphedema due to any causes.

Exclusion criteria were as follows: patients with clinical or iconographic evidence of cancer, recurrence or distant metastases, patients that cannot ensure adequate follow-up after treatment, patients that have discomfort with heating and constrictive bandage treatments, patients with previous history of dermatolymphangioadenitis or vascular embolization who refuses to sign the informed consent, and patients with extra measure limb or too large to be placed in the cure cabin. A

free shuttle bus was arranged by the hospital to transfer patients. The Declaration of Helsinki protocol was followed, and preoperatively, all patients gave informed consent for the procedure. The research program is approved by the review committee of Shanghai the Ninth People's Hospital. Data storage was performed in consistence with good clinical practice (GCP) guidelines.

Far infrared radiation treatment

Far infrared radiation therapy machine is independently researched by the Ninth People's Hospital Affiliated to Shanghai JiaoTong University [28]. The surface is packaged by stainless steel that can resist high temperature on the internal ring which is installed in a quartz lamp with eight FIR lights that can emit rays with a wavelength between 6.0 and 14.0 μ [20]. The fuselage is equipped with temperature control device that can adjust the temperature in the cabin.

The treatment takes 2 h per day, with the machine at a stable temperature of 42 °C, and the length of treatment is 4 weeks (five working days per week), totaling 20 days. Meanwhile, the researchers advised patients to strengthen self-nursing skills, such as extremity hygiene, prevention of skin damage, and avoidance of dermatophytosis following international guidelines [29].

Patient evaluation

The amount of fluid One to 2 days before and after the FIR treatment, using a multiple frequency bioelectrical impedance analysis machine (Inbody 3.0,Biospace Korea), researchers detect the amount of extracellular fluid, the fluid in the health limb, and the fluid in the pathologic extremity. After FIR treatment, the modification value of fluid is evaluated in this manner: Change value of extracellular fluid = Extracellular fluid volume before treatment − Extracellular fluid volume after treatment. Change value of fluid in affected extremity = (the amount of fluid in affected extremity before treatment − the amount of fluid in the health extremity before treatment) − (the amount of fluid in pathologic extremity after treatment − the amount of fluid in health extremity after treatment) [30].

Measurements of limb circumference One to 2 days before and after the FIR treatment, using the same tape, researchers measured the circumference of both the normal and lymphedematous extremities. Upper extremity circumference measurements are taken at the level of the midhand, the most prominent wrist crease identified at wrist hyperextension, cubital crease, 10 cm distal to cubital crease, and 10 cm proximal to cubital crease. Lower extremity circumference measurements are taken 5 cm proximal to the base of toe, 5 cm proximal to the lateral malleolus, 15 cm distal to the superior border of patella, and 10 and 20 cm proximal to the superior border of patella. A manual operation including measurement details is distributed to the evaluators. After FIR treatment, the change value of circumference is evaluated in this manner: Change value of circumference of pathologic extremity = (circumference of lymphedematous limb treatment − circumference of normal extremity before treatment) − (circumference of lymphedematous extremity after treatment − circumference of normal extremity after treatment) [31].

Thickness of skin and subcutaneous tissue One to 2 days before and after the FIR treatment, using ultrasound, researchers have measured the thickness of skin and subcutaneous tissue of both the normal and lymphedematous extremities. Dual images are obtained using a Mindary Digital Ultrasound Imaging System with a 10-MHz transducer. There were five detection points: upper 1/3 of arm/thigh, lower 1/3 of arm/thigh, upper 1/3 of forearm/leg, lower 1/3 of forearm/leg, and center of back of the hand/center of the instep. Researchers have recorded the thickness of skin and subcutaneous tissue of each point. After FIR treatment, the change value of thickness is evaluated in this manner: Change value of thickness = (thickness of affected extremity's skin/subcutaneous tissue before treatment − thickness of unaffected extremity's skin/subcutaneous tissue before treatment) − (thickness of affected extremity's skin/subcutaneous tissue after treatment − thickness of unaffected extremity's skin/subcutaneous tissue after treatment) [31].

Quality of life One to 2 days before and after the FIR treatment, using a quality of life scale [30, 31], the researcher has assessed the quality of life about the patients with chronic lymphedema. The quality of life scale is evaluated upon the degree of limitation during daily life patient, which has been divided into five grades, and given a different score. Zero points mean the most severe level that daily life has been limited, whereas 5 points mean the highest level of quality of life when the quality of life is not limited at all.

Adverse reactions Daily marks of patient's treatment are recorded to assess the patients' compliance and register any adverse reactions which occurred during the treatment, as well as rash, burns, or infection.

Laboratory index evaluation

Harvesting of samples Once the informed consent is signed, the patient is conducted in the aseptic operation room, 1–2 days before the treatment and 1–2 days before the final treatment, to harvest fluid and blood from the lymphedematous tissue, using acupuncture and intravenous transfusion. The amount of 0.5 ml tissue fluid and 0.5 ml blood is harvested and stored at 4 °C, then centrifuged at

2500*g* for 10 min, and collected the supernatant. The supernatant is stored at 4 °C and centrifuged at 12,000*g* for 5 min, then the resultant fluid is collected and analyzed [30].

Detection of cytokines associated to the swelling Using protein microarray (Raybiotech, USA) to detect IL-6 Leptin in the supernatant liquids, using ELISA (R & D, USA) to detect Hyaluronan in the supernatant fluids, and using BCA protein concentration determination kit (Sigma, USA) to detect total protein in the supernatant fluids, the specific test items and classification are referred in Table 1.

The formula to calculate the mass of macromolecules (hyaluronan and total protein) in lymphedema extremities $M = V * C'$; $V = \sum_{k=1}^{4} V'_k$; $V'_k = h_k(C_k^2 + C_k C_{k+1} + C_{k+1}^2)/12\pi$ [25] (Fig. 1), where *M* is the mass of a kind of macromolecules in lymphedema extremity, *V* is the sum of all extremity segment volumes, *C*' is the concentration of a kind of macromolecules in tissue fluid, *V*' is the volume of an extremity segment, *C* is the circumference at each end, and *h* is the distance between the ends. Therefore, comparing with the normal extremity, the extra mass of a kind of macromolecules in the lymphedematous extremity (Extra-M) = ($V_{\text{affected extremity}} - V_{\text{unaffected extremity}}$) C'. The change of the Extra-M after FIR treatment (ΔM) = Extra − $M_{\text{before treatment}}$ − Extra-$M_{\text{after treatment}}$ [30].

The formula to calculate the mass of macromolecules (hyaluronan and total protein) in serum $M = V'' * C''$, where *M* is the mass of a kind of macromolecules in serum, *V*" is the volume of the serum in the whole body, and *C*" is the concentration of a kind of macromolecules in serum. Since *V*" was constant relatively before and after treatment, the mass changes of a kind of macromolecules in serum of the whole body after far infrared ray treatment (ΔM) = $M_{\text{before treatment}} - M_{\text{after treatment}} = V''$ ($C''_{\text{before treatment}} - C''_{\text{after treatment}}$) [30].

Table 1 Statistic analysis on laboratory outcomes

Items	P (Serum)	P (Tissue fluid)
Leptin	0.260	0.005
Hyaluronan	0.074	0.419
M-Hyaluronan/Extra-M- Hyaluronan	0.074	0.000
Total protein	0.348	0.411
M-Total protein/ Extra-M- Total protein	0.348	0.000
IL-6	0.042	0.145

M, mass of hyaluronan or total protein in serum; Extra-M, ($\text{Volume}_{\text{lymphedema}}$-$\text{Volume}_{\text{healthy}}$) × concentration, mass of extra hyaluronan or total protein in tissue fluid of lymphedematous extremity; The other items without M are presented by concentrations

Statistical methods

We use the paired *T* test to compare the changes of extracellular fluid, fluid in lymphedematous extremity, circumference of extremities, thickness of skin and subcutaneous tissues, concentration of cytokines, macromolecules (total protein and hyaluronan), and score of the quality of life before and after the FIR treatment.

All data analyses are used by SPSS 19 software; $p < 0.05$ means the data changes are significant.

Results

On a total of 32 patients, 11 patients were affected by upper extremity lymphedema and 21 by lower extremity lymphedema. The rate of the patients at the stage II was 52.5% and at the stage III was 47.5%. The inclusion and exclusion procedure can be referred to Fig. 2. A variety of different causes resulted from the survey including primary and secondary lymphedema; the etiological classification is described in Table 2. A photographic image shows the improvement of a patient pre- (Fig. 3a, b) and post-treatment (Fig. 3c, d).

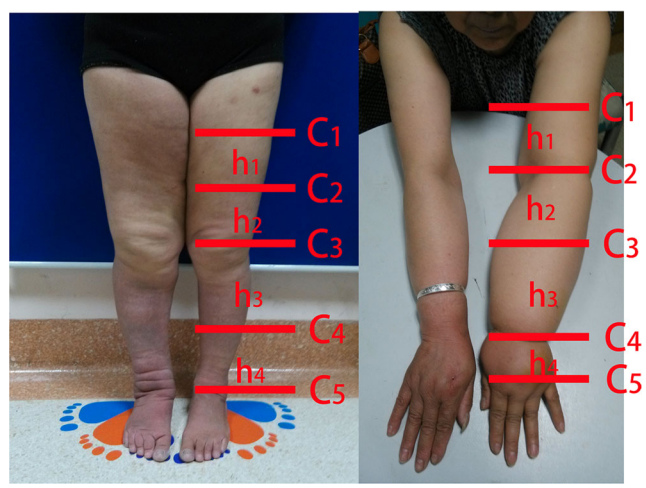

Fig. 1 Calculation of upper/lower extremity volume using a summed truncated cone model. V (Volume) = $\sum_{k=1}^{4} h_k(C_k^2 + C_k C_{k+1} + C_{k+1}^2)/12\pi$. A summation of four truncated cones' volumes approximates upper/lower extremity volume (mL). $C_{1\text{-}5}$ (cm) and $h_{1\text{-}4}$ (cm) denote circumferences and heights of each truncated cone, respectively. In the *left picture*, C_1 is the circumference at 20 cm above the superior border of patella, C_2 is the circumference at 10 cm above the superior border of patella, C_3 is the circumference at the superior border of patella, C_4 is the circumference at 15 cm below the superior border of patella, and C_5 denotes circumference at the ankle. In the *right picture*, C_1 denotes circumference at 10 cm above the cubital crease, C_2 is the circumference at the cubital crease, C_3 is the circumference at 10 cm below the cubital crease, C_4 is the circumference at the wrist, and C_5 is the circumference at the dorsum of the hand

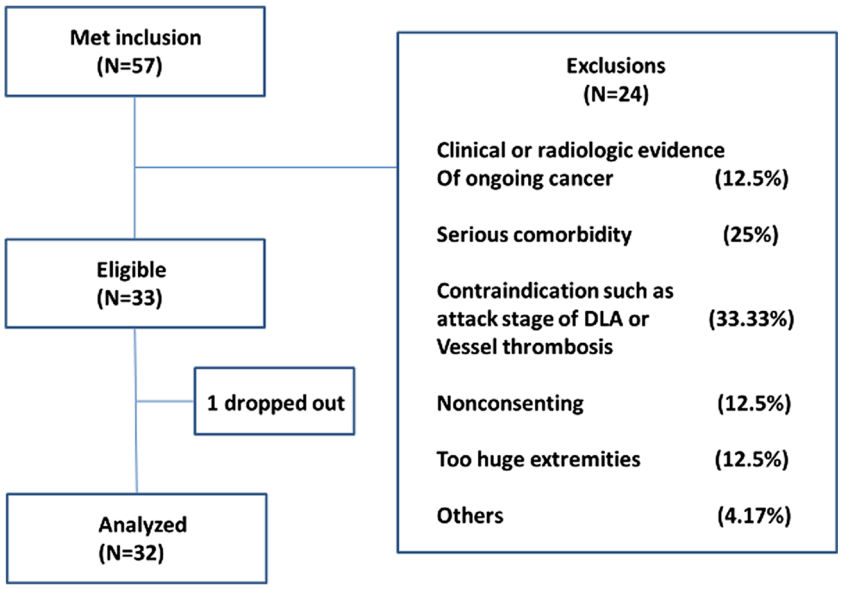

Fig. 2 CONSORT diagram of patient flow. There were 57 patients meeting the inclusion, 24 of whom were excluded and 1 dropped out. Finally, 32 patients were analyzed

Clinical index evaluation

Extracellular fluid and fluid in the extremities Before FIR treatment, the weight of extracellular fluid in patients' bodies was 13.513 ± 2.616 kg, the weight of fluid in lymphedematous extremities was 8.212 ± 2.234 kg, and the weight of fluid in normal extremities was 3.773 ± 1.613 kg. After FIR treatment, the weight of extracellular fluid was reduced ($p < 0.001$), the modification of the value was 0.763 ± 0.259 kg, the weight of fluid in lymphedematous extremities reduced ($p < 0.001$), and the change value was 1.204 ± 0.737 kg (Fig. 4). The result has showed that the FIR can decrease the weight of fluid in lymphedema extremities and extracellular fluid.

Circumference of extremities Before FIR treatment, the circumference of affected extremities was 36.088 ± 13.483 cm and in the normal extremities was 31.413 ± 10.362 cm. After FIR treatment, the circumference of affected extremities was reduced ($p < 0.001$); the modification of the value was 2.044 ± 1.313 cm (Fig. 4). The result has proved that FIR can effectively improve the swelling condition of lymphedema extremities.

Table 2 Lymphedema etiology

Diagnosis	Percent
Primary lymphedema	15.6
Venous insufficiency	3.13
Breast cancer	25
Cervical cancer	9.38
Ovarian cancer	12.5
Uterine cancer	3.13
Hodgkin's lymphoma	3.13
Trauma	6.25
Infection	18.75
Other	3.13

Thickness of skin and subcutaneous tissue Before FIR treatment, the skin thickness of affected extremities was 0.235 ± 0.117 cm and the thickness of subcutaneous tissue was 0.759 ± 0.578 cm; the skin thickness of normal extremities was 0.131 ± 0.042 cm and the subcutaneous tissue thickness was 0.205 ± 0.123 cm. After FIR treatment, the thickness of skin and subcutaneous tissue in lymphedematous extremities was reduced ($p < 0.001$); the modification of values was 0.067 ± 0.093 and 0.318 ± 0.35 cm respectively (Fig. 5). The scope of dark space was reduced, and the echogenic line became clearer. The result has showed that FIR can improve the swelling in skin and subcutaneous tissues of extremities lymphedema.

Quality of life Before FIR treatment, the score of quality of life was 0.625 ± 2.060. After FIR treatment, the score of quality of life improved ($p < 0.001$); the variation of the value was 1.375 ± 0.942 (Fig. 4). This has demonstrated that FIR can enhance the quality of life in lymphedema patients.

Adverse reactions No adverse reactions were recorded.

Laboratory index evaluation

On a total of 32 patients, 11 (34%) were randomly selected for laboratory evaluation. Before and after treatment, these patients donated a few samples of blood and tissue fluid harvested from the affected extremities. Between them, six cases were in the stage II and five cases were in the stage III.

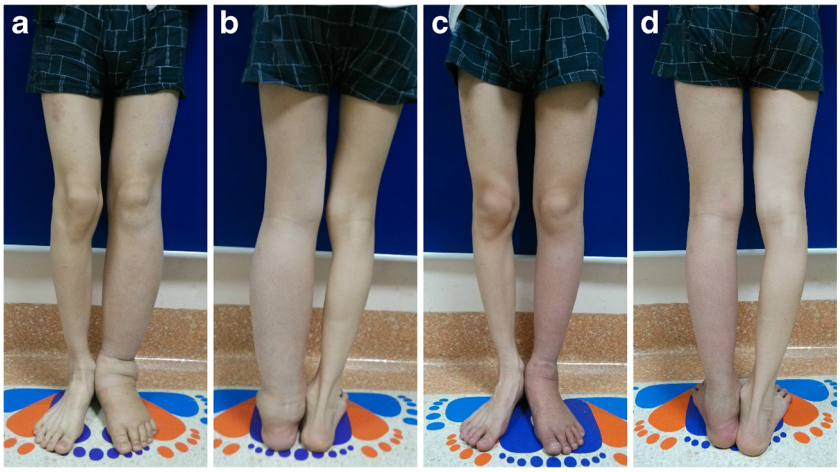

Fig. 3 A photographic image shows the improvement of a patient pre- (**a** and **b**) and post-treatment (**c** and **d**)

Cytokines associated to the swelling Before FIR treatment, the concentrations of IL-6 in serum and tissue fluid were 8.476 ± 5.688 and 169.100 ± 395.696 pg/ml, the concentrations of leptin in serum and tissue fluid were 8372.100 ± 6427.399 and 27475.752 ± 4604.382 pg/ml, the concentrations of hyaluronan in serum and tissue fluid were 60.490 ± 26.557 and 271.480 ± 3.867 ng/ml, and the concentrations of total protein in serum and tissue fluid were 232.2 ± 18.250 and 137.700 ± 8.982 μg/ml, respectively (Table 1). After FIR treatment, the concentration of IL-6 in serum is increased to −0.023 ± 0.036 pg/ml ($p < 0.05$) (Fig. 6). The other cytokines in serum did not change significantly ($p > 0.05$). In tissue fluid samples, leptin is reduced to 11456.210 ± 12656.400 pg/ml ($p < 0.01$). The other cytokines in tissue fluid did not change significantly ($p > 0.05$). These results showed that FIR can increase the concentration of IL-6 in lymphedema patient's serum and reduce the concentration of leptin in local lymphedema tissue fluid.

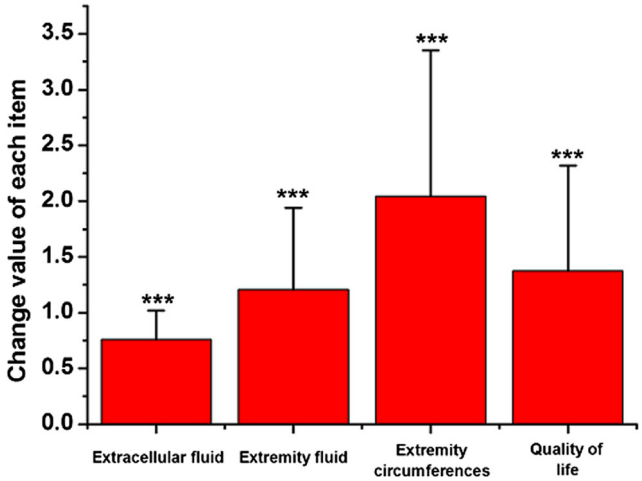

Fig. 4 Change value of extracellular fluid, extremity fluid, extremity circumferences, and quality of life after treated by far infrared radiation. ***$p < 0.001$

Mass of macromolecules We have calculated the mass of macromolecules by formulas. The results showed that the mass of hyaluronan (M-Hyaluronan) and mass of total protein (M-Total protein) in the whole body blood did not change significantly ($p > 0.05$) after FIR treatment. While before FIR treatment, the Extra-M-Hyaluronan in affected extremity was 0.451 ± 0.240 mg and Extra-M-Total protein was 0.225 ± 0.112 kg. After FIR treatment, the Extra-M-Hyaluronan and Extra-M-Total protein in affected extremity is reduced to 0.184 ± 0.269 mg and 0.088 ± 0.134 kg, respectively ($p < 0.001$) (Fig. 6). These results proved that FIR can reduce the mass of macromolecules in local lymphedema tissues.

Discussion

The infrared radiation is an invisible portion of the electromagnetic spectrum with wavelength range of 750 nm–100 μ, frequency range of 400–3 THz, and photon energy range of 12.4 meV–1.7 eV. It is located between the long wavelength red edge of the visible and the short edge of the terahertz (starting at 3 THz) spectral bands [32]. The application of FIR to biological structures creates alterations on cells, cell membranes, cell fluids, especially water, and DNA/proteins. It has mainly three biological effects on soft tissues: radiation, vibrational, and heat [19, 20]. Radiation and vibrational effects boost the free charge and stimulate ion oscillation, which would cause macromolecules denaturation and crashing of proteins. Then, smaller pieces of macromolecules can be easily absorbed by tissues. At the cellular level, the radiation causes alteration of cell membrane potentials and mitochondrial metabolism. Considering the relevant concentration of water in lymphedema patients, FIR effect creates a serial of biological activities such as the association of water molecules with ions (caused by solvation or confinement effect). In addition, the heat can penetrate, as a gentle radiant energy, up to 4 cm beneath the skin producing several biological effects as

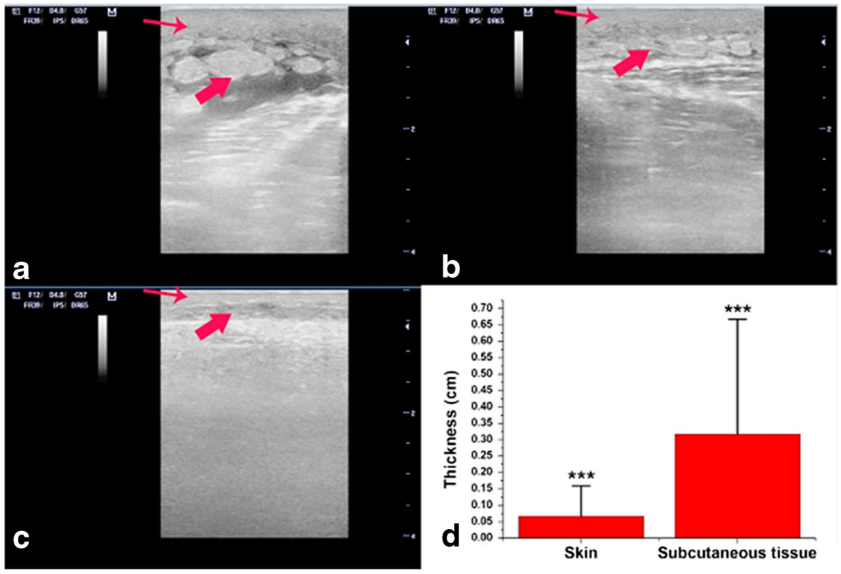

Fig. 5 The performance of ultrasound. The thickness of skin and subcutaneous tissue reduced after being treated by far infrared radiation. At the same time, the scope of dark space reduced and the echogenic line became clearer. *Small arrow*, the layer of skin; *large arrow*, the layer of subcutaneous tissue. **a** The extremity with lymphedema before far infrared radiation treatment. **b** The extremity with lymphedema after far infrared radiation treatment. **c** The healthy extremity. **d** The change value of thickness of skin and subcutaneous tissue in extremity with lymphedema. ***p <0.001

well as local vessel dilatation and increase the capillary circulation [16–18]. Liu et al. have demonstrated that local hyperthermia can stimulate Langerhans' cells, macrophages, and endothelial cells. It can enhance the immune system and promote microcirculation flow. These activated macrophages can incorporate and hydrolyze the excess proteins in lymphedema tissues, which cause the colloid osmotic pressure reduction in tissues and promote tissue fluid flowing back into the circulatory system [17, 33–35]. Hu et al. have also confirmed that local hyperthermia can help to increase the microcirculatory blood flow removing chronic inflammation and promoting tissue recovery [36–38].

For more than 80 years from the first research on extremities lymphedema, the typical clinical manifestations include the increasing of circumference, local fluid deposition, hyperblastosis, and decreasing quality of life [39, 40]. Quantitative studies, such as bioelectrical impedance analysis, has been applied to detect fluid changing in lymphedema

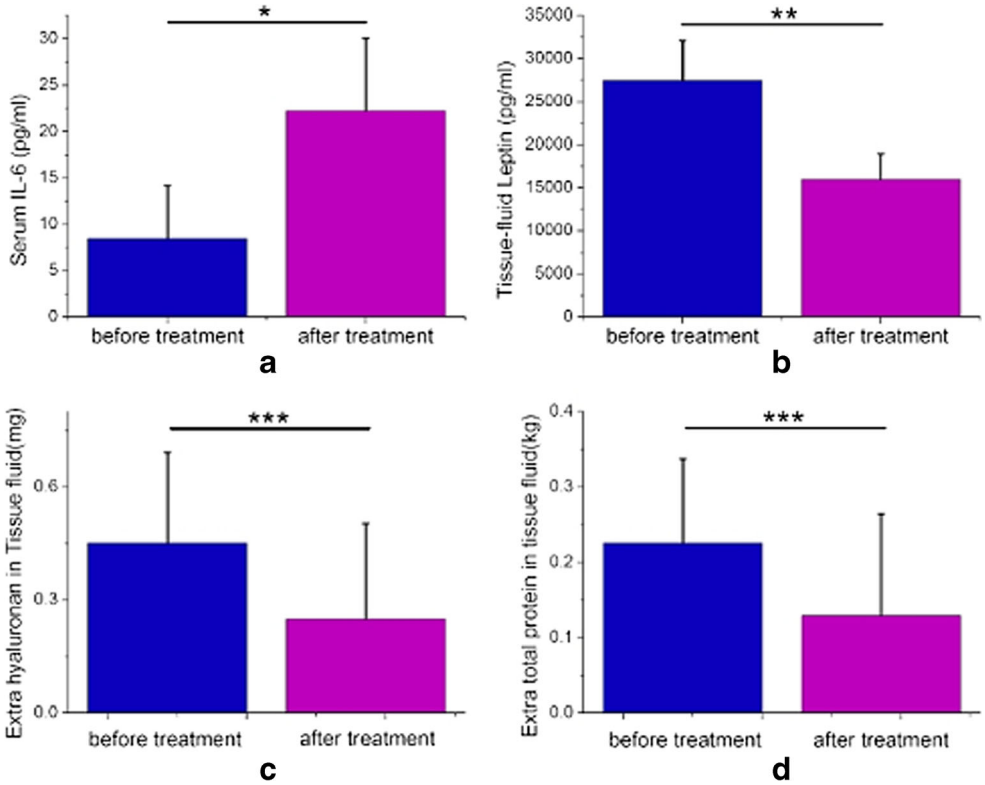

Fig. 6 The concentration of cytokines and extra mass of macromolecules in tissue fluid. **a** The concentration of IL-2 in tissue fluid before and after treatment. **b** The concentration of leptin in tissue fluid before and after treatment. **c** The extra mass of hyaluronan in lymphedematous extremity compared with healthy extremity calculated by formula [25] before and after treatment. **d** The extra mass of total protein in lymphedematous extremity compared with healthy extremity calculated by formula [25] before and after treatment. *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$

extremity from the 1990s and showed that the buildup fluid in lymphedematous extremity is much more than in normal extremity [41]. In our research, we demonstrated that after FIR treatment, the amount of fluid in lymphedematous extremity is reduced, the circumference of affected extremity is decreased ($p < 0.05$), and quality of life is improved ($p < 0.05$) (Fig. 4). It is clear that FIR can be able to reduce the volume of fluid in lymphedematous extremity and improve the quality of life due to an increase of microcirculation flow in the lymphedema tissues (Fig. 3a–d) [16, 33–35].

Suehiro et al. have analyzed the ultrasonic images about lymphedema extremities, and they found that cutaneous and subcutaneous echogenicity are increased, the echo-free space images is increased, tissue structure became unclear, and the cutaneous and subcutaneous thickness are increased [42]. In our research, we showed that after FIR treatment, the echo-free space in the ultrasonic images of lymphedema skin and subcutaneous tissues is decreased; tissue structures of which became clear and thickness is reduced ($p < 0.05$) (Fig. 5). It proved that FIR has improved the swelling condition of extremities lymphedema as a result of the reduction of fluid deposition in the lymphedema tissues, thanks to the simultaneous association with other substances decrease such as fat, protein, and hyaluronan.

It has been described that the lymphatic fluid is rich in lipids. Therefore, when the lymphatic circulation is obstructed, fat deposition would certainly occur [43, 44]. Dylke et al. [8] have noted that fat deposition phenomenon may occur in both primary and secondary lymphedema tissues. In addition, Lin et al. [9] have proved that leptin can promote fat metabolism and fat deposition and stimulate the leptin through positive feedback. At the meantime, Cuzzone et al. [45] mentioned that IL-6 can inhibit the fat deposition in internal environment. In our survey, we found that FIR can reduce the concentration of leptin in lymphedema tissue fluid and increase the concentration of IL-6 in serum ($p < 0.05$) (Fig. 6). That means fat deposition in lymphedema tissues is improved by FIR, and the positive feedback has stimulated the reduction of leptin concentration, thanks to the heat effect, which promoted lymphatic collateral circulation to transport lipids [17]. The increase of IL-6 in serum should also be induced by the extra lipid or IL-6 transported from the lymphedema tissues through lymphatic collateral circulation. That could inhibit the fat deposition in the whole body.

The lymphatic system has the function to transport lymph fluid which is rich in proteins [12]. Therefore, protein deposition always occurs in lymphedema tissues [46]. These proteins have the abilities to hold and collect water, making the swelling condition of lymphedema worse. In our study, we have observed that although the concentration of proteins in tissue fluid of lymphedema extremities did not change significantly after FIR therapy (Table 1), the circumferences of affected extremities are reduced ($p < 0.05$). Following the formula [31], we proved that the change of Extra-$M_{total\ protein}$ ($\Delta M_{total\ protein}$) was significant ($p < 0.05$) (Fig. 6) and FIR can improve the swelling of lymphedema extremities by promoting lymphatic collateral flow as well as decreasing the extra total protein in affected extremities.

Liu et al. [11] have noted that hyaluronan deposition occurs in lymphedema tissues, and this macromolecule can also hold and collect water contributing to the swelling condition of lymphedema. In our research, we found that the concentration of hyaluronan in tissue fluid of lymphedema extremities did not change significantly after FIR treatment (Table 1), but the circumference of affected extremities reduced ($p < 0.05$). We applied the formula [31], mentioned in methods, to calculate and prove that the change of Extra-$M_{Hyaluronan}$ ($\Delta M_{Hyaluronan}$) is significant ($p < 0.05$) (Fig. 6). That showed FIR could not only promote lymphatic circulation as well as reduce fluid, fat, and protein, but also decrease the extra hyaluronan in lymphedema extremities. These results have revealed FIR treatment has therapeutic effect on all the four major factors that form and exacerbate the swelling of extremities.

Limitation of the study are represented by the machine that can only treat extremities lymphedema; it cannot be applied for the treatment of perineal, neck, or trunk lymphedema. Finally, we believe applying bandages following FIR treatment can be more beneficial and enhance the FIR effect.

Conclusion

We present our experience of treating extremities lymphedema with far infrared radiation in a series of patients. Our preliminary results and analysis are very promising. We found that the procedure is safe and effective, improving the lymphedema burden, reducing measurements of circumference of lymphedema extremities, decreasing thickness of skin and subcutaneous lymphedematous tissue, and improving the patients' quality of life. Laboratory examination showed the treatment can also decrease the deposition of fluid, fat, hyaluronan, and protein, improving the swelling condition. We believe FIR treatment could be considered as both an alternative monotherapy and a useful adjunctive to the conservative or surgical lymphedema procedures. In the end, the real and significant biological effects of FIR represent possible future applications in wide range of the medical field.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Human and animal rights and informed consent All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or

comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

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