

PHYSIOTHERAPEUTIC REHABILITATION OF LYMPHEDEMA: STATE-OF-THE-ART

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ABSTRACT

Lymphatic diseases, especially lymphedema, represent a serious problem in the health community. We investigated strategies and methods for physiotherapeutic rehabilitation of lymphedema by carrying out a comprehensive search of the Medline and Embase databases from 1990 to 2016 to identify relevant published studies, articles, and reviews. Approaches for conservative management of lymphedema include the following: manual lymphatic drainage, lymphedema rehabilitation exercises, compression therapy, skin care, pneumatic compression, elevation of the extremities, thermal therapy, complete decongestive physiotherapy (CDT), taping, and aqua lymphatic therapy. Treatment of lymphedema with CDT, which is a combination of four methods (manual lymphatic drainage, lymphedema rehabilitation exercises, compression therapy, skin care), can achieve a 45-70% reduction in lymphedema volume. Prerequisites for successful physiotherapy are the availability of physicians, nurses and therapists who are specifically trained, educated, and experienced in each method. CDT is the most effective treatment as it reduces the symptoms of lymphedema and improves patients' functionality, mobility, and quality of life. Although other therapeutic techniques have demonstrated positive results, these surveys are limited and more studies are needed to confirm findings.

Keywords: lymphedema, rehabilitation, treatment, CDT, compression

Lymphedema is a combination of pathologic conditions characterized by excessive local accumulation of interstitial fluid which is rich in proteins. It occurs as the result of an imbalance between lymph production and the transport capability of the lymphatic system. Lymphedema can be either primary or secondary (1-3).

The treatment of lymphedema started in 1868 with the development of manual lymphatic drainage (MLD) by Professor von Monsegeil. Later, in 1892 (1). Alexander von Winiwarter, in his book "Billroth's Book of German Surgery", described the four pillars for the treatment of lymphedema: lymphatic massage with very gentle pressure, inelastic bandaging, special skin care, and exercises (2). In early 1930, Dr. Emil Vodder refined this lymphatic massage and its manipulations which are still used today.

The number of patients worldwide who suffer from lymphedema is estimated at 140-250 million. However, it is important to note that the incidence of lymphedema reported in the literature varies (1). Approximately 10% of cases of primary lymphedema are congenital, whereas 90% of cases have no apparent genetic connection. The prevalence of primary lymphedema in the US, regardless of cause, is about 1.15/100,000 people under the age of 20. Overall, primary lymphedema

affects 1-2 million people in America and it is twice as common in women as in men. Additionally, primary lymphedema is three times more common in the lower extremity than in the upper and in two thirds of cases it is bilateral (4).

As far as secondary lymphedema is concerned, the most frequent cause in Western countries is surgery and/or radiotherapy for cancer. In Europe, the incidence of lymphedema after cancer treatment is 15-28% in the upper extremity. It can occur from a few days to 20 years after the treatment. The incidence of lymphedema in the lower extremity after cancer therapy varies among surveys from 40% to 80% (5,6) In regions of Asia, Africa, and America, we see the most common cause of lymphedema worldwide in filariasis due to infection by mosquito-borne worms. Filariasis is estimated to infect more than 129 million people in tropical and subtropical regions around the world (7).

The purpose of this study was to review lymphedema management focusing on evidence-based strategies and investigational approaches.

METHODS

We carried out a comprehensive search of the Medline and Embase databases from 1990 to 2016 to identify published studies describing modern strategies for the conservative treatment of lymphedema. Reference lists of appropriate review articles were searched to identify studies missed by the database search. Reports from retrospective and prospective randomized controlled trials and original articles concerning lymphedema were included. Only articles in English were reviewed and studies with fewer than 20 patients were excluded.

RESULTS

Lymphedema treatment aims to alleviate symptoms, prevent progression, and reduce risk of skin infection. Complete decongestive

therapy (CDT) is currently recognized as the standard of care in lymphedema treatment. However, this systematic review summarizes current evidence in the literature and presents the latest strategies and methods for conservative physiotherapeutic management of lymphedema, including CDT, complementary, and other alternative therapies. These conservative treatments include manual lymphatic treatment, rehabilitation exercises, skin care, compression therapy, intermittent pneumatic compression, elevation, thermal therapy, taping, and aqua lymphatic therapy.

Manual Lymphatic Treatment

MLD is intended to stimulate lymph nodes and increase rhythmic contractions of the lymphatics to enhance their activity so that stagnant lymphatic fluid can be rerouted (8-10). MLD is composed of four main strokes: stationary circles, scoop technique, pump technique, and rotary technique (11).

The manipulations of MLD have some common components. All strokes are applied from the center to the periphery, so as to drain the proximal regions and prepare them to receive stagnated lymph from the distal regions (12). Additionally, the common denominator of all strokes is that they have a phase of “pressure,” or working phase, and a relaxation phase, or resting phase. During the working phase, the lymphatic structures are stretched; thus, their activity is increased and this, in combination with the slight pressure of the hands, achieves drainage of the lymph fluid in the desired direction (11). During the resting phase, the lymphatics are refilled with lymph from the periphery.

A special feature of all MLD strokes is the pressure used. This must be of lower intensity than in traditional massage so as not to damage or alter the superficial lymphatics. However, the pressure should be sufficient to achieve the desired effect of drainage. Finally, the frequency of application that is appropriate for strokes is once per second with each stroke repeated 5-7 times at each point.

Studies have shown that MLD is effective both as a preventative treatment (13) and as a postoperative rehabilitation treatment, and has optimal results when it is combined with the other elements of CDT (12,14,15).

Lymphedema Rehabilitation Exercises

Patients with lymphedema need to perform a safe type of exercise in order to reduce lymphedema volume, increase muscle strength, maintain a good level of mobility, reduce their weight, and increase their quality of life (16,17). The mechanism liable for the beneficial effects of exercise is the muscular pump. Lymph fluid is promoted through muscle contraction and is drained towards more proximal regions. In addition, exercise enhances protein absorption and increases lymphatic transport due to increases in inspiration and expiration and the cyclic decrease in intrathoracic pressure (18-20).

Some types of exercise applied are stretching, aerobic, and rehabilitation exercises either with or without resistance. Simple rehabilitation exercises include exercises in all joints, e.g. shoulder flexion, elbow flexion, horizontal abduction, and more. Exercises with light weight have been proved not to affect the volume of lymphedema adversely (21,22). Although at first the extremity may become swollen, the volume of accumulated fluid is reduced after 24 hours (19,23,24). However, exercises should be performed with caution and for low repetitions with little weight particularly at the initiation phase (25).

Stretching is a type of exercise that contributes to reducing skin scars and helps muscles and joints increase their flexibility. Stretching exercises must be applied and held for at least 5 seconds, gradually increasing with time (24). Aerobic exercise comprises rhythmic exercise for at least 30 minutes (25). It activates large muscle groups and its intensity should be between 70% and 85% of maximum achievable heart rate (25,26). Aerobic exercise improves physical fitness and reduces body weight. This kind of

exercise includes swimming, cycling, walking, and dancing (27).

Any exercise program should take into account the limits of each patient's abilities. The movements should not be painful and exhausting. Between more strenuous exercises, breathing exercises may be applied in rest periods. It is worth mentioning that many surveys advise patients to wear elastic garments during exercise to exert pressure on the capillaries and improve the lymphatic return. Although there are studies showing that during exercise garments can temporarily increase the volume due to reduced oxygen supply, this is followed by a sense of restored well-being as a result of preheating and "compliance of the materials" (24). Proper exercise with bandage protection is beneficial for limb muscle contraction, preventing additional swelling and facilitating lymphatic flow. However, overstretching and high-intensity exercise should be avoided (27,28).

Generally, it is acceptable for patients to either wear or not wear compression garments during exercise, provided that they wear suitable garments during the remaining hours of the day (29,30).

Skin Care

Skin care is stressed in manual approaches to lymphedema. The skin of patients with lymphedema is usually very sensitive, dry, and itchy due to disturbances of skin metabolism as a result of the macro- and microcirculation alterations which make it susceptible to inflammation and infection. By virtue of the impaired healing process, any skin injury may lead to severe inflammation and infection causing a worsening of the condition. For this reason, therapeutic and protective measures are essential components (31-33).

Compression therapy is another factor that may lead to a dry, broken, and sensitive skin that is prone to injuries. Along with positive effects, there is also a negative

interaction between the skin and the means of compression (medical bandages and garments). The main reasons for this are the mechanical effects and absorption properties of compression bandages and garments. However, the massage effect that they offer while moving over the skin is intentional because it positively affects the microcirculation (34,35).

Because of direct contact with the skin and consequent abrasion, high mechanical pressure is also created on the corneal layer (the uppermost layer of the epidermis). Moreover, because of this very close contact with the skin, the fibers of the bandages and garments absorb sweat and skin oil, damaging the normal thin hydrolipidic layer of the skin and the protective acid layer. The aim is to keep the skin in a normal and healthy state, or to heal it as well as possible. Substances that are missing, such as water, natural moisturizing factors, and lipids, should be restored using medical skin products. Attention should be given to the medical compression garments prescribed because the elastic fibers in some of them are destroyed by the oil found in products such as Vaseline and paraffin, decreasing the effectiveness of the compressive garments.

Therefore, in order to keep the skin flexible and durable, patients should choose a mild, soap-free cleansing lotion that is neutral (pH=7) or slightly acidic (pH=5) for daily use as well as bath oils that replenish the skin oil. Patients should take care to completely dry the skin after a bath or shower, especially in deep skin folds, to minimize the risk of liquid "chambers" leading to cutaneous fungal infection. After the skin has been cleaned, the hydrolipidic layer and acid mantle of the skin must be hydrated using soft pharmaceuticals (34,36).

Nevertheless, products for skin care should be used sparingly and applied with gentle massaging movements. Compression garments should not be applied if the products have not been fully absorbed. Every skin infection should be treated and cleaned by a

doctor. During treatment, special attention should be paid to the care of secondary skin lesions resulting from radiation. The physiotherapist should discuss the skin care with the physician prior to treatment. Continual cooperation of a multidisciplinary team is essential for the optimal treatment of lymphedema (37,38).

Compression Therapy

Compression therapy is a very important tool in the treatment of lymphedema. Even when MLD is performed correctly, swelling does not decrease without compression (in most cases). On the other hand, even if MLD is not performed but there is satisfactory compression, a reduction of edema can be observed. Compression bandages should remain on the extremities until the next session of MLD. Products used for compression therapy are low-stretch bandages and elastic garments (elastic stockings/sleeve/gloves) (39,40). Bandages not only balance the elastic tissue deficiency but also increase tissue pressure, which is positively correlated with lymph flow. Furthermore, compression therapy aims to inhibit outflow from capillaries by exerting pressure on subcutaneous tissue to prevent tissue fluid transfer associated with gravity and to improve venous return (41,42). Bandages are either applied to exert a specified pressure on the tissues or serve as a resistive layer against pressure of the muscles. Bandages are classified under several criteria, according to the type of the fibers (elastic cloth or resistant rubber), degree of stretchiness, and degree of force (tensile) (43,44). Pressure should be evenly distributed all over the limb. The distal part of the affected limb is bandaged at the highest pressure which is reduced proximally. Additionally, when the limb is in motion, short-stretch bandages maintain their integrity as the muscles contract against them and provide a semi-rigid support structure when the muscles reach working pressure. This also reduces capillary filtration,

resulting in further edema reduction (41). Compression therapy is contraindicated in acute inflammatory conditions such as cellulitis, congestive heart failure, and acute venous thrombosis. This treatment should also be carefully selected in cases of sensory paralysis, nerve paralysis, or peripheral arterial occlusive disease (it is also contraindicated in limbs with severe ischemia) (45). It is important to mention that the success of the treatment largely depends on the materials used.

Complete Decongestive Physiotherapy (CDT)

The best global treatment of lymphedema according to the international guidelines of the International Society of Lymphology is CDT (complete decongestive physiotherapy) (46), which can effectively reduce the volume of lymphedema, improve patients' mobility (47,48), and increase quality of life (49-51). The therapy comprises two phases. Phase I (the intensive phase) consists of the mobilization of fluid and the initiation of a decrease in the proliferated connective tissue. Phase II (maintenance phase) maintains the swelling reduction and aims for optimization of connective tissue reduction (52-54). CDT treatment, and especially Phase I, includes the above-mentioned components: manual lymph drainage, lymphological compression bandages, in combination with remedial exercises adapted to the age and general health of the patient, as well as physiotherapy where required, and instructing the patient in self-treatment measures and skin care (55). Phase II is like Phase I, but with more manual lymph drainage and the wearing of fitted compression stockings. Depending on the degree of connective tissue involvement, stage I lymphedema demonstrates the increase in volume predominantly due to an increase in interstitial fluid, stage II displays the increase in volume due to both an increase in interstitial fluid content and an increase in connective tissue, and stage III (elephantiasis) involves the addition of

lymphostatic fibrosclerotic tissue alterations (54).

If therapy is initiated in stage I, Phase I, in which the CDT measures are applied daily is of short duration. If therapy is initiated in stage II or III lymphedema, the necessity and duration of therapy increase for both Phases I and II. Generally the patient will require at least 2-4 weeks of intensive treatment (55,56). Phase II should last for months or for years (57-60). Prerequisites of successful combined physiotherapy are the availability of physicians (i.e. clinical lymphologists), nurses, and therapists specifically trained, educated, and experienced in this method, acceptance of health insurers to underwrite the cost of treatment, and a biomaterials industry willing to provide high-quality products (61,62). For instance, compressive bandages, when applied incorrectly, can be harmful and/or useless. Combined pressure therapy may also be of use for palliation, for example, to control secondary lymphedema from tumor-blocked lymphatics. Treatment is typically performed in conjunction with chemo- or radiotherapy directed specifically at producing tumor regression. Theoretically, massage and mechanical compression could promote metastasis in this setting by mobilizing dormant tumor cells although only diffuse carcinomatous infiltrates that have already spread to lymph collectors as tumor thrombi might be mobilized by such treatment. Because the long-term prognosis for such an advanced patient is already dismal, any reduction in morbid swelling is nonetheless decidedly palliative (63,64).

Intermittent Pneumatic Compression

There are devices designed for automatic decongestion by exposing the limbs to compression via pneumatic cuffs similar to a boot or a sleeve. These apply differentiated compression in order to move the edema from the periphery to the center of the limb (shoulder, hip). It is important to check for the existence of venous insufficiency prior to

treatment since it is a contraindication (65,66). Besides permanent reduction in the circumference of the limb, some studies observed an increase in the elasticity of the tissues and a decrease in skin ulcerations (66), while others reported that compression of the affected limb leads to the formation of tissue channels as paths for the decongestion of the edematous fluid.

Low-pressure pneumatic compression (30-60 mmHg) can be quite effective and is less risky compared to high-pressure compression which has complications (67-69). The use of any kind of compression therapy requires an adequate arterial blood supply to the limb. This treatment is contraindicated in ischemic limbs because it can prevent arterial blood flow and promote severe ischemia or even necrosis. However, some studies report use of higher pressures, for example, Pappas et al, who used a protocol of 80-110 mmHg (70).

Prerequisites for the use of pneumatic compression therapy as an auxiliary procedure are as follows:

1. There must be no edema in the corresponding quadrant of the trunk and the pathways must be open to alleviate a risk of causing congestion at the root of the limb where the flow is impaired;
2. It should be ensured that the quadrant of the trunk to be loaded is emptied by manual lymphatic treatment before and after the compression treatment.

The majority of studies emphasize that intermittent pneumatic compression should be used as a supplement to CDT and its components, either in Phase I, or in Phase II as a maintenance measure (65,71-73). Finally, it is worth mentioning that intermittent pneumatic compression is an effective technique for reducing edema volume, increasing joint mobility, and alleviating subjective symptoms.

Elevation

Physicians usually recommend that

patients elevate the affected limb and sleep with the arm or leg elevated. However, this advice only applies to patients who are in the initial phase of lymphedema. In addition, it is not very practical for a patient with arm or leg lymphedema to function during the day while keeping the arm or leg elevated. Even if the edematous limb is placed on two pillows before sleep, it is doubtful that it will be in the same position on waking in the morning. If the swelling is reduced, this should be maintained by application of low-stretch elastic garments (74).

Thermal Therapy

The application of thermal therapy induces hyperemia leading to an increase in the lymphatic load. For this reason, thermotherapy is contraindicated in areas of the body with swelling, or areas at risk of lymphatic fluid accumulation. Such areas are the body quadrants that are adjacent to the edematous areas. Although the combination of heat, skin care, and external compression has been used successfully by professionals in Europe and Asia in thousands of patients, there are not many studies demonstrating exclusively the value of thermal therapy in the management of lymphedema.

Liu and Olszewski observed the effects of thermotherapy in patients with lymphedema. A significant reduction was noticed in the lymphatic load of the limbs. The therapy was applied for 30-45 minutes a day for 15 days. Using microwaves as a heat source, the subcutaneous tissue temperature was increased to 39-40°C. A reduction in the flow volume per unit of time was observed when temperatures were below 41°C.

On the other hand, cryotherapy is appropriate for treatment of edematous limbs in particular cases. In these cases, the ideal is to use gentle cryotherapy. This can be achieved by applying cold packs and cooling patients for 15-20 minutes in a region that is wrapped with a damp cloth. Long-term exposure to cold and damp packs is not suitable for any

patient since the inevitable saturation of the skin enhances fungal infections.

Positive results were also observed when cold air was used in conjunction with CDT. It is not possible to provide instructions regarding the time of application of cold air because it depends on the characteristics of each device. However, in any case, cold air must not be applied for long enough to induce reactive hyperemia (74).

Taping

Medical tape has been used for more than 40 years and has evolved considerably. The basic elements of medical tape were developed in the 1970s in Japan. Steady taping for the immobilization of injured joints was first applied at the end of the 19th century, and it was further developed in the mid-20th century by several physicians and physiotherapists, such as Montag and Lohfink, and McConnel (75). Multiple manufacturers with different names have evolved around the world, and there are now over 500 different tapes and brand names.

Surveys have shown that the application of Kinesiology Taping is an effective method for lymphedema management at an early stage. Additionally, it is a new and safe therapeutic option in patients for whom use of other methods is contraindicated (76). According to Bialoszewski et al, lymphatic taping along with ligatures significantly reduced the lymphedema of lower limbs using the Ilizarov method (77).

Tsai et al conducted a survey to compare the use of Kinesio Taping and bandages in secondary lymphedema after breast cancer. The results showed no significant difference between the two groups but the duration of application and patient compliance was better in the group with the taping. It should be noted that the survey was conducted in Taiwan, which has a warm climate that is rich in moisture, so taping in these conditions was a more pleasant choice (78).

In addition, taping is suitable for areas

such as the face and genitalia where bandaging is difficult or impossible. Taping is applied directly without inhibiting or limiting circulation and creates space by elevating the skin structure and stimulating fluid dynamics. The circulation of lymph in the lymphatic vessels is facilitated by the reduced pressure prevailing under the tape. Taping for lymphatic congestion is implemented in different directions using the spiral or the cross technique (79). The latter is used to create a more intensive effect especially in severe forms of edema.

The tape is applied to the skin with no pressure. The length of the tape is determined by the distance of the edema from the nearest local lymph nodes that operate. The shape of a tape consists of a 3-5 cm base with 4 "tentacles" extending to the required length. The color is chosen by the patient according to their preference. This is purely for the psychological and placebo effect since all tapes have the same stiffness irrespective of color. In mechanical failures of the lymphatic system (primary, secondary lymphedema), the course of the tape follows the same orientation as the manual lymphatic techniques. The course is always to the nearest local lymph node still operating (80).

The same contraindications as for compression bandages, such as cardiac edema or arterial occlusive disease, apply to elastic tape, which should also be discontinued if any skin change or sensitivities are observed after the taping. The taping normalizes the circulation, so the positioning of the tape over a thrombus may cause embolism. In generalized edema, associated with conditions such as heart and kidney problems where circulation should not be further increased, the use of taping is contraindicated. Great attention should be also given in cases of diabetic foot with neuropathy since the patients will not feel wrinkles or blisters created in the skin.

Finally, a proper evaluation of the patient and the application of a suitable tape technique in each case is very important.

The elastic tape is not a substitute for CDT but it is a useful adjunct for treating lymphedema along with the traditional treatment plan (75).

Aqua Lymphatic Therapy

Aqua lymphatic therapy is an alternative method for managing lymphedema and combines the physical properties of water, exercise, compression, and techniques for lymphatic drainage. Aquatic therapy uses the buoyancy, resistance, and hydrostatic pressure that water offers in order to enhance the mobility and compression exerted on the suffering extremity (81).

Initially when a patient performs the exercises at a depth where the water reaches the level of the chest, the weight of the body is reduced by 90%. Therefore, people with lymphedema directly feel their extremities to be lighter, their confidence is increased, and they can exercise for a longer time in the water. Moreover, by exercising in water, it is possible to increase muscular contraction, the pulse of neighboring blood vessels, and the movement of the diaphragm. All these are elements that enhance lymphatic circulation. In hydrotherapy, the one additional factor that enhances lymph circulation is buoyancy, which exerts an upward force counteracting the effect of gravity (82).

Another property of water is hydrostatic pressure which creates a gentle compression without need to wear compression garments. The hydrostatic pressure also increases in relation to the depth of water with greater depth providing greater hydrostatic pressure. Thus, when the entire lower extremity is immersed in water, the pressure that is exerted on the foot is greater than the pressure on the thigh, and this simulates the normal process of lymph drainage.

Additionally, water offers 12 times more resistance than air so exercise in water increases muscle tone and strength while enhancing the lymphatic circulation. Finally, the temperature of the water plays an

important role in the performance of aqua lymphatic therapy. The optimal temperature for patients is considered to be 32°C for mild and moderate exercise (83,84). Lower temperatures apply only in high-intensity exercise. Otherwise, shivering with consequent muscle contraction may occur (85).

Each session of aqua lymphatic therapy includes skin care, a manual element, a compression element, and an exercise element. The order in which the exercises are applied is important (84). Initially, we have to drain the proximal body regions. Therefore, the patient takes slow breaths and applies by him/herself techniques on the chest and armpits in order to empty these areas. Then some exercises are applied to the shoulder zone and torso (86) after which the drainage in the distal areas begins. The patient starts with a light massage from the thigh to the ipsilateral quadrant of the trunk. Then the light massage proceeds to the lower extremity, ankles, and toes. The program continues with exercises at the hip joint, knee, and ankle. It is important to mention that the undulations of the water created by the movements of the body exert a gentle massage on the patient's body that enhances the lymphatic transport (82).

Important Therapeutic Considerations

Lymphedema is a condition for which it is not easy to find a definitive treatment. The most common method for lymphedema treatment is CDT with several studies (see below) concluding that CDT is effective and has a positive effect on the patient's quality of life.

Many studies have isolated parts of CDT and demonstrated their effectiveness. A study by Johanson et al showed that MLD in conjunction with compression bandages reduced the volume of lymphedema by 20% (15). Zimmermann et al showed that MLD reduces lymphedema by 25% while 70.6% of the women who did not start implementing MLD promptly after surgery developed lymphedema (12). Additionally, Ezzo et al

reported that the combination of MLD with compression bandaging reduces lymphedema by 7.11% more than compression bandaging alone (9). However, both the abovementioned studies, as well as many others, suggest that a combination of the parts of CDT is optimal since it reduces lymphedema by 45-60%.

Dimakakos et al (87), Ko et al (57), Liao et al (54), Morgan et al (88) and Oshnari et al (38) demonstrated a 50-70% reduction of lymphedema after CDT treatment. In addition, according to Moseley et al (20), classical CDT is more effective than combined pressure therapy, which is a combination of MLD with pneumatic compression that reduced lymphedema by an average of 30%. It is also worth mentioning that a plethora of research [e.g. Schmitz et al (21,22), Johansson et al (19) and Kilbreath et al (23)] highlights the importance of exercise, even with the use of weights since weakness, pain, the feeling of the swollen limb, range of motion, and quality of life are all improved through exercise. The efficacy of complementary therapeutic techniques, such as compression therapy, elevation of the affected limb, hydrotherapy and taping, varies from 5-11%.

An important component for the success of CDT and the maintenance of those effects is patient compliance. Ko et al (57) conducted research on 299 patients with lymphedema (149 upper and 150 lower limbs) who were treated with CDT for an average of 15.7 days with a follow-up of 9 months. The investigators found that 86% of patients who showed compliance with the program retained 90% of their initial reduction whereas non-compliant patients lost up to 33%.

CONCLUSIONS

Lymphedema affects a significant segment of the population and for this reason it is important to find an effective treatment. CDT has been recognized as the most effective evidence-based treatment as it reduces negative effects of lymphedema such as swelling, pain, stiffness, and sense of

heaviness. Additionally, CDT increases muscle strength, functionality, mobility, and quality of life. Although other therapeutic techniques have demonstrated positive results, the studies are limited and more research is needed to confirm and broaden these findings.

CONFLICT OF INTEREST AND DISCLOSURE

All authors declare that no competing financial interests exist.

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