Lymphology 44 (2011) 168-177

CHANGES IN TISSUE WATER AND INDENTATION RESISTANCE OF LYMPHEDEMATOUS LIMBS ACCOMPANYING LOW LEVEL LASER THERAPY (LLLT) OF FIBROTIC SKIN

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ABSTRACT

Our goal was to determine effects of low-level-laser-therapy (LLLT) on skin water and tissue indentation resistance (TIR) in patients with arm (N=38) or leg (N=38) lymphedema. Skin water was determined from tissue dielectric constant (TDC) measurements and TIR determined from measurements of force resulting from tissue indentations of 3-4 mm. A limb-location with fibrosis was identified by palpation and treated with an LLLT device for one minute at each of five points within a 3 cm^2 area. TDC and TIR at these sites and corresponding sites on the contralateral limb were measured prior to LLLT (pre-LLLT), immediately after LLLT (post-LLLT) and after a manual lymphatic drainage (MLD) session (post-MLD). Results, from arms and legs, showed that post-LLLT values of TIR and TDC were significantly less than pre-LLLT. TIR values remained significantly reduced at post-MLD whereas TDC values were not significantly different from pre-LLLT values. On follow-up visit, 17 previously LLLT treated legs were sham treated with an inactive LLLT unit and measurements replicated. A TIR and TDC change-pattern similar to that obtained with the active LLLT was obtained, but sham-related reductions in TIR and TDC immediately post sham-treatment were significantly less than achieved with the prior active LLLT treatment.

Keywords: LLLT treatment, lymphedema, fibrosis, tissue dielectric constant, tissue water, tissue hardness, tonometry

One complication of lymphedema is the development of fibrosis in which the skin and underlying tissues of lymphedematous regions become hardened. A consequence of this form of fibrosis is that it makes treating the underlying lymphedema much more difficult since the fibrosis is thought to interefere by encapsulating fluid and reducing the efficiency of manual lymphatic drainage therapy (MLD) to remove excess fluid. A few reports have suggested that low level laser therapy (LLLT) when used to treat the axillary region may act to 'break-up' fibrosis and otherwise soften fibrotic regions of tissue remote to the site of treatment. Rufina and colleagues (1) reported that LLLT applied to the axillary region for four weeks was associated with up to a 33% increase in softness of forearm tissue when measured four weeks after the final treatment. Earlier reports (2) indicated a forearm softness increase of about 20% after 10 weeks of LLLT directed at the axillary region but a regression in this softening was observed when assessed subsequently (3). Contrastingly, hardening of the affected arm was reported during and immediately after LLLT treatment whereas a softening trend was stated to emerge three months after treatment had ended (4). The

TABLE 1
Demographic Summary

	Arm Lymphedema	Leg Lymphedema
N (Total)	38	38
N (Female)	38	19
Age (Years)	69.7 ± 15.0	69.1 ± 14.7
Height (in)	62.6 ± 3.1	65.5 ± 4.1
Weight (lbs)	165 ± 37	220 ± 73
BMI (Kg/m^2)	29.7 ± 6.7	36.0 ± 10.6
Lymphedema Duration (Months)	33.4 ± 40.6	36.0 ± 142.9

Entries are mean ± SD.

reports describing tissue hardness changes with LLLT generally also indicate reductions in arm edema volume (1,2,4). Other studies using LLLT, but not measuring its possible effect on tissue hardness, have also reported reductions in arm edema volume (5-7). The LLLT mechanisms that might be involved in either reducing tissue hardness or edema volume are speculative in that at present they need to be derived from isolated studies of LLLT effects on experimental animals that have demonstrated mainly anti-edema (8-11) and some tissue matrix changes (12-14). None-the-less, LLLT devices are being used clinically for treating lymphedema so there is a need to better characterize potential aspects of such therapy. Because there is very little known about the effects of LLLT on the directly treated tissue the present study was undertaken to quantitatively characterize the acute effects of a single laser treatment of LLLT when applied directly to lymphedematous limbs at sites designated as having clinical fibrosis.

METHODS

Subjects

Subjects (N=76) were persons who had been referred to the clinic for treatment of their lymphedema (arms or legs) and who had some amount of clinically identifiable fibrosis as judged by palpation. Prior to participating in the research component of this study, the study was explained to each subject and they signed an institutional review board approved informed consent. Ultimately included in the active laser treatment part of the study were 38 women with arm lymphedema subsequent to breast cancer related treatment and 38 subjects (19 male and 19 female) with leg lymphedema secondary to venous insufficiency, gynecological surgery, prostrate surgery, or other conditions. Demographic and other features of this study group are summarized in *Table 1*. In addition, 17 subjects with leg involvement were re-evaluated one week after their active LLLT treatment during an MLD session in which the same research protocol was done except that the laser was not activated; this is termed the sham LLLT treatment. For this subset of subjects, effects of the active LLLT treatment were compared to those of sham treatment.

Measurements

All quantitative measurements were

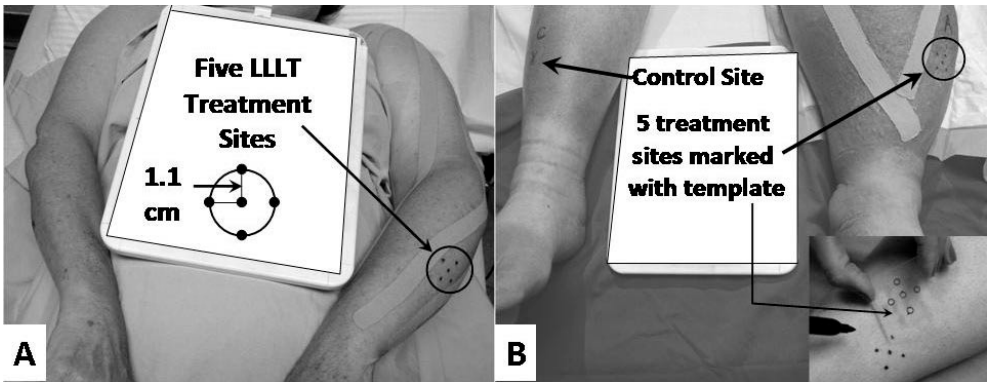

Fig. 1. Target site location and marking. A. Five LLLT treatment sites marked on an affected arm. B. Five treatment sites marked on an affected leg. All target sites marked with the template shown in B. Template has dimensions as shown in A. Control limb measurements made at the control site at a corresponding anatomical location.

made on the affected and contralateral limbs with the subject in a supine position on a padded examination table.

Limb Girth

Prior to the subject's scheduled MLD session done according to the Vodder method (15), the affected limb was visually examined and palpated to determine a region in which significant fibrosis was present. At the approximate center of this region a template was used to mark a center point and also mark four circumferential points located 1.1 cm from the center as shown in *Fig. 1* as done on an arm (A) and on a leg (B). The approximate area of the target treatment area was 3.8 cm^2. The girths of the limbs (both affected and control limbs) were measured around the marked center point using a Gulick-type tape measure pulled to a constant tension as illustrated in *Fig. 2-A*.

Tissue Dielectric Constant (TDC)

After the girth measurements, the tissue dielectric constant (TDC) of the skin and underlying tissue at the center region of the target site and its contralateral side were determined using the Moisture Meter-D (Delfin Technologies Ltd., Kuopio Finland) with the probe held gently on the skin as shown in *Fig. 2-B*. The probe used for this purpose had an effective penetration depth of 2.5 mm and thereby mostly included the tissue from the skin surface down to the effective depth. The principles and basis of this method has been previously described (16-20) and its use widely reported (21-25). In brief, a 300MHz signal is generated within a control unit and is transmitted to the tissue via the probe that is contact with the skin. The probe itself acts as an open ended coaxial transmission line. The portion of the incident electromagnetic wave that is reflected depends on the dielectric constant of the tissue, which itself depends on the amount of free and bound water in the tissue volume through which the wave passes (16,17,19,26). Reflected wave information is processed within a control unit and the relative dielectric constant, which is dimensionless, is displayed which is an index of the tissue water. For reference, pure water has a value of about 78.5. TDC measurements were made in triplicate and the average used to characterize the TDC value at affected and contralateral limb targets.

Tissue Indentation Resistance (TIR)

The tissue indentation resistance (TIR) is

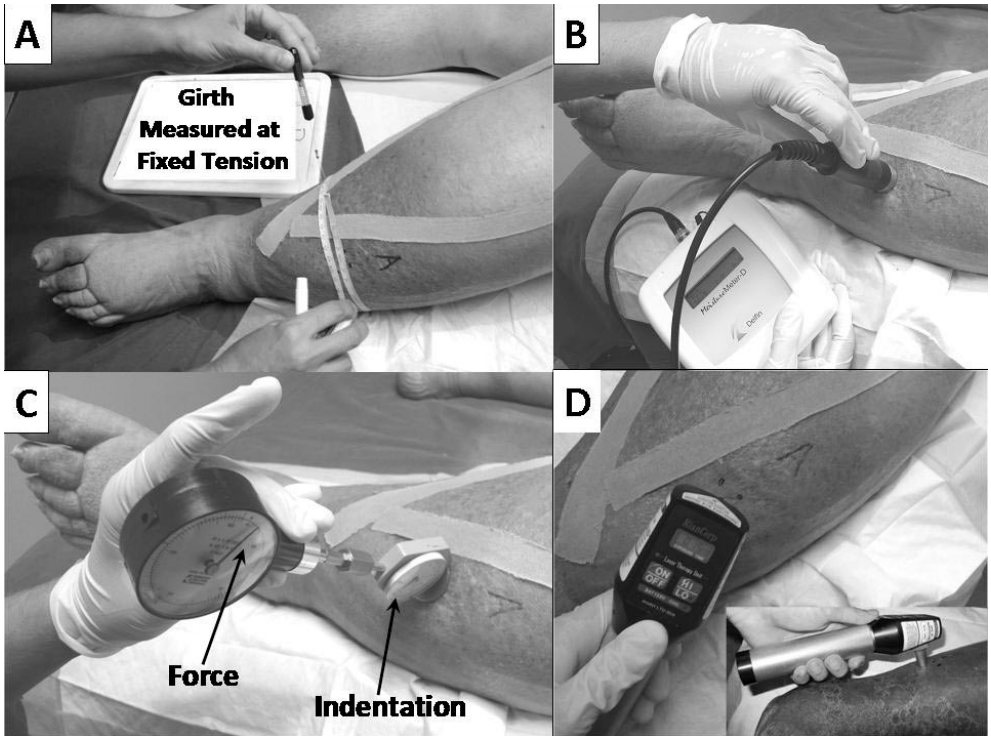

Fig. 2. Measurements and LLLT application. A. Girth measured at the center of the target site using a fixed tension tape measure. B. Tissue dielectric constant (TDC) measured at the target site. C. Indentation force measured as an index of the tissue's indentation resistance. For affected limbs the central indenter is displaced inward by 4 mm and 3 mm and the corresponding force recorded. D. LLLT applied for one minute at each of the five marked target sites.

an index of the relative hardness of the skin and subcutaneous tissue. Such measurements have frequently been made with tonometers (27-29) in which a fixed mechanical load is used to cause an indenter to move into tissue being measured and the vertical movement of the indenter measured. Accordingly, less indentation for a fixed load the greater the tissue hardness. An alternative method, which is the one used in the present study, is to indent the tissue to certain depth and measure the force required to produce that indentation. Accordingly the greater the required force for a fixed indentation the greater is the tissue hardness. The method and its features have previously been described (30) and are illustrated in *Fig. 2-C*. Advantages of this method over mechanical gravitational loading tonometers is that the hand held device does not require the device to be supported by the tissue and does not have to be in a completely vertical orientation. In operation the indenter is placed at the target tissue site and the tissue resistance measured by indenting to a standardized indentation depth and recording the force required to achieve this indentation. In practice the indentation depth is achieved within 3-5 seconds and the force meter holds the indentation force value for easy reading. The measured force (in grams) for a given indentation is used as the TIR parameter; A greater force value for a given indentation corresponds to a higher TIR value. In this study indentation depths of 3 mm and 4 mm were used on the affected limb. The control limb was subjected to an indentation depth of 4 mm only. Prior to the start of the TIR measurement patients were asked to relax their arm as much as possible in order to

minimize the effect of muscle clenching on the measured TIR value. Although not all patients were able to relax to the same amount, each appeared to be able to relax arm muscles similarly for each of the three TIR measurement intervals (pre-LLLT, immediately post-LLLT and after the MLD session).

Low Level Laser Therapy (LLLT)

After measuring baseline (pre-treatment) parameters (girth, TDC and TIR) the target tissue was treated with the laser for five minutes with each of the five marked sites receiving one minute of treatment. Treatment is achieved by placing the cone-shaped head of the laser on a marked target site as illustrated in *Fig. 2-D*. The laser device used in this study was the RianCorp LTU 904H (RianCorp Pty Ltd., Henley Beach, South Australia, Australia). The unit is a portable, rechargeable, battery powered device that emits a pulsed 904 nanometer beam with an average output of 5 mw from a treatment head of 0.2 cm^2 in size. This is the same type of LLLT device used in some previous lymphedema related studies (4,6).

Protocol Sequence

The above series of measurements (girth, TDC and TIR) were done prior to the LLLT treatment (Time = T0) and repeated starting one minute after completing the five minute LLLT sequence (Time = T1) and repeated again after finishing the MLD session (Time = T2). The MLD session started about one minute after completing the T1 measurement set and lasted (mean ± SD) 52±2 minutes. Initial measurements (arm girths) were started after the patient had been in a relaxed supine position for between 10-12 minutes. Patients remained in the supine position at least until they had had all pre-LLLT measurements completed, had received their active or sham LLLT treatment, and had their immediate post-LLLT or post-sham measurements. They remained in a supine or near supine position for the duration of the MLD session and were in the same supine position when the final measurement set was done.

Statistical Analysis

Overall differences among parameter values obtained at T0, T1 and T2 were tested using a general linear model (GLM) for repeated measures with the values at T0, T1 and T2 being the within measures (SPSS, version 13). Given the presence of significant overall difference ($p<0.05$), follow-up tests used within-subject contrasts, properly adjusted with the Bonferroni correction, to determine the significance of the paired-differences. Differences in parameter values between paired-limbs and between active and sham treatments for affected legs were tested using the nonparametric Wilcoxon test. Separate analyses were done for the arms and for the legs. An alpha level less than 0.05 ($p<0.05$) was taken as statistical significance.

RESULTS

Arms

All results are expressed as mean ± SD. GLM results indicated an overall significant difference ($p<0.001$) among the affected arm values at the three measured time points (T0, T1 and T2) for TDC and indentation force values, but no significant differences among control arm parameter values. Results showed (*Table 2*) that affected arm pre-treatment (T0) values for TDC (43.3±9.9), indentation force (297±107 g) and girth (26.9±4.2 cm) were all significantly greater ($p<0.001$) than values measured on the contralateral arm at corresponding anatomical sites. After applying LLLT to the affected arm for five minutes there was a significant reduction ($p<0.001$) in TDC and indentation force to values of 39.5±9.8 and 222±113 g. These correspond to reductions by 8.2±12.5% and 27.4±18.9% for TDC and force respectively. Girth values were insignificantly

TABLE 2
Parameter Values for 38 Arm Pairs
(mean ± SD)

	TDC Value		Indentation Force (gms)		Girth (cm)	
Measurement	Affected Arm	Control Arm	Affected Arm	Control Arm	Affected Arm	Control Arm
Pre-Treatment (T0)	43.3±9.9	26.4±5.8‡	297±107	224±100‡	26.9±4.2	22.8±3.5‡
Post-Treatment (T1)	39.5±9.8**	26.4±6.1‡	222±113**	213±096	26.7±4.3	22.6±3.2‡
Post-MLD (T2)	43.3±9.7	27.1±5.8‡	243±102**	213±106†	26.8±4.2	22.6±3.3‡

TDC is the tissue dielectric constant to an effective depth of 2.5 mm and Indentation Force is the force in grams measured for an indenter displacement into tissue of 4 mm. Girth is the circumference measured at the center of the treated site. ** p<0.001 compared to Pre-Treatment, † p<0.01 compared to Affected arm ‡p<0.001 compared to Affected arm

TABLE 3
Parameter Values for 38 Leg Pairs
(mean ± SD)

	TDC Value		Indentation Force (gms)		Girth (cm)	
Measurement	Affected Arm	Control Arm	Affected Arm	Control Arm	Affected Arm	Control Arm
Pre-Treatment (T0)	42.6±9.8	34.8±10.0‡	381±167	327±174†	40.9±13.0	36.6±11.6‡
Post-Treatment (T1)	35.5±10.9**	35.6±9.8	314±162**	330±175	40.8±13.1	36.7±11.8‡
Post-MLD (T2)	39.6±12.1	35.7±10.0	355±159*	308±154†	40.8±13.0	36.7±11.6‡

TDC is the tissue dielectric constant to an effective depth of 2.5 mm and Indentation Force is the force in grams measured for an indenter displacement into tissue of 4 mm. Girth is the circumference measured at the center of the treated site. **p<0.001 compared to Pre-Treatment, †p<0.01 compared to Affected leg; ‡p<0.001 compared to Affected leg

changed from the pre-treatment values (26.9±4.2 vs. 26.7±4.3, p>0.5). Affected arm values measured at the end of the MLD treatment session (T2) showed that TDC had increased from its immediately post-LLLT value and its final value (43.3±9.7) was now insignificantly different than the pre-treatment value. Contrastingly, although the measured 4 mm indentation force was increased from its T1 value, its post-MLD value (243±102 g) remained significantly less (p<0.001) than the pre-treatment value. The reduction at T2 as compared to pre-treatment was 17.8±18.7%. A similar pattern of force reduction after LLLT was found for 3 mm indentation forces of the affected arm as shown in *Table 4*. The pre-treatment force (161±75 to 111±65 g) was significantly reduced (p<0.001) at both T1 and T2. Control arm parameter values (TDC, indentation force and girth) were insignificantly changed from T0 through T1.

Legs (Active LLLT)

As with the arm results, GLM results for legs indicated an overall significant difference (p<0.001) among the values obtained at the three measured time points (T0, T1 and T2) for affected leg TDC and for TIR as indicated by the measured indentation force values. Again similar to the arm results, there was no significant differences among any parameter values for the control leg. Results showed (*Table 3*) that affected leg

TABLE 4
Affected Limb Indentation Force and its Change

	Indentation Force (gms)		% Change from Pre-Treatment	
Measurement	Affected Arm	Affected Legs	Affected Arm	Affected Legs
N	38	38	38	38
Pre-Treatment (T0)	161 ± 75	265 ± 153		
Post-Treatment (T1)	111 ± 65**	200 ± 139**	-27.9 ± 18.2	-26.4 ± 18.4
Post-MLD (T2)	123 ± 63**	232 ± 138**	-19.8 ± 21.9	-10.3 ± 23.0

Values are mean ± SD for Indentation Force (grams) measured for an indenter displacement into tissue equal to 3 mm. ** p<0.001 compared to Pre-Treatment

pre-treatment (T0) values for TDC (42.6±9.8), indentation force (381±167 g) and girth (40.9±13.0 cm) were all significantly greater than values measured on the contralateral legs at corresponding anatomical sites. After applying LLLT to the affected leg for five minutes there was a significant reduction (p<0.001) in TDC and indentation force to values of 35.5±10.9 and 314±162 g. These corresponded to reductions of 16.8±16.7% and 18.5±15.1% for TDC and force respec-tively. Girth values were insignificantly changed from the pre-treatment values (36.6±11.6 vs. 36.7±11.8, p>0.5). Affected leg values measured at the end of the MLD treatment session (T2) showed that TDC had increased from its immediately post-LLLT value so that its final value (39.6±12.1) was less than but now not significantly different from the pre-treatment value (p=0.07). The measured 4 mm indentation force increased from its T1 value so that its post-MLD value (355±159 g) was less than but still significantly different (p<0.05) than the pre-treatment value. Indentation forces to 3 mm (*Table 4*) indicate a similar pattern to the 4 mm indentation outcome with both the T1 and T2 values remaining significantly less than the LLLT pre-treatment force values. Control leg parameter values (TDC, indentation force and girth) were insignificantly changed from T0 through T1.

Legs (Active LLLT and Sham Treatment)

Comparisons of the pattern of changes associated with active LLLT and sham treatment of affected legs (N=17, *Table 5*) show them to be similar to those described above for the full complement of LLLT treated legs (N=38). Both LLLT and sham treatments produce an early (T1) reduction in both TDC and TIR followed by a return toward pre-treatment values by the end of the MLD session. There is however a greater statistical significance (p<0.001) of the LLLT reduction than the significance (p<0.05) of the sham treatment reduction for all measured parameters. In addition, for the active LLLT, the post-MLD (T2) indentation forces remained significantly less than pre-LLLT (T0) forces (p<0.05) whereas for sham treatment there was no significant difference between pre-treatment values for any parameter. Further, although both active LLLT and sham treatments caused reductions in all parameters, the percentage reduction in TDC and indentation forces caused by the five-minute active LLLT was also significantly greater than for the sham treatment as shown in *Table 6*.

DISCUSSION

The main goal of this study was to determine if a single localized five minute

TABLE 5
Parameter Measures for 17 Affected Legs That Had LLLT and Sham Treatment (mean ± SD)

	TDC Value		Indentation Force (4 mm)		Indentation Force (3 mm)	
Measurement	LLLT	SHAM	LLLT	SHAM	LLLT	SHAM
Pre-Treatment (T0)	40.8±8.0	38.5±5.8	353±102	319±100	243±100	185±91
Post-Treatment (T1)	33.9±9.6**	36.3±6.1*	278±102**	293±104*	170±85**	161±71*
Post-MLD (T2)	38.6±9.9	40.0±8.0	322±104*	304±102	208±91*	178±87

TDC is the tissue dielectric constant and Indentation Force is the force in grams that measured for an indenter displacement into the tissue equal to 4 mm or 3 mm. **p<0.001 compared to Pre-Treatment, *p<0.05 compared to Pre-Treatment

TABLE 6
Percentage Reduction in TDC and Indentation Force of Affected Legs That Had Both Active LLLT and Sham Treatment

	TDC Value		Indentation Force (4 mm)		Indentation Force (3 mm)	
Measurement	LLLT	SHAM	LLLT	SHAM	LLLT	SHAM
Reduction (%)	17.2±16.7	5.3±7.5	30.2±14.5	11.7±18.1	33.2±27.1	11.1±14.8
p-value	0.011		0.004		0.002	
N	17	17	17	17	17	17

Entries are values (mean ± SD) for the percentage reduction in TDC and force from pre-treatment to immediate post treatment associated with either active LLLT or sham treatments. TDC is the tissue dielectric constant and Indentation Force is the force in grams measured for an indenter displacement into the tissue equal to 4 mm or 3 mm. P-values were computed based on the nonparametric Wilcoxon test for the differences between LLLT and SHAM treatment.

LLLT treatment applied directly to lymphedematous tissue would reduce the treated tissue's dielectric constant (TDC), indentation resistance, or girth. In this context, TDC is used as an index of the relative tissue water content, the force required to indent the tissue is used as an index of the indentation resistance, and the local circumference used as a direct measure of the limb's girth.

Considering the entire group (N=76), the main findings revealed a pattern of change characterized by a large and statistically significant reduction in both TDC and TIR immediately after the LLLT with a return toward pre-treatment values of both parameters at the end of a standard MLD session that was on average 52 minutes post-LLLT. The immediately post-LLLT reduction in TDC and TIR, measured one minute after LLLT application, occurred for affected arms and legs with no significant change in TDC or TIR of control limbs. However, by the end of the MLD session TDC did not remain significantly less than pre-LLLT values for either arms or legs. Contrastingly, although at the end of the MLD session the reduction in indentation forces tended to be less than they were immediately post-LLLT, the forces remained significantly less than pre-LLLT values for indentation depths of 3 mm and 4 mm for both arms and legs. At no time

were there any statistically significant LLLT related changes in girth for either arms or legs with this acute protocol.

Considering the subgroup of 17 subjects who received both active LLLT and sham treatments of their affected legs, the main findings revealed a pattern of changes similar to the pattern described above for the entire group. Further, the patterns observed for the active LLLT and sham treatments were not qualitatively different from each other. Thus for both active LLLT and sham treatments there was an immediate post-LLLT or post-sham reduction in both TDC and indentation forces that tended toward pre-treatment values at the end of the MLD session. Although qualitatively similar, the active and sham treatments resulted in significantly different quantitative changes. The immediate post-treatment reduction was significantly greater for the active LLLT than for the corresponding reduction for the sham treatment. This was true for reductions in TDC and indentation forces to both 3 mm and 4 mm as summarized in *Table 6*.

The interpretation of the above findings is clouded by the qualitative similarity of responses to active LLLT and to sham treatment, at least for the subgroup of 17 legs so evaluated. However, both the observed pattern and the quantitative changes measured provide a foundation for speculation as to the underlying events. A common finding among active and sham treatments is the initial reduction in TDC and indentation forces. One explanation of this result is that the mechanical effects of placement of the laser head combined with the weight of the laser unit in contact with the tissue is sufficient in and of itself to initially cause movement of underlying edematous fluid out of the measuring site. This could account for the initial reduction in TDC. The initial force reduction could be in part due to the same action, possibly combined with a mechanical action of the laser head on the tissue itself that transiently "break-ups" some of the hardened underlying tissue. The second common finding of both active and sham treatments is the tendency for the reductions in both TDC and force to lessen by the end of the MLD session. Based on the speculated process causing the initial reductions, this might occur when initially displaced lymphedema fluid re-enters the measurement site and the initial mechanically induced tissue softening partially recovers. Although the above speculative processes could explain the common qualitative features between active and sham treatments, they do not explain the significantly greater amount of initial reduction associated with active LLLT treatment. Thus, based on our current information, it is our tentative interpretation that the observed initial reductions in TDC and indentation force are partially mechanically related and partially related to an unknown aspect of the LLLT treatment. The nature of such an "unknown aspect" is again speculative but may be related to one or more of the variously described in vitro and in vivo effects of laser light (1,4-7,12). It is suggested that further systematic study of LLLT as it relates to treatment of lymphedema and its complications are needed to better characterize its utility and possible mechanisms of action.

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