Forearm Skeletal Muscle Ultrasound Properties In Women With Breast Cancer-Related Lymphedema

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ABSTRACT

Breast cancer-related lymphedema is associated with forearm muscle quality and reduces grip strength, but not muscle thickness.

Jesse Whyte

Breast cancer-related lymphedema affects 1 in 4 breast cancer survivors. Chronic lymphatic fluid accumulation in the affected limb is associated with skin and subcutaneous fat tissue characteristics; however, little is known in what manner skeletal muscle function and quality are altered in the affected limb. We set out to determine the differences in muscle quality and handgrip strength between a group of women with stage 2 breast cancer-related lymphedema and healthy controls. Ultrasound data was recorded from hand and wrist extensor muscles on the dorsal forearm in the affected and unaffected arms of women diagnosed with stage 2 breast cancer-related lymphedema and both arms from the healthy control group. The ultrasound data were converted into images where muscle thickness (MT) and muscle echo-intensity (MEI) were measured using computer software. We discovered that MT was not affected by the breast cancer-related lymphedema condition. However, handgrip strength (HGS) and indices of muscle quality (HGS/MT and HGS/MEI) are diminished, suggesting an increased amount of non-contractile (e.g., fibrotic) tissue alterations in the affected arm.

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Introduction

Breast cancer net survival rates have significantly improved over the last 20 years and will continue to rise as treatment precision and efficacy increase (Canadian Cancer Statistics, 2019). However, increased survivorship has resulted in an increase in the number of treatment related side-effects reported, with 60% of breast cancer survivors reporting one or more symptoms of upper-body morbidity (Hayes et al., 2012). Side-effects from breast cancer treatments include swelling of the arm (breast cancer-related lymphedema), poor shoulder range of motion, pain, numbness, tingling, stiffness, breast / shoulder pain, and weakness (Hayes et al., 2012). Among the many side-effects, breast cancer-related lymphedema (BCRL) is perhaps the most insidious disorder affecting approximately 25% breast cancer survivors; characterized by chronic accumulation of lymphatic fluid in the affected limb. Due to the absence of standardized assessment protocols and diagnosis threshold, BCRL incidence rates vary widely (6% to 80%) (Hayes et al., 2012). Long-term complications from BCRL include a decrease in quality of life, increased psychological distress, functional impairments, decreased social life quality and an increased potential for infections (Bojinovic-Rodic et al., 2016).

Predicting which patients will develop BCRL is not currently possible. However, there are factors that increase the risk of developing BCRL because of breast cancer treatments. Factors include such as surgical invasiveness, location of lymph node dissection, the presence of post-operative complications, radiotherapy treatment location, and taxane-based chemotherapy (Kim et al., 2016; Soran et al., 2019). Other risk factors related to lifestyle are having a BMI greater than 25kg/m^2 at the time of diagnosis and leading a sedentary lifestyle (Li & Yuan, 2016; Murdaca et al., 2012; Paramanandam & Roberts, 2014; Rockson, 2016; Schmitz, 2010; Soran et al., 2019). Patients with post chemotherapy arm swelling at their 6 and 12 months follow up visits were also more likely to develop BCRL (Kilbreath et al., 2016). Typically, BCRL onset is within the first 3 years after treatment (Bates, 2010; Mortimer & Rockson, 2014), and is diagnosed clinically by measuring arm volume and a qualitative assessment.

Although the resulting tissue characteristic changes due to BCRL have been previously investigated at the level of the skin and subcutaneous fat, it remains unknown in what manner chronic accumulation of lymphatic fluid affects muscle quality, muscle thickness and echo-intensity. Whether changes to muscle quality parameters influence functional capacity of the

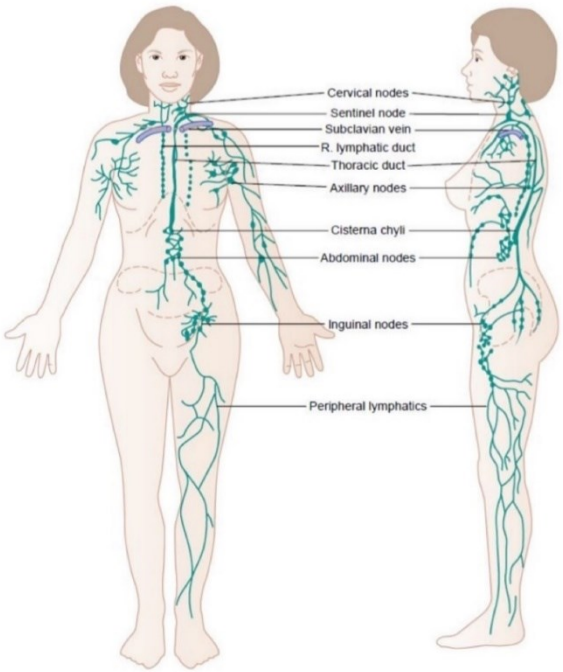
affected arm remains to be seen. Moreover, a better understanding of how BCRL affects the muscles will aid clinicians in prescribing therapeutic exercises to prevent irreparable tissue alterations.

Lymphatic System Physiology

The lymphatic system plays three important roles in our body: (1) the maintenance of fluid balance within the tissues, (2) the absorption of fat and fat-soluble vitamins from the digestive system, and (3) the initiation of a primary immune response to infection and the collection of refuse materials (Mortimer, 1998; Mortimer & Rockson, 2014; Soran et al., 2019). Excess fluid and biological materials in the capillary bed that are too large for the blood vessels to pick up (e.g., proteins, colloids, fat, and bacteria) enter the lymphatic system and are returned to the circulatory system via the proximal lymphatic collectors (Mortimer, 1998). Figure 1 illustrates the primary collectors in addition to the primary lymph nodes. Bacteria passing through the lymph nodes trigger an immune response, signaling an increase in white blood cells to the area to combat an infection. When lymphatic flow is impaired immune response is weakened or halted, increasing the risk of infection (Guyton & Hall, 2006). It is therefore imperative that lymphatic flow is maintained.

Figure 1

The Lymphatic System



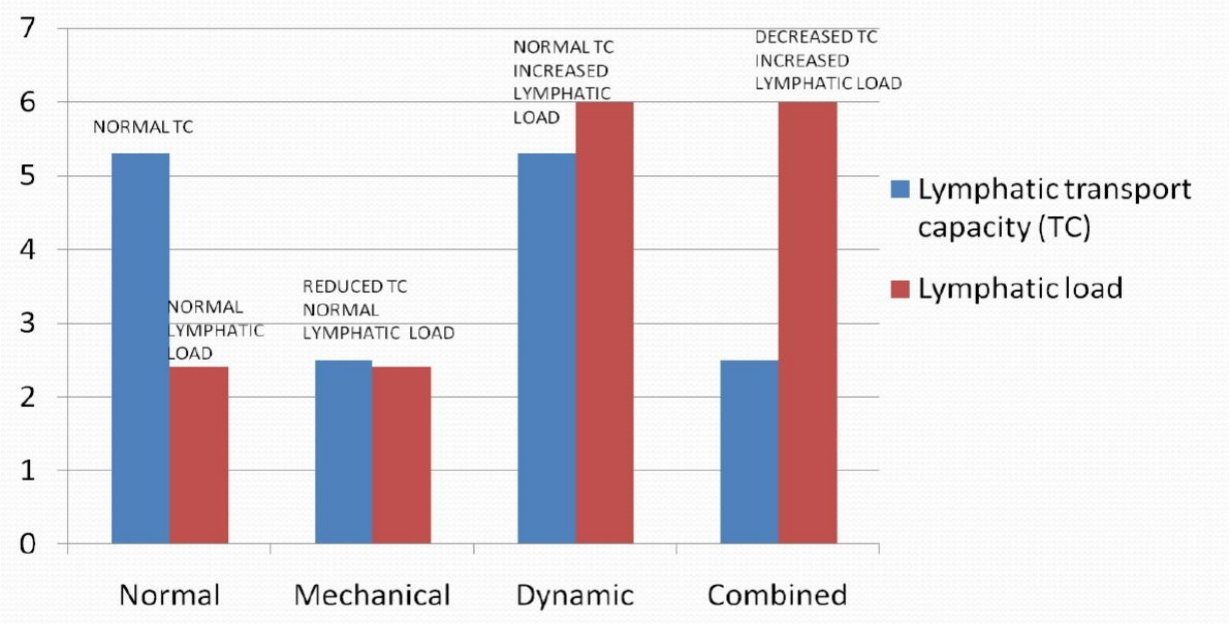
Lymphatic circulatory network, lymph nodes, and primary collecting ducts (Guyton & Hall, 2006).

Lymphatic Insufficiency

Classically, BCRL was understood to be caused by reduced lymphatic flow due to surgical intervention and radio therapy that damages lymph nodes. Recent advances in BCRL now show that there is a chronic increase in the lymph fluid volume in the arm, resulting in local lymphatic network transport capacity overload (Modi et al., 2007; Weissleder & Schuchhardt, 2008). Eventually, chronic lymphatic overload leads to a cascading lymphatic network breakdown (Stanton & Mortimer, 2003), increasing the load on the remaining system (see Figure 2). Initially limb volume is temporarily increased in response to acute lymph accumulation, however chronic accumulation of lymph can lead to irreversible limb volume increases and decreased tissue quality. Volume differences between limbs and subjective findings determine staging of BCRL.

Figure 2

Modes of Lymphatic Overload



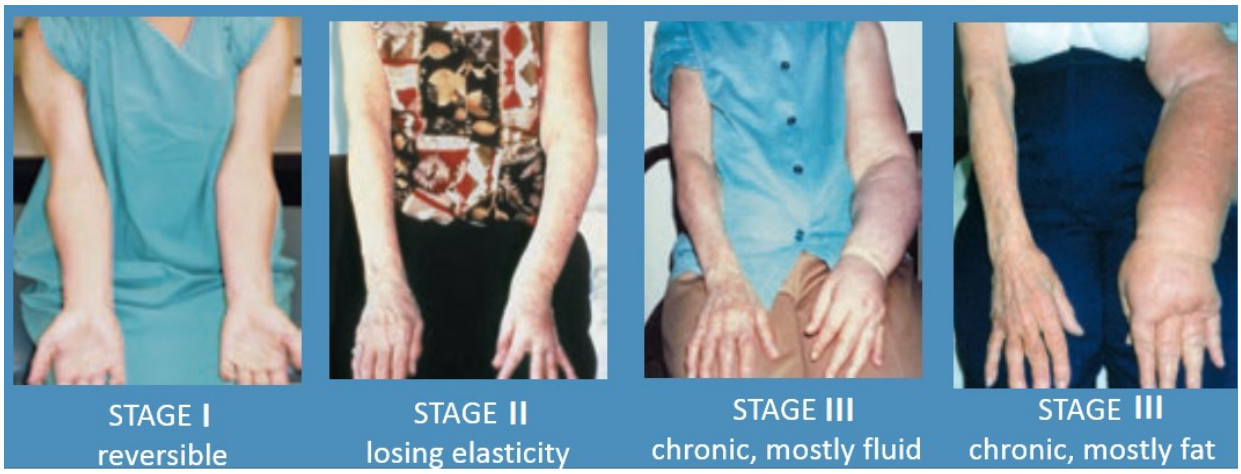
Under *normal* conditions the lymphatic load is less than transport capacity (TC). With *mechanical* lymphatic failure, transport capacity is reduced. Under *dynamic* conditions there is a temporary increase in lymphatic load (e.g. heart failure, lymphedema, venous obstruction)(Mortimer & Levick, 2004) that may surpass transport capacity. Finally, both mechanisms (mechanical lymphatic transport capacity failure and a dynamic increase in lymphatic load) can be combined (Weissleder & Schuchhardt, 2008).

Lymphedema Staging

The BCRL condition is a progressive disorder, and if left untreated the affected tissues will eventually develop irreversible changes. The National Lymphedema Network (NLN) has standardized BCRL staging based on qualitative and quantitative criteria ("2016 Consensus Document of the International Society of Lymphology," 2016) (Figure 3). Stage I, or non-visible BCRL, is characterized by lymphatic channels that are damaged from treatments. Patients report a feeling of heaviness and edema by the end of the day from the effects of gravity that subside with overnight elevation. As BCRL progresses to stage II, swelling appears in the affected limb accompanied by pitting edema and is no longer reversible with elevation. Stage III is characterized by irreversible tissue alterations in the form of fibrotic lesions resulting from the chronic presence of lymphatic fluid in the affected tissues. Extensive skin changes occur including lymphostatic elephantiasis, hyperkeratosis, pachydermia, papillomatosis, hyperpigmentation and inflammation (Honnor, 2006; Weissleder & Schuchhardt, 2008). Current BCRL assessment techniques use a combination of objective measurements and subjective findings.

Figure 3

Breast Cancer-Related Lymphedema Staging



(National Lymphedema Network, 2017)

BCRL measurement and evaluation techniques

Techniques used by clinicians to evaluate BCRL include quantitative limb measurements and qualitative findings. Qualitative indications such as tissue pitting, skin colour changes, Stemmer's sign, and patients' response to the LYMQOL ARM questionnaire (Stanton et al., 2000) are noted along with limb volume measurements to stage BCRL and establish a treatment plan. It is therefore essential for the tools used by clinicians be time and cost effective.

The threshold for diagnosing BCRL is a 10% volume difference between the affected and unaffected limb (Stanton et al., 2000) and is assessed using either water displacement volumetry, circumferential tape measurements (CTM), perometry, or bioimpedance spectroscopy (Hidding & Viehoff, 2016; Seward et al., 2016; Taylor et al., 2006). Each method for assessing arm volume offers advantages and disadvantages in terms of cost, accuracy, and reproducibility (Hidding & Viehoff, 2016) (Table 1). Yet none can assess tissue characteristics and muscle quality changes due to BCRL. Recently, arm circumference has been measured using ultrasound, integrating skin and subcutaneous fat thickness as a proxy (Kim et al., 2021). Using ultrasound to

Table 1:

Arm Volume Measurement Techniques

Measurement Instrument	Body Part	ICC_{intra} (95% CI)	Variance	ICC_{inter} (95% CI)	Variance	Weighted SEM (Variance)	Weighted Mean SDC (Variance)
Bioimpedance spectroscopy	LE	.89 (95% CI = .88, .90	0.10				
Volumeter	UE	.99 (95% CI = .99, .99)	0.02	99 (95% CI-.99, .99)	0.3	0.7% (0.8%)	3.6% (2.7%)
CTM	UE	.99 (95% CI = .99, .99)	0.04	99 (95% CI-.99, .99)	0.9	2.8% (3.2%)	6.6% (2.6%)
Perometer	UE	.99 (95% CI = .97, 1.00)	0.00			2.1% (2.6%)	5.6% (4.2%)

CI = confidence interval, ICC = intraclass correlation coefficient, SEM = standard error of measurement, SDC = smallest detectable change, ICC_{inter} = interclass correlation coefficient for interrater reliability, ICC_{intra} = intraclass correlation coefficient for intrarater reliability, LE = lower extremity, UE = upper extremity. CTM = circumferential tape measurement. Adapted from (Hidding & Viehoff, 2016)

measure arm circumference is novel; accessibility, speed of measurement, and ease of use is unmatched against CTM. Once the presence of BCRL is identified, patients' symptoms are used to guide management.

BCRL Management Techniques

Currently, there are several methods available to practitioners for managing chronic lymphedema; low level laser therapy, combined decongestive therapy (CDT), manual lymphatic drainage (MLD), and exercise (Armer et al., 2016).

CDT is a blended therapy designed to maintain or reduce limb volume via a combination of low-stretch cotton bandages, custom fit compression garments, regular MLD, and exercise. Patients are educated on the importance of regular exercise, self-examination of skin, and skin care to prevent infection. While CDT does not currently have a standardized protocol (Armer et al., 2016), a year-long study found that only 7% of participants in their intervention group developed BCRL compared to 25% in an education only control group (Lacomba et al., 2010). Due to CDT's established effectiveness, it is the primary treatment option selected by clinicians (Armer et al., 2016; Doherty & Morgan, 2006; Fu, 2014; Garza et al., 2017; Ridner et al., 2011).

Therapeutic exercise is a vital component of CDT. Historically, clinicians advised against exercise for fear of triggering lymphedema or exacerbating symptoms (Schmitz, 2010). Concerns were that exercise may provoke the onset of BCRL due to an acute increase in lymph production 24 hours after a single bout of exercise. More current research has shown that the concept was based on a lack of evidence (Schmitz, 2010; Singh et al., 2016), reaffirming the importance that exercise plays in the management of BCRL.

Sedentary patients are of particular concern. Deconditioned patients operate at a higher percentage of their work capacity during activities of daily living leading to an increased risk of injury (Schmitz, 2010). It is therefore imperative that exercise prescription be straightforward and simple to adhere to. Regular exercise performed by patients increases their work capacity (Magel et al., 1978) and decreases the load on the lymphatic system (Schmitz, 2010). Resistance training is one mode of exercise that does not require specialized equipment and can be performed regularly in the convenience of the patient's home. Regular resistance training has been shown to improve strength and help maintain BMI (Paramanandam & Roberts, 2014).

Low level laser therapy is a recent approach that has been used to promote lymphangiogenesis with moderate success (Smoot et al., 2015). It is hypothesized that the energy transferred through laser light promotes lymph node healing, reduces tissue fibrosis and augments lymph flow through the axillary lymph nodes (Dirican et al., 2011; Lima et al., 2014; Omar et al., 2012; Smoot et al., 2015). Perhaps with further research, low level laser therapy will prove to be a viable treatment option for clinicians.

Current BCRL management techniques rely heavily upon patient reporting and regular follow ups by physicians. A better understanding of the when tissue changes begin to occur due to the chronic accumulation of lymphatic fluid and the underlying inflammatory state can further improve symptom management and arm volume reductions. US imaging has the potential to assess early tissue quality changes, allowing BCRL to be cared for earlier in its progression and monitor patient's response to lymphedema treatment.

Ultrasound

Ultrasound (US) is a non-invasive imaging technique that uses high-frequency sound waves to evaluate tissue properties in vitro (Strakowski, 2016). US functions by submitting a piezoelectric crystal to an electrical charge to elicit vibrations at a precise frequency. A sound wave is generated by the vibrating crystal that is then transmitted into the tissues. As sound waves encounter tissues of discrete acoustic properties, they are reflected back to the US transducer to be displayed on screen as an image (Strakowski, 2016). Dense tissues (e.g. bone, connective tissue) reflect more sound waves back to the US transducer than less dense tissues such as muscle and fat (Strakowski, 2016).

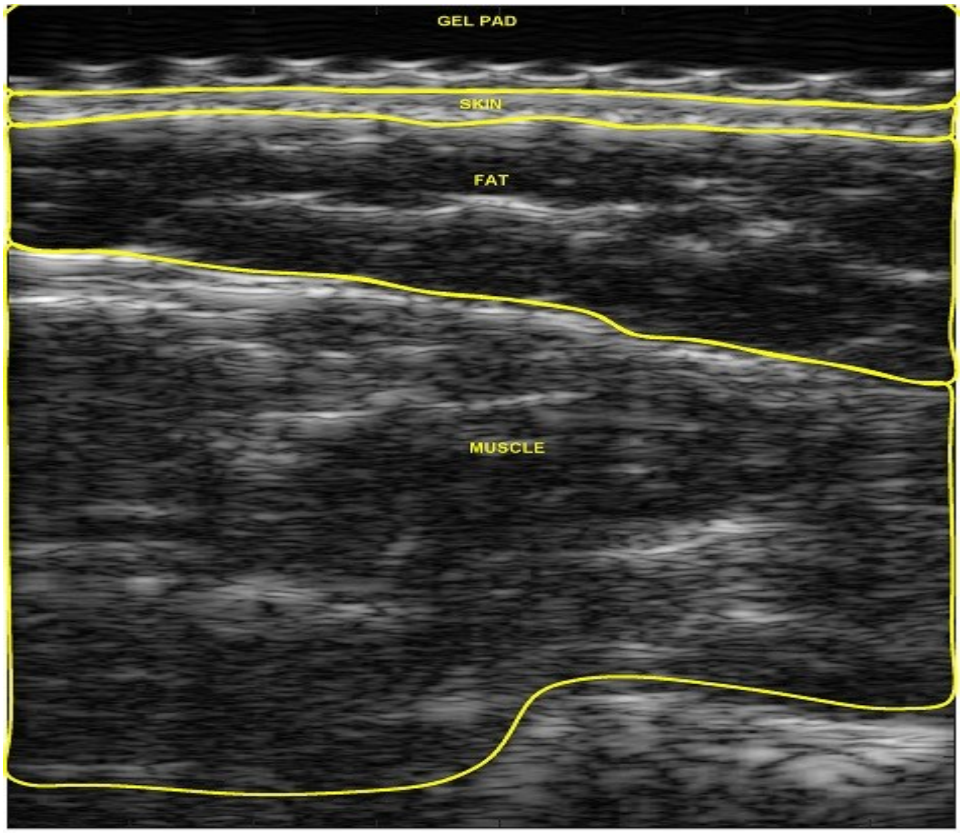
As sound waves traverse the tissues they are attenuated, generating heat and reducing the strength of the US signal. Attenuation occurs as the sound waves are reflected, refracted, and / or absorbed by the medium they are traversing. As the sound waves traverse the tissue, they are absorbed, resulting in the generation of heat, increasing tissue temperature. Refraction occurs when a sound wave crosses tissue borders at an angle, diverting the signal away from the US transducer. Reflection of sound waves is what produces US images, as the signal is "bounced" back towards the surface of the skin and received by the US transducer (Strakowski, 2016).

Different US frequencies are used to image tissues at specific depths. Common frequencies used by US systems rage from 2 MHz – 15 MHz. Low frequency signals (i.e., longer wave lengths) resist attenuation and can penetrate deep into the tissues while high frequency signals (i.e., shorter wave lengths) are absorbed by the tissues and cannot penetrate as deeply. However, low frequency signals lack definition while high frequency signals result in an image with increased detail (Strakowski, 2016).

Tissues found within our body have unique acoustic properties and are presented in figure 4. Bone displays as a hyper-echoic (i.e., highly reflective, bright regions) line with acoustic shadowing beneath it as the signals are unable to penetrate the surface. Muscle and fat are both hypo-echoic (i.e., low reflection, dark regions) and are separated by hyper-echoic lines of fascia that define tissue borders and muscle bellies. Tissues affected by disease display differently from healthy tissue when viewed with US (Bradley & O-Donnel, 2002).

Figure 4

Ultrasound Sonogram



A sample B-mode 2D axial sonogram of the lateral left distal arm (proximal to the elbow) from one of our participants depicting the characteristic grey scale representation of skin, subcutaneous fat, and muscle layers.

Elastography is a recent advancement in US imaging that is used to investigate tissues' mechanical properties. Images produced by elastography display relative tissue strain (suppleness) or displacement in real-time. Tissue strain is computed from the US radiofrequency data using Young's Modulus (used to calculate an objects elastic properties) and Poisson's ratio (used to calculate the lateral to axial strain ratio) (Ophir et al., 2011). Softer tissues experience more strain (displacement) when compressed while denser tissues experience less strain (Adriaenssens et al., 2012). US elastography is still in the early stages of development (Ophir et al., 2011), with research ongoing in several domains, including breast cancer and chronic lymphedema (Suehiro et al., 2014).

US elastography has been used to assess BCRL and is still in the early stages of development. One study showed promise in establishing differences between lymphedematous tissue and normal tissue (Righetti et al., 2007), while another failed to find significant differences (Suehiro et al., 2014). Recently, elastography was used to compare tissue strain ratios between affected and unaffected arms in BCRL (Hashemi et al., 2019). The technique used by Hashemi et al., (2019) involved using US data in post processing to compare skin, fat and muscle against a known constant (gel pad). They found that tissue affected by BCRL demonstrated a decreased amount of strain (displacement) compared to healthy tissue. It is feasible that changes in tissue strain occur prior to changes in appearance on B-mode US. Further research using US to track BCRL development and the resulting tissue changes is needed.

Rationale and Objectives

Rationale

The primary method for identifying BCRL prior to stage 2 is reliant upon educated, self-reporting, patients. Once diagnosed, BCRL treatment is stage dependent and comprises of symptom management and patient education. CDT is commonly used to reduce limb volume in BCRL that has progressed beyond stage 1, using compression garments and exercise to maintain or reduce limb size (Armer et al., 2016). Current evaluation techniques require a 10% disparity between limb volumes at the time of assessment to diagnose BCRL, which may or may not be present prior to stage 2. US assessment is a novel approach that could allow attending physicians to observe tissue changes before limb volume changes occur as part of regular patient follow ups. Early identification of tissue changes could feasibly facilitate management and prevent many side-effects. US assessment is an objective method for assessing tissue quality, reducing some of the subjectivity found in qualitative methods. Earlier diagnosis of BCRL can prevent permanent tissue changes and reduce long term health care costs, leading to a better quality of life for the patient.

Objectives

The present research assessed differences in muscle quality in the forearms of women affected by stage 2 BCRL using B-mode ultrasound. Parameters that were investigated include handgrip strength (HGS), muscle thickness (MT), muscle echo-intensity (MEI) and two measures of muscle quality (HGS/MT and HGS/MEI). Measurements were obtained from the affected and unaffected forearms of women diagnosed with unilateral stage 2 BCRL. For comparative purposes, the forearms of healthy women with no history of breast cancer or lymphedema were assessed.

Primary research questions

1. Is there a difference in muscle quality (e.g., HGS/MT and HGS/MEI) between affected and unaffected forearms in women with stage 2 BCRL and healthy arms?
2. Is there a difference in muscle thickness between affected and unaffected and healthy forearms in women with stage 2 BCRL?
3. Is there a difference in muscle echo intensity between forearms of women with stage 2 BCRL and healthy women?
4. Is there a difference in handgrip strength between women with stage 2 BCRL and healthy women?

Hypotheses

Based on the research questions our hypotheses are:

1. Women classified with stage 2 BCRL will exhibit decreased muscle quality (e.g., HGS/MT and HGS/MEI) on the affected side compared to the unaffected side and healthy arms when assessed using B-mode ultrasound.
2. Muscle thickness will be reduced in the affected forearms of women with stage 2 BCRL compared to unaffected forearms and healthy arms.
3. Muscle echo intensity will be decreased suggesting lower muscle quality in the affected forearms of women with stage 2 BCRL compared to unaffected and healthy forearms.
4. Handgrip strength will be impaired in the arms affected by BCRL compared to the unaffected and healthy arms.

Forearm skeletal muscle ultrasound properties in women with breast cancer-related lymphedema

Abstract

Background: Breast cancer-related lymphedema (BCRL) has been shown to alter skin and subcutaneous fat thickness; however, little is known about changes in skeletal muscle thickness and muscle quality of the affected arm. We set out to determine if there were differences in muscle thickness (MT), muscle echo intensity (MEI), handgrip strength (HGS), and indices of muscle quality (HGS/MT and HGS/MEI) between the lymphedema group (LG) and healthy control group (CG). **Methods:** Using B-mode ultrasound in the axial plane, we recorded the raw radiofrequency data from the dorsal side of forearm muscles in the affected and unaffected arms of women diagnosed with unilateral, stage 2 BCRL (LG, n=20) and both arms of the control group (CG, n=20). The radiofrequency data were converted into images and measurements of MT and MEI were made using ImageJ software. MEI was assessed using computer graded grey scale. HGS was measured by dynamometry. Differences in MT, MEI, HGS, HGS/MT and HGS/MEI were analyzed using paired t-tests. **Results:** When compared to the control group, HGS was significantly lower in the affected arms (LGAA) (LGAA, 22.03 ± 7.36 vs. CG, 26.62 ± 6.94 kg; $p = 0.022$), yet muscle thickness was not different. MEI was significantly greater in the LGAA when compared to both the unaffected arm (LGUA) (LGAA, 86.61 ± 21.41 vs. LGUA, 70.34 ± 16.3 au; $p = 0.001$) and CG arms (LGAA, 86.61 ± 21.41 vs. CG, 70.82 ± 3.03 au; $p = 0.0001$). The HGS/MT of the LGAA was significantly lower than the CG (LGAA, 1.88 ± 0.74 vs. CG, 2.79 ± 1.59 kg/mm; $p = 0.002$). Similarly, HGS/MEI was significantly lower in the LGAA than the LGUA (LGAA, 0.274 ± 0.119 vs. LGUA, 0.359 ± 0.152 kg/au; $p = 0.006$) and CG arms (LGAA, 0.274 ± 0.119 vs. CG,0.418 ± 0.133 kg/au; $p = 0.002$). **Conclusions:** In this study, MT is unaffected by the lymphedema condition while MEI is elevated. However, HGS is diminished in the LGAA when compared to the CG. The decline in HGS could be related to the muscle quality as HGS/MT and HGS/MEI were significantly lower in the LGAA when compared to the CG.

Introduction

Breast cancer-related lymphedema (BCRL) will affect 25% to 50% of women following breast cancer treatments (Hayes et al., 2012). The onset of BCRL is inconsistent, affecting some patients in the months following surgery and others years later (Mortimer, 1998). Associated changes in arm volume have a large impact on the mental health of patients', their ability to perform activities of daily living and are at increased risk of infection or disability (Tobin et al., 1993). Lymphatic channels are fragile and damaged at the surgical site, leading to lymphatic fluid escaping into the interstitial space. In the short term, arm volume increases due to an accumulation of interstitial fluid and compromised lymph channel flow. Over time, stagnating lymph within the tissues results in an increased incidence of inflammation (Rockson et al., 2019); a process that may contribute to localized changes in tissue thickness and mechanical properties of the affected arm. For example, the skin and subcutaneous fat of the affected arm are known to undergo transformational changes in both thickness and composition (Ashikaga et al., 2005; Rockson et al., 2019; Szuba & Rockson, 1997) as well as altered tissue strain (Hashemi et al., 2019).

Ultrasound elastography has been used to demonstrate decreased tissue strain (lacking compliance) found in the arms of women with stage 2 BCRL (Hashemi et al., 2019). When compared to the unaffected arm, there was a decrease in tissue compliance within skin, subcutaneous tissue, and skeletal muscles in both the forearm and upper arms of the affected limb. With the reduced suppleness in the skeletal muscles of the affected limb, it is conceivable that the functional capacity (maximal isometric muscle strength) may be compromised. But we cannot exclude the possibility that muscle size (muscle thickness and cross-sectional area) may also be contributing to the decreases in functional capacity and strength.

Isometric handgrip strength (HGS) is the gold standard for measuring upper body strength and is well correlated to morbidity in many populations. Decreased isometric muscle strength of the affected limb, when compared to a healthy control group, has been shown previously in women six months after breast surgery (Gomes et al., 2014). Currently, it is unknown if HGS will return to normal values following a longer recovery period (i.e., greater than 6 months) from surgery. The prevailing thought behind HGS deficit is possibly a combination of issues including fear of movement or exertion, the presence of neuropathic pain, or a decrease in muscle volume brought

on by disuse (Cantarero-Villanueva et al., 2011; Galiano-Castillo et al., 2011; Winters-Stone et al., 2008).

Muscle thickness (MT) has been used as a proxy for strength development capacity (Abe et al., 2014). Moreover, the amount of strength development per millimeter of MT is an index of forearm muscle quality that may provide more relevant functional arm capacity information (Abe et al., 2014). Increases in MT and cross-sectional area are positively correlated to strength (Akagi et al., 2008; Matta & Simao, 2011; Selva Raj et al., 2017; Seynnes et al., 2007). In addition, muscle echo intensity (MEI) is negatively correlated to muscle strength. Increased MEI has resulted in a decline in strength development (Watanabe et al., 2013). Increased MEI is likely a result of increased fatty infiltration and fibrotic lesions that could negatively affect contractile shortening (Pillen et al., 2009). Several studies have shown that increased MEI reduces strength in men and women of different ages (Muraki et al., 2013; Watanabe et al., 2013). Whether similar observations in the affected arms of BCRL patients remains to be determined.

In the present study, we sought to compare the affected arms (LGAA) and unaffected arms (LGUA) in BCRL patients to the arms of a healthy control group (CG) using diagnostic US imaging. We investigated the relationships among HGS, MT, and MEI in addition to indices of muscle quality (e.g., HGS/MT and HGS/MEI). We hypothesized that MT would be reduced and directly related to the decrease in HGS in women with BCRL. Furthermore, we anticipate that the indices of muscle quality (HGS/MT and HGS/MEI) will be significantly lower in the forearms of BCRL when compared to the control group. Collectively, these hypotheses will lead us to postulate that muscle quality (HGS/MT and HGS/MEI) can explain why there is a reduction in strength capacity of the affected arms of women with BCRL.

Methods

Patients

Twenty women (56 ± 14.8 years) with Stage 2 BCRL were recruited from the McGill Lymphedema Research Program. Inclusion criteria for the lymphedema group (LG) were: (1) unilateral stage 2 BCRL in the maintenance stage (i.e., stable), and (2) had been treated for unilateral breast cancer. An additional twenty healthy women (48 ± 20.8 years) were recruited

from the Montreal community. Inclusion criteria for the control group (CG) were: (1) participants had no history of breast cancer, lymphedema, or any other inflammatory disease, and (2) were in general good health. Exclusion criteria for both groups were: (1) women currently receiving treatment for breast cancer, (2) those who had lymphedema other than stage 2 or bilaterally, and (3) who had been diagnosed with other diseases (e.g., liver, heart, kidney, etc.). Demographic data of the participants are found in Table 1.

This study was approved by the McGill University Health Centre Research Ethics Board (MUHC-REB). All patients provided written informed consent prior to participating in the study. Both groups followed the same procedures and had their height, weight, body composition, bilateral grip strength and ultrasound measurements taken in one clinic visit.

Anthropometrics

The weight of each participant was measured using a digital scale (Detecto, Model 750, ± 0.1 kg), and height measurements were taken against a wall mounted height scale (Seca, ± 0.1 cm).

Body composition

Patients underwent a full-body dual-energy X-ray absorptiometry (DXA) scan to determine body composition (Lunar Prodigy Advance, GE Healthcare, Madison, WI, USA). Body fat (total, segmental and percentage) and lean body mass of each participant was calculated using enCORE 2006 v.10.50.086 software on Microsoft Windows XP. The participant removed all jewelry and lay supine on the scanning bed with legs positioned in internal rotation using a plastic form with Velcro straps. Care was taken to ensure the participant was relaxed and lying with all limbs within scanning borders.

Hand grip strength

Hand grip strength (HGS) was measured using a handgrip dynamometer (Jamar, Sammons Preston, Bolingbrook, IL) following previously validated procedures (Wong, 2016). Briefly,

each participant was seated comfortably in a chair with their shoulder fully adducted, elbow flexed to 90 degrees and their forearm parallel to their thigh, with their feet firmly planted on the floor. Two trials per side were completed with one minute of rest between trials. Results for both trials on both arms were recorded.

Ultrasound data recording

US measurements were taken on the dorsum of the forearm at two locations bilaterally: 10cm distal to the ante-cubital crease (mid-forearm) and at the proximal radial head (proximal forearm). Landmarks were denoted with skin safe ink to facilitate consistent US placement. Each participant was seated comfortably with the test arm resting palm down on a treatment table set at mid-chest height. US radio-frequency data was collected using an Alpinion E-Cube US system (Bothell, WA) with the L3-8 transducer with an at-the-center frequency of 10 MHz and the sampling rate of 40MHz. The US head was held perpendicular to a gel pad separating the transducer from the skin with ample gel on both sides. A single static, axial (head on view) image per location was recorded to an external USB storage device.

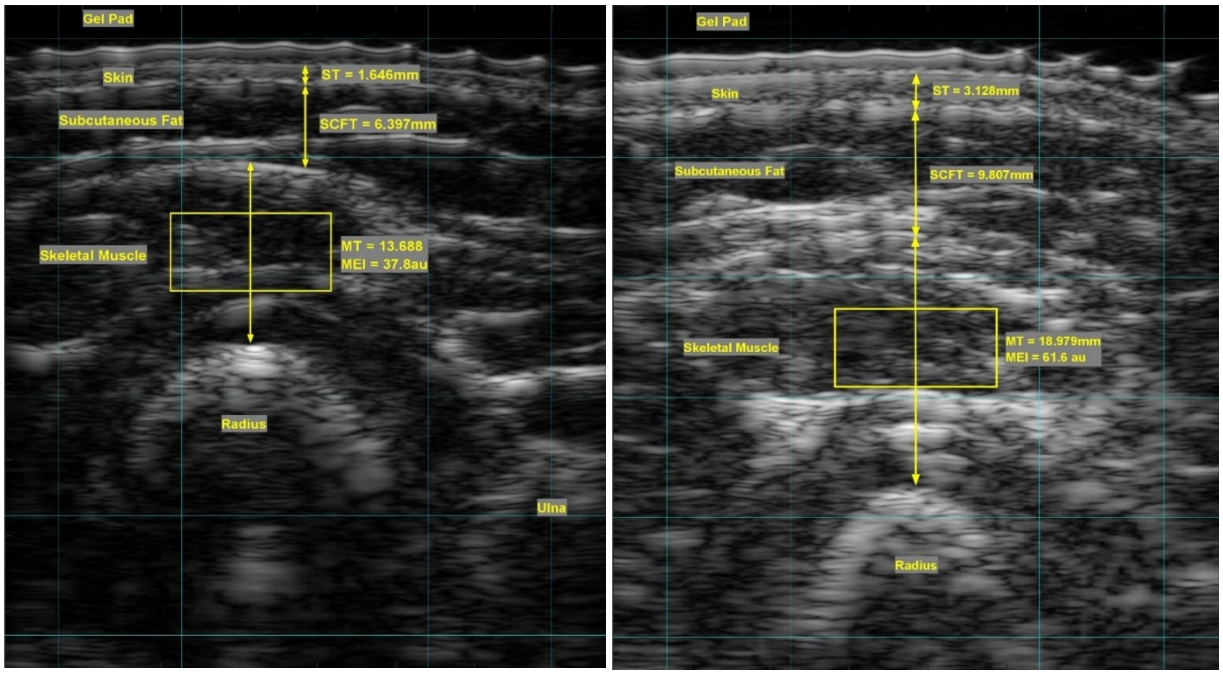
Data conversion

The present study used an US system capable of recording raw image data for post processing of the images. Each data file contains radio-frequency data and the pixel-by-pixel information used to create the image. Mathworks (Matlabs r2017b) scripting was used to strip non-image related data and the remaining information was converted into an image. Sample code is found in appendix 1. Open-source software, ImageJ2 (http://imagej.net) was then used to set the image scale (0.0288mm/pixel) and record measurements for tissue thickness and echo intensity.

Figure 1 demonstrates the 1 cm^2 grid overlay that was placed on each image to ensure measurements for skin and subcutaneous fat were taken at the center. Skin thickness (ST) was measured from the bottom of the gel pad at the first set of echo intense lines (skin surface) to the next set of echo intense lines at the border of the subcutaneous fat. Subcutaneous fat thickness (SFT) was measured from the bottom of the skin layer to the fascial layer covering the muscle.

Figure 1

Sample Ultrasound Images



A B

Sample measurements done on US images in post-processing located on the lateral distal elbow of the left arm. CG arm (A) and LGAA (B).

Skeletal muscle was measured from the center of the bone at the bottom of the image (the radius) up to the fascia separating the subcutaneous fat layer from the muscle.

MEI was also measured with ImageJ2. A rectangular selection was used to represent our region of interest (ROI) standardizing the measurement between images. The rectangular ROI dimensions for MEI was 25% of the MT by 500 pixels wide, centered at the point there MT was measured.

Statistical Analyses

Statistical analyses were performed using Prism (version 8.4.3; GraphPad Software for Windows). All values are shown as the mean ± standard deviation. Correlations between HGS, MT and EI were calculated using Pearson's correlation coefficients. Unpaired Students' t-tests were used to determine differences in patient characteristics (body fat, etc..) and for each

dependent variable (HGS, MT, MEI, HGS/MT, and HGS/MEI) in the LGAA, LGUA, and CG. Statistical significance was defined as a $p \leq 0.05$.

Results

Study participants were BMI matched (LG, 32.1 ± 7.2 vs. CG 29.0 ± 4.2 kg/m^2, p = 0.101), with an average age of 56 ± 14.8 years in the LG and 48 ± 20.8 years in the CG (p = 0.184). Mean time since BCRL onset in the LG was 10.51 ± 6.21 years having finished breast cancer treatments 10.59 ± 6.59 years ago. The LG group weighed more (p = 0.03), had a greater percent body fat (p = 0.023) and total fat (p = 0.021) compared to the CG women. However, lean body mass (LBM) was not significantly different between groups (p = 0.363). Patients' demographic data are summarized in Table 1.

Table 1
Participant Data

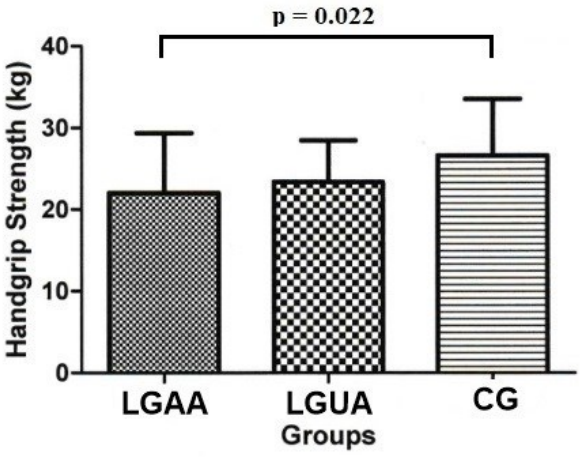
Variable	LG (n=20)	CG (n=20)	P-Value
Age (yrs)	56 ± 14.8	48 ± 20.8	0.184
Height (m)	1.62 ± 0.07	1.59 ± 0.06	0.198
Weight (kg)	84.6 ± 18.4	73.9 ± 11.1	0.030*
BMI (kg/m^2)	32.1 ± 7.2	29.0 ± 4.2	0.101
Body Fat (%)	47.5 ± 6.9	42.4 ± 6.4	0.023*
Total Fat (kg)	39.1 ± 13.1	30.5 ± 8.1	0.021*
Total Lean (kg)	41.6 ± 5.8	40.1 ± 4.5	0.363
BMD (g/cm^2)	-0.673 ± 1.077	-0.110 ± 1.411	0.200
Time with BCRL (years)	10.51 ± 6.21	n/a	

LG = Lymphedema Group; CG = Control Group; BMI = body mass index; BMD = bone mineral density; BCRL = breast cancer-related lymphedema. *p≤0.05.

The HGS of the CG (26.62 ± 6.94 kg) was significantly greater than the LGAA (22.03 ± 7.36 kg; p = 0.022) but not the LGUA (23.38 ± 5.12 kg; p = 0.089), and the LGAA was not statistically different from the LGUA (p = 0.183) (Figure 2). Forearm MT was not significantly different between groups (LGAA, 12.06 ± 6.33 vs. CG, 11.27 ± 5.32 mm, p = 0.138; LGAA, 12.06 ± 6.33 vs. LGUA, 11.70 ± 6.40 mm, p = 0.250) (Figure 3). MEI in the

Figure 2

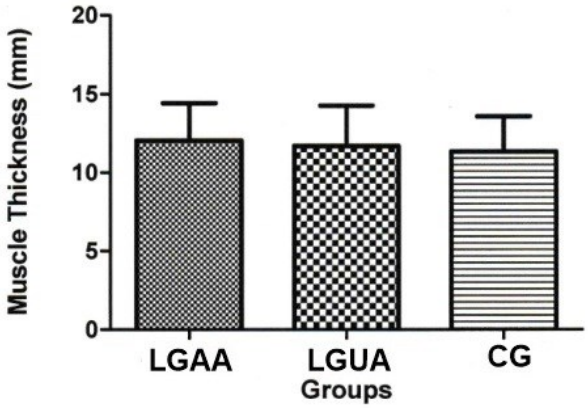
Handgrip Strength Data



Handgrip strength (HGS) differences between LGAA, LGUA and CG. Statistical significance at $p \leq 0.05$.

Figure 3

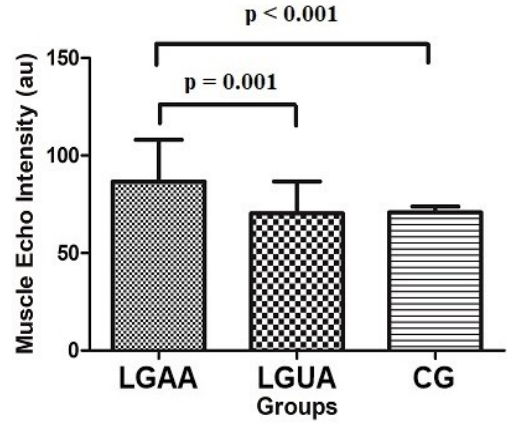
Forearm Muscle Thickness



Forearm muscle thickness (MT) differences between LGAA, LGUA and CG. No significant differences between groups were found.

Figure 4

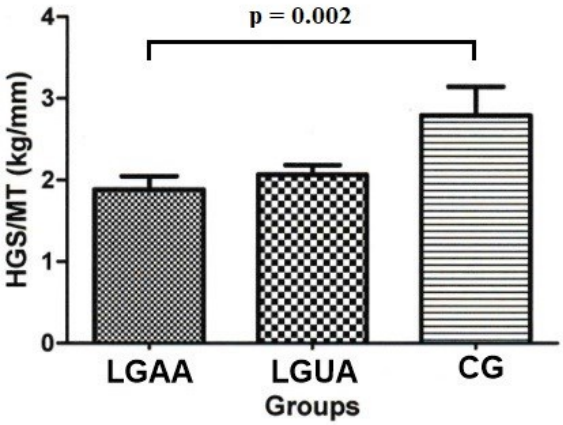
Forearm MEI



Forearm MEI differences between LGAA, LGUA and CG.

Figure 5

Forearm muscle quality: HGS/MT



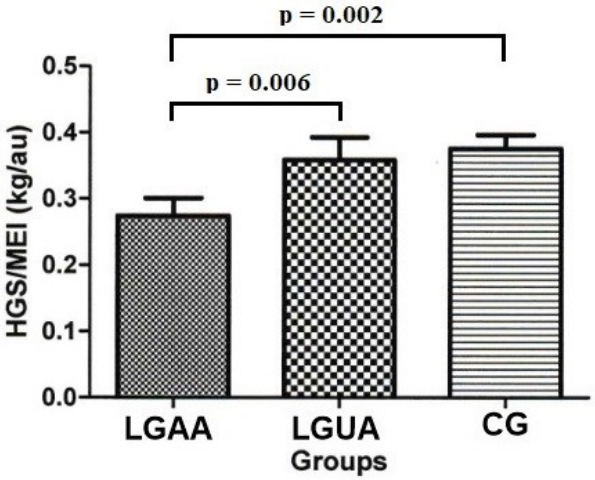
Forearm muscle quality (HGS/MT) differences between LGAA, LGUA and CG.

Figure 6

affected forearm was significantly higher than the CG (86.61 ± 24.77 vs. 65.65 ± 19.41 au, $p < 0.001$). Likewise, the MEI of the LGAA was significantly greater than the LGUA (86.61 ± 24.77, 70.34 ± 22.05; $p = 0.001$) (Figure 4).

Force production of the forearm muscles in relation to per unit of muscle thickness (HGS/MT) had the CG at a significantly greater value than the LGAA (CG, 2.57 ± 1.13 vs. LGAA 1.88 ± 0.736 kg/mm, $p = 0.002$) (Figure 5). Muscle quality (HGS/MEI) was significantly lower in the LGAA than the CG (LGAA, 0.274 ± 0.119 vs. CG 0.418 ± 0.133 kg/au, $p = 0.002$) and the LGUA (LGAA, 0.274 ± 0.119 vs. LGUA, 0.359 ± 0.152 kg/au, $p = 0.006$) (Figure 6).

Forearm muscle quality: HGS/MEI



Forearm muscle quality (HGS/MEI) differences between LGAA, LGUA and CG.

Skin thickness (ST) in the LGAA was significantly greater than the CG arms (LGAA, 2.21 ± 0.785 vs. CG, 1.65 ± 0.249 mm, $p = 0.001$) and the LGUA, (LGAA, 2.21 ± 0.785 vs. LGUA,

Table 2

Skin and Subcutaneous Fat Thickness

Tissues	**Tissue Thickness (mm)**	**P-value**		
Skin		LGAA vs. LGUA	LGAA vs. CG	LGUA vs. CG
Affected arm (LGAA)	2.21 ± 0.785			
Unaffected arm (LGUA)	1.68 ± 0.408	**<0.001***	**<0.001***	0.284
Control arm (CG)	1.65 ± 0.249			
Subcutaneous fat				
Affected arm (LGAA)	10.00 ± 5.50			
Unaffected arm (LGUA)	6.41 ± 4.06	**<0.001***	**<0.001***	**0.039***
Control arm (CG)	5.18 ± 1.85			

AA = affected arm; LGUA = unaffected arm; CG = Control Arms; All values are expressed as mean ± standard deviation, *p≤0.05.

1.68 ± 0.408 mm, p = 0.001). Subcutaneous fat thickness (SFT) was also significantly greater in the LGAA than the CG (LGAA, 10.00 ± 5.50 vs. CG, 5.18 ± 1.85 mm, p = 0.001) and the LGUA (LGAA, 10.00 ± 5.50 vs. LGUA, 6.41 ± 4.06 mm, p = 0.01) (Table 2).

Table 3 lists the correlations between HGS and MT. The LGAA had no correlation between HGS and MT (p=0.70), while the LGUA had a weak, non-significant, relationship (p=0.13). Our CG had a moderate positive relationship trending towards significance (p=0.06).

Table 3

Correlations between HGS and MT

Group	r-value	p-value
LGAA	0.09	0.70
LGUA	0.35	0.13
CG	0.44	0.06

HGS = Handgrip strength, MT = Muscle thickness, LGAA = Lymphedema group affected arm, LGUA = Lymphedema group unaffected arm, CG = Control group.

Discussion

In the present study, standardized US and handgrip dynamometry techniques were used to examine the relationship between HGS, forearm MT, and forearm MEI in women with stage 2 BCRL and healthy controls. As a result of this study, the following three findings of major importance were revealed: (1) HGS was significantly lower in the LGAA compared to the CG; (2) Forearm MT was unaffected by the BCRL condition; however, the MEI in the LGAA was significantly lower than the CG; and (3) muscle quality indices (HGS/MT and HGS/MEI) were significantly lower in the forearm muscles of the women in the LG versus women in the CG.

The impairment of HGS is an established indicator for morbidity in a wide range of populations (Cantarero-Villanueva et al., 2012; Norman et al., 2010, 2011; Rantanen et al., 1999; Stalenhoef et al., 2002), and remains a relevant, simple, and non-invasive field test. Cantarero-Villanueva et al. (2012) found a fair to moderate relationship between HGS and fitness in breast cancer patients 6 months into adjuvant therapy. Norman et al. (2011) in their study on cancer patients, including those with breast cancer, summarized some clinical relationships by stating that: “impaired grip strength is an indicator of increased postoperative complications, increased length of hospitalization, higher rehospitalization rate, and decreased physical status”. Others have

associated impaired HGS with an increased risk of falls in the elderly (Stalenhoef et al., 2002) and were more likely to have difficulty with self-care (Rantanen et al., 1999). In our cohort of BCRL patients, there was a significant difference in absolute HGS which is linked to reduced muscle quality (HGS/MT, HGS/MEI) and could feasibly be experiencing coexisting neuromuscular abnormalities (e.g., decreased motor nerve conduction) compared to the healthy CG.

It is understandable that women who have recently undergone breast cancer interventions (e.g. surgery, chemotherapy and radiotherapy) and subsequently developed chronic lymphedema would likely have restricted arm use due to pain, experience arm weakness, have fear of use, as well as having reduced usage of the affected arm and a lack of upper body activity leading to a strength deficit in their affected arm (Cantarero-Villanueva et al., 2012; De Groef et al., 2016; Gomes et al., 2014; Lee et al., 2015; Smoot et al., 2010). Short-term HGS losses after breast cancer treatments have been measured at 6-months (Gomes et al., 2014), 1-year (De Groef et al., 2016) and 2 years post intervention (Rietman et al., 2004). The present study reveals significant HGS impairment more than a decade after finishing treatments (10.59 ± 6.59 years). Our LG have been living with BCRL for 10.51 ± 6.21 years thus providing ample time and opportunity to regain any strength deficit that may have been present during the post-surgical recovery period. Yet this was not the case, suggesting that factors reflecting long-term symptom burden such as chronic inflammation, the development of fibrotic lesions and decreased MT within the muscles of the affected arm and nerve damage from surgery and / or radio therapy may be instrumental in the overall decrease in strength.

In the present study, forearm MT was not significantly different between groups, despite the link between MT and maximal voluntary contractile strength (Abe et al., 2014; Akagi et al., 2012; Bickerstaffe et al., 2015; Muraki et al., 2013). Our study results show that the women in the LG had the same MT than their CG counterparts and were unable to generate the same HGS. It is important to note that compared to the CG, the women in the BCRL group were significantly heavier, had a greater percentage of body fat, and total fat that would place them in the obese category. Women with this anthropometric profile have exhibited lower HGS values when compared to non-obese and overweight women (Woo et al., 2007). In fact, there is a strong negative relationship between obesity and grip strength in middle-aged and elderly women

(Gubelmann et al., 2017). Although several factors can partially explain this relationship, it is interesting to note that an obesity-induced, chronic low-grade inflammation may affect strength and muscle quality (Custodero et al., 2020; Stenholm et al., 2011). A similar hypothesis has been forwarded to explain the differences in tissue properties and the inability to generate HGS in women with BCRL (Custodero et al., 2020; Ly et al., 2017; Schaverien & Aldrich, 2018).

Our correlational analysis between HGS and MT reveal a functional disconnect between HGS and MT in the LG. The LGAA had no relationship ($p = 0.70$) between HGS and MT and a weak relationship in the LGUA ($p=0.13$). The CG on the other hand, demonstrated a moderate relationship with a trend towards significance ($p=0.06$). Similar moderate to strong relationships were found in healthy subjects with respect to muscle strength and MT (Abe et al., 2014; Kawai et al., 2018; Wilhelm et al., 2014). The functional disconnect between MT and HGS in our cohort could be explained by the differences in muscle quality.

We compared two muscle quality indices, HGS/MT and HGS/MEI. The strength to thickness ratio (HGS/MT) between the LG and CG demonstrate that there is less force being generated per mm of muscle thickness in the LG. Which factors that contribute to a reduction in muscle strength are currently unknown; however, it is feasibly related to the abnormalities that have been observed in the lymphedemic arm. Abnormalities such as increases in intramuscular fat, the widespread low level, chronic inflammation, and the development of fibrotic lesion surrounding the muscle fiber cross-bridges. Fibrous infiltration into the muscles may interfere with the strength generating capacity by altering the pennate angle or impeding the actin-myosin cross-bridging thereby reducing myofibrillar shortening and force production.

MEI is a widely accepted method for evaluating muscle health (Arts et al., 2010; Kawai et al., 2018; Nishihara et al., 2014; Pillen et al., 2009; Rech et al., 2014; Watanabe et al., 2013; Wilhelm et al., 2014). Arts et al. (2010) demonstrated normative MEI values in forearm muscles of women, noting that age was positively correlated with US brightness. Leg quadricep muscles were positively correlated with echo-intensity to age in older participants (Nishihara et al., 2014; Watanabe et al., 2013) while those with reduced functional ability also had a positive correlation to MEI (Rech et al., 2014; Wilhelm et al., 2014). Kawai et al., (2018) demonstrated a negative correlation between MEI and muscle strength in a sarcopenic population. Our results show a positive relationship between MEI and the presence of BCRL, indicating an increased deposition

of US reflecting tissues, similar to those found by (Tassenoy et al., 2006). Our findings are consistent with studies that have found differences between healthy and diseased skeletal muscle (Ashikaga et al., 2005; Devoogdt et al., 2014; Heckmatt & Dubowitz, 1988; Kawai et al., 2018; Nishihara et al., 2014; Pillen et al., 2009; Scholten et al., 2003; Tassenoy et al., 2011) and young vs. old muscles (Watanabe et al., 2013; Welch et al., 2018; Yoshiko et al., 2018). Numerous studies have shown that the increase in MEI is negatively correlated with muscle strength (Watanabe et al., 2013), which corroborate our HGS results. To our knowledge, this is the first published assessment of the relationship between MEI and HGS in women with long-term BCRL. Regardless of the etiology, undesirable changes to tissue characteristics occurring at the level of the skin and subcutaneous fat caused by chronic BCRL may also be changing characteristics of the affected skeletal muscles of the lymphedemic arm.

The onset of BCRL is characterized by an accumulation of interstitial fluid due to impaired transit of lymph along the lymphatic channels resulting from surgical intervention (e.g., axillary lymph node dissection) and therapeutic doses of ionizing radiation. Reduced lymphatic flow leads to the build-up of inflammatory cells and mediators such as eicosanoid leukotriene B_4 (Hespe et al., 2017; Ly et al., 2017). In the later stages of BCRL, inflammatory biomarkers initiate a cascade of histopathological changes that leads to tissue remodeling as evidenced by skin hypertrophy and adipose tissue hyperplasia. Furthermore, lesions appear in the skin and adipose tissue in the presence of pro-fibrotic cytokines such as IL-4 and IL-13 (Hespe et al., 2017). The sequence of events leading to tissue remodeling and adipose tissue hypertrophy could explain the increased tissue thickening and changes in mechanical properties that have been observed in this and other studies (Devoogdt et al., 2014; Suehiro et al., 2013; Tassenoy et al., 2006).

In the present study, we found significant skin remodeling and adipose tissue hypertrophy that would support the presence of inflammation and fibrotic lesions. Numerous studies have previously found significant changes in skin and subcutaneous fat thicknesses in women with early and late stage BCRL (Choi & Seo, 2014; Lee et al., 2015; Mellor et al., 2004; Soran et al., 2019; Suehiro et al., 2016). ST and SFT values measured in the LGAA in the present study were like those found by Soran et al. (2019), though normative values for changes in skeletal muscle quality in BCRL are lacking and future research is needed in this domain.

Strengthening the findings in the present study is how image measurement bias was managed. As measurements were done in post-processing, the author was not present during US image recording and blinded from the groups by randomizing the order in which the images were viewed.

Limitations

The present study had several limitations. First, the small sample size limited statistical strength. However, use of a non-BCRL control group in this study offered a comparison that was not done in by others. Second, despite being BMI matched, our experimental group had a higher percent body fat compared to the healthy control group. The greater percent body fat may have contributed to the differences in muscle function and properties other than just the lymphedemic condition. Thirdly, previous studies investigating the relationship between forearm MT and HGS assessed forearm flexors, which are found on the anterior aspect of the forearm (Abe et al., 2016). In the present study, we examined the forearm extensors which are located on the dorsal aspect of the forearm. Although, the forearm flexors are the primary movers use during handgrip dynamometry assessment, the extensors (e.g., m. extensor carpi radialis brevis, m. extensor carpi radialis longus, and the m. extensor digitorum) have been shown to be significantly recruited in the gripping movement (Bystrim & Kilbom, 1990; Hagg & Milerad, 1997; Hoozemans & van Dieën, 2005). In fact, the extensor muscles of the forearm have been shown to contribute more to the fatigue process during intermittent hand gripping than the flexors (Hagg & Milerad, 1997). Future research, however, should incorporate both the anterior and dorsal muscle of the forearm.

Conclusion

Decreased handgrip strength in the affected arm of our LG participants is not related to changes in forearm MT. When compared to the healthy participants in the CG, the HGS/MT ratio was significantly lower in the LGAA indicating that there is inferior strength development per unit of MT. Reduced strength development may be related to MEI; as the echo intensity in the LGAA had significantly greater levels of MEI. Increased forearm MEI and reduced HGS may be related to the inflammatory process and profibrotic lesions that have been previously observed in skeletal muscle tissue (Pillen et al., 2009). Efforts to reduce the pro-inflammatory process such

as with local or whole-body exercise may provide some non-pharmacological relief to women in the later stages of breast cancer-related lymphedema and warrants further investigation. Correspondingly, further research to establish when changes in tissue quality and MEI begin to occur is needed.

Conclusion

As the numbers of breast cancer survivors developing BCRL grow, early diagnosis and treatment are vitally important to minimizing patient morbidity and increasing quality of life. US is a promising method for evaluating tissue properties in vitro, with the potential to identify early onset BCRL. US has been used to demonstrate tissue thickness changes in the skin and fat as well as changes in tissue strain. In the present study, reduced skeletal muscle quality in the forearm is now evident in women with stage 2 BCRL using B-mode US. HGS was diminished in our LG, not because of changes in MT but because of decreased muscle quality. More research is required to further identify what tissue changes occur during the development of BCRL in breast cancer survivors and when they occur. Also required is research into how tissue quality changes a as result of CDT. Specifically, how regular exercise alters the affected tissues and if there are protective qualities to preventing the onset of BCRL.

Appendix

Matlabs code to extract image data from raw US files:

```
clear
% Convert matrix to image(ConMat2img) allows the user to select a raw
% US data file (*.mat) and then display the data on screen to save it
% as an image for further processing in the software of their choice.

% ------------------------------------------------------------------
% --- First, we need to prompt the user to select their data file ----
% ------------------------------------------------------------------
% In the case of Alpinion RF US data, the files are saved in a format
% which ends in "_BDATA_RF.mat", so we will only display those to
% minimize confusion.

% Prompt user for the file:
[filename, filepath] = uigetfile('*_BDATA_BF.mat', 'Select data
file');

% End program if user cancels
if filename == 0
   return;
end

% Temporarily add the file path to this MATLAB session
addpath(filepath);

% Join the name and location into one variable
UserFile = strcat(filepath, filename);
```

```
% Now we need to load the file into our workspace. Since "UserFile"
% now contains the file path and file name that we want to work with,
% we load it and then display the data as an image in a new figure:

load(UserFile);

% Here we are removing the top 400 data points of the file since it is
% does not contain important data (too close to sound head). The data
% file is an array of 2304x384 data points.

Im1 = BfData(400:2150,:);
MaxIm = max(Im1(:));
Im1 = Im1/MaxIm;

% The Hilbert function used to convert RF data into an image:
BM_IMA = log(abs(hilbert(Im1))+.01);

% Let us apply a little smoothing to the image so it looks pretty:
BM_IMA_GB = imgaussfilt(BM_IMA,1);

% Now we display the image on screen:
figure();
imagesc(BM_IMA_GB);
```

```
% Setting the aspect ratio helps with visualization since the
% transducer head is recording information that is 5cm deep
% and 3.8cm wide.
set(gca,'dataAspectRatio',[1 4 1]);
colormap(gray);

% Let us now save the file to disk for the user:
pattern = '.mat';
replacement = '';
fname=regexprep(filename,pattern,replacement);
Fname_save = ['./B-modes/' fname];
print(Fname_save,'-dtiffn',['-r' num2str(1200)]);

close
clear
clc
```

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