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ORIGINAL ARTICLE

Progression of Venous Disease is Associated with Biomechanical and Morphological Changes in the Calf Muscle Pump

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ABSTRACT

Background: Chronic venous disease (CVD) is a common progressive disorder. Calf muscle incompetence due to muscle weakness and ankle movement abnormalities is an important factor in CVD, but the biomechanical and morphological characteristics of the calf muscle remain unknown

Aim: To evaluate the biomechanical and morphological characteristics of the calf muscle in subjects with CVD and healthy controls.

Place and duration of study: Study was conducted at University of Social Welfare and Rehabilitation Sciences, Tehran, Iran, for the duration of six months, from January, 2021 to June, 2021.

Materials and methods: In this case-control study, sixty patients with CVD in three equal groups (mild: C1 – C2, moderate: C3 – C4, severe: C5 – C6) and 20 healthy subjects in a control group participated. The shear wave elastography (SWE) and thickness of medial gastrocnemius muscle (GM) were measured using an ultrasonography.

Results: The results of analysis of variance (ANOVA) showed significant differences in SWE and thickness values between groups for medial GM ($P<0.05$). There was a statistically significant decrease in thickness and a significant increase in SWE in patients with CVD. A positive and negative correlation was discovered between disease grades and the medial GM SWE and thickness in patients with CVD, respectively.

Conclusion:A change in the SWE and thickness of the calf muscle compared to the control group indicates a biomechanical and morphological change in the calf muscle pump. The SWE and thickness values of the calf muscle may be valuable information in the diagnosis and follow-up of patients with CVD.

Keywords: Calf muscle pump; Chronic venous disease; Thickness; Ultrasonography; Stiffness

INTRODUCTION

Calf muscle pump incometence is one of the major risk factors for chronic venous disease. The contraction of the muscles of the lower extremities especially the gastrocnemius, compresses the venous system and propels venous blood from the foot to the heart(1).

According to the literature, previous studies have reported that dysfunction of the muscle pump leads to impaired venous return, reduced blood perfusion and venous stasis(1, 2). These events into edema, changes in subcutaneous tissue and fibrosis of the skin, and eventually tissue breakdown and venous ulceration(3). Other factors that may contribute to calf muscle pump failure include diminished strength in the calf muscle itself and the nerves that supply the muscle as well as limitation of ankle range of motion particularly during walking(4, 5).

In this sense, calf muscle pump failure might be related to changes in muscle morphology(6). These can be evaluated using ultrasound imaging technique, particularly the calf muscle thickness, which is a key indicator for assessing contractile strength(6). In addition, the muscle stiffness is one of the essential indicators of force generation, joint range of motion, or physical function. Passive muscle stiffness is referred to as passive elasticity or passive muscle tone. The pronounced increase of the passive muscle stiffness in immobilization and chronic pain disordear indicates that stiffness adapts to mechanical stimulation and this stiffness can be evaluated by ultrasound elastography(7-9).

SWE is an ultrasound elastography technique that uses shear waves to measure tissue stiffness quantitatively. This provides more accurate information about histological changes in tissues and a key marker of tissue health(10). Therefore, the use of a quantitative and objective evaluation method such as elastography and B-mode ultrasound could be used to examine the stiffness and thickness changes of the calf muscle pump and also provide a good index for the evaluation of patients with CVD and determining disease progression.

We investigated the hypothesis that calf muscle stiffness and thickness are impaired in limbs with CVD and may contribute to the poor calf pump function associated with venous disease progression.

MATERIALS AND METHODS

Patients and controls: In this case-control study, 20 healthy control subjects and 60 subjects with a diagnosis of CVD were enrolled in this study. All CVD subjects presented venous blood reflux in at least on of the lower limb veins with a reflux duration of greater than 0.5 second(s) based on Doppler ultrasound findings(11) and CEAP (clinical, etiological, anatomical, and pathological) clinical classification in the range C1 – 6 (12). Before study enrolment, subjects were informed about the purpose and

procedures of the study and signed an informed consent. The study received ethical approval by the University of Social Welfare and Rehabilitation Sciences ethics committee. Sixty subjects were enrolled in 3 equal patient groups and 20 healthy subjects in one control group. The allocation of patients in each group was based on the CEAP clinical classification of venous disease (mild: C1 – C2, moderate: C3 – C4, severe: C5 – C6 respectively)(12).

Exclusion criteria included uncompensated cardiorespiratory insufficiency; recent venous thrombosis; diabetes; ankle-brachial pressure index greater than 0.9; arthritis; previous stroke; previous limb fracture; ulcers over the area of the ankle joint and at the upper third of the distance between the popleteal ridge and the lateral maleollus; painful ulcers; current use of venoactive drugs and opioid or alcohil; pregnancy; cancer; infection; body mass index greater than 40; current treatment for their lower extremity(6, 13-16). subjects in all groups were matched according to age and sex. All groups were comparable in terms of weight, height and body mass index (BMI).

Thickness Measurements: Real-time imaging of the medial GM was performed using an ultrasonography set (Axiplorer; supersonic imaging Aix-en-provence, France) with a trancducer linear array frequency of 4 – 15 MHZ(17). Imaging was performed at the upper third of the distance between the popleteal ridge and the lateral maleollus with subjects lying prone and at the state of rest and during maximal active ankle plantarflexion. The distance between the proximal and distal aponeurosis in the medial GM was traced to measure the muscle thickness(Figure 1)(6).

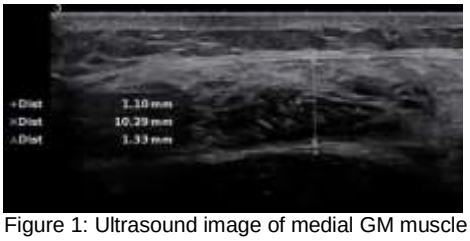

Figure 1: Ultrasound image of medial GM muscle G gastrocnemius muscle

SWE Measurements: The SWE was calculated to assess the relative stiffness of the medial GM muscle in a selected region of interest. SWE (KPa) values were calculated from the measured shear wave propagation velocity and tissue density to assess the relative elasticity for each ROI(18). the examiner properly aligned the transducer with medial GM fibers, while using a large amount of gel to reduce the effect tissue deformation. Then, the examiner kept the probe for 5 seconds until a map of muscle SWE value in a selected region of interest (ROI) was displayed on the monitor screen(10, 17). When the image was suitable and with at least artifact, the image was freezed and then three circles in ROI with size 1 × 1 mm² were placed at a given distance in the vertical axis of the medial GM muscle (Figure 2).

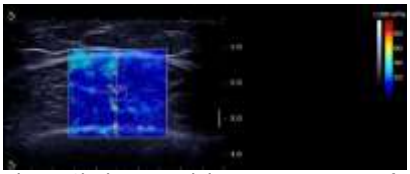
Figure 2) shear modulus measurement of medial GM muscle

This procedure was performed at the state of rest and during maximal active ankle dorsiflexion. In addition, To eliminate the effects of subject's weight, the calculated SWE and thickness were divided based on their weight. The normalized SWE and thickness were used for further analysis. All ultrasonographic measurements were performed by an expert radiologist. The SWE and thickness for the medial GM muscle was obtained in at least 3 measurements, and the average values were used for the statistical analysis.

Statistical analysis: All Statistical analysis were performed by using SPSS software version 16.0 (SPSS Inc, Chicago, IL, USA), for a significance level of $\alpha < 0.05$. The Kolmogorov–Smirnov test was used to investigate the normal distribution of the variables. Data were presented as mean ± standard deviation (SD). Differences among groups were tested through ANOVA with post hoc testing by Tukey's studentized test. Receiver operating characteristic (ROC) curves were plotted to determine the best cutoff value. The sensitivity, specifcity and accuracy were calculated based on SWE and thickness measurements of medial GM muscle. The relationship between the SWE and thickness values and venous disease grades was calculated using Pearson coefficient of correlation. Intraclass correlation coefficient (ICC) was used to assess the level of repeatability. The interpretation of reliability coefficient was based on a general rule with the ICC: <0.25 no correlation; 0.25-0.5 fair; 0.5-0.75 moderate to good; and >0.75 good to excellent correlation(19).

RESULTS

All patients (60 adults) with CVD were presented pathological venous reflux and classified into 3 groups depending on the CEAP clinical classification in the range C1 – 6 for CVD. The results of the Kolmogorov–Smirnov test showed normal distribution of all variables including the SWE and thickness of medial GM and demographic characteristics in four groups(p>.05). There were no significant differences in age, height, weight and body mass index (BMI) between the groups(p>.05, analysis of variance)(Table 1).

Table 1: Demographic data of participants in four groups

Variable	Control Group	CEAP1,2 Group	CEAP3,4 Group	CEAP5,6 Group	P-Value ANOVA
number	20	20	20	20	
Age (years)	53.90±11.47	52.32±13.01	54.48±10.65	57.70±11.24	0.748
Height (cm)	166.15± 5.17	165.97±5.75	168.50±4.90	167.30±6.14	0.712
Weight (kg)	70.55±6.19	70.20±6.05	72±7.15	71.42±6.37	0.824
BMI (kg/m2)	25.47±1.31	26.57±1.47	24.83±1.66	25.73±1.43	0.381

Values are reported as mean ± SD.

*Statistically significant difference between groups.

The SWE of medial GM was significantly different between groups (P<0.05, ANOVA). The SWE was significantly increased in severe CVD (C5-C6) group compared with the other groups (P<0.05). In addition, moderate CVD (C3-C4) group was statistically different from mild CVD (C1-C2) and the control groups (P <0.05). There were no significant differences between mild CVD (C1-C2) and the control groups. Medial GM thickness also differed significantly between groups (P <0.05, ANOVA) and decreased in severe CVD (C5-C6) group when compared to the other groups (P<0.05, ANOVA, Tukey). Muscle thickness showed a stepwise decrease related to increasing grade of venous disease, although there was no significant difference between mild CVD (C1-C2) and the control groups(Table 2).

Table 2: shear wave elastograhy measurements in the CEAP groups

Parameter	CVD Classification	CEAP0	CEAP1,2	CEAP3,4	CEAP5,6	p-value
GM SWE	(Rest)	6.58 ± (1.76)	7.24 ± (1.97)	13.39 ± (3.27)	25.10 ± (4.41)	<0.001
GM SWE	(Stretch)	10.83 ± (3.41)	10.81 ± (3.18)	19.47 ± (4.54)	42.06 ± (7.51)	<0.001
GM Thickness	(Rest)	16.62 ± (1.37)	15.46 ± (0.87)	14.56 ± (2.04)	12.18 ± (1.16)	<0.001
GM Thickness	(Contracted)	17.75 ± (1.12)	16.47 ± (0.82)	15.35 ± (1.93)	13.01 ± (1.29)	<0.001

GM: gastrocnemius muscle; GSF: gastrocnemius superficial fascia; GDF: gastrocnemius deep fascia

Data is shown as Mean ±(SD)

Furthermore, the main effect of ankle position on SWE and thickness of the medial GM was significant, thus indicating an increase in stiffness and a decrease in thickness with stretching and contraction of calf muscles, respectively. A positive and signifIcant correlation was found between disease grades and SWE of the medial GM in the range of r = 0.84 to 0.89; P < .001. The correlation coefficients between disease grades and thickness were in the range of r = 0.81 to 0.86; P < .001. Between SWE and thickness of the medial GM, a negative correlation was found (r = 0.78 to 0.80; P < 0.001).

Analysis of the characteristic curve of the receiver operator showed a maximum value, which indicates high diagnostic accuracy in detecting muscle defects in venous disease through SWE and thickness. The sensitivity, specificity and accuracy of the SWE and thickness values are shown in Table 3. The results of the reliability tests showed highly reliable (Rosner, 2015) measurements for the SWE with ICC = 84 for the CVD subjects and ICC = 93 for the normal subjects. Also, the thickness with ICC = 79 for the CVD subjects and ICC = 86 for the normal subjects.

DISCUSSION

In this study, we assessed the clinical usefulness of stiffness and thickness in evaluating calf muscle involvement in patients with CVD in comparison to healthy subjects. The findings of the present study showed impaired changes in the SWE and thickness values of the calf muscle, which is in the line with previous studies that have reported abnormal SWE and thickness in the soft tissues such as nerve, tendon, muscle and skin in various diseases, including chronic low back pain, neck pain, plantar fasciitis, bedsores, etc(20). In addition, we found a signifcant correlation between disease grades and SWE and thickness values. So these results confirmed our hypothesis that the SWE and thickness values of the medial GM are affected in CVD. These values can also provide important data in the evaluation of calf muscle pump in patients with CVD.

Impaired calf muscle function, especially gastrocnemius, is a major factor to the etiology of CVD(15, 21). A literature review of the role of the calf muscle in chronic venous disease revealed histopathological changes in calf muscle including atrophy, muscle necrosis and denervation(22). On the other hand, various studies have emphasized the role of ultrasound findings such as muscle thickness as a key scale in assessing contractile strength(23).

Criso'stomo et al. investigated the gastrocnemius muscle thickness and its relationship with the contractile strength of the calf muscle pump in the patients with CVD and healthy controls. They reported that there was no difference in the GM thickness value compared to control participants. In addition, there was no relationship between the clinical severity of the CVD and the muscle architecture changes(6). However, calf muscle thickness does not appear to be a major determinant of muscle pump performance.

In fact, in their study, patients were on a CEAP in the range C1 – 3 (only one subject was C4) and had no significant difference in GM thickness value compared to control participants. In contrast, we found a number of correlations between increased severity of CVD and GM thickness value(6). In our study, patients were in the range C1 – 6 and GM thickness was significantly reduced in the severe and the moderate CVD groups (C5-C6) compared to other groups. Several studies have reported that patients with severe CVD and leg ulceration(C5-C6) have a measurable deficiency in the calf muscle pump strength(3, 21). These findings are similar to our findings, which demonstrated a steeper decrease in the thickness of the calf muscle in participants with severe CVD group. It is suggested that calf muscle impairment as a result of reduced calf muscle thickness may itself be responsible for calf muscle pump failure in patients with severe CVD and leg ulceration.

A novel aspect of our study was that we calculated the quantitative thickness value and estimated cutoff value of medial GM by using ultrasonography to evaluate the calf muscle pump as another important factor in the etiology of the disease. The estimated cutoff value of the GM thickness can be used in clinical practice to predict the onset and progression of venous disease. The receiver operating characteristic curve analysis results were maximum (0.84; 95% confidence interval, 0.74–0.94), and cutoff values 14.47mm (rest condition) and 15.41mm

(contracte condition) were used for muscle thickness defects in CVD.

In our study, calf muscle stiffness was significantly increased in the moderate and severe CVD groups. According to available evidence, muscle pump dysfunction is probably caused by a decrease in calf muscle strength with a decrease in ankle joint movement. Dix et al. showed a decrease in ankle range of motion in all grades of CVD, from simple varicose veins to active venous ulcers(2). Although their study suggests that venous hypertension may lead to decreased ankle movement, our study also considered an increase in calf muscle stiffness in patients with venous disease.

Bowers and Castro presented that tightness of the gastrocnemius muscle is a common finding in the pathology of foot and ankle joint(24) and there is a direct relationship between muscle stiffness and the flexibility(25). Therefore, with the increasing stiffness in the muscle structure, the relationship between length-tension curve in the calf muscle is impaired. Consequently, altered length-tension relations may affect the amount and the nature of the ankle motions. This may lead to an altered function of calf muscle pump, aiming to ambulatory venous haemodynamics in patients with CVD. in the present study, it can be concluded that although limited ankle movement contributes to the poor calf pump function, it is possible that but a gradual increase in calf muscle stiffness and a decrease in calf muscle strength may reduce the range of motion of the ankle.

We found the quantitative SWE of the medial GM to be relatively high in the patients with CVD compared to the healthy participants. The receiver operating characteristic curve analysis results were maximum (0.87-0.88; 95% confidence interval, 0.77–0.98), and Cutoff values 14.9 kPa (rest condition) and 23.87 kPa (stretch condition) were used for muscle SWE defects in CVD.

limitations of our study are that the measurements of thickness and SWE were in a prone and nonweightbearing position. Ankle movements in a upright and weightbearing position may provide a more accurate assessment of SWE and thickness in relation to the normal functioning of the calf muscle pump. Future studies should evaluate the role of the other components of calf pump function included veins, fascia, nerve and other calf muscles. Additionally, we did not record the electromyography activity or dynamic strength of the calf muscle to reveal whether any differences exist in the calf muscle strenght in the groups. Further research to study the electromyography activity, dynamic strength, ultrasonography of the calf muscles simultaneously will help researchers to develop a better understanding of the possible muscular impairment in subjects with CVD.

In conclusion, a qualitative analysis of the calf muscle in patients with CVD showed a statistically insignificant decrease in thickness and increase in stiffness, according to the ultrasonography findings. This study provides a better understanding of the possible biomechanical and morphological changes in the calf muscle in patients with CVD, and it is a guide to use along with other diagnostic tools and treatment programs.

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