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Shear Wave Elastography to Evaluate Unilateral Acute Limb Swelling: A Novel Approach

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Shear wave elastography; Lymphedema; Venous insufficiency; Cellulitis; Lipoedema

1. Abstract

1.1. Background: This study was designed to determine the role of Shear wave elastography (SWE) in the evaluation of a patient with acute unilateral limb swelling and to determine if it can differentiate between the common causes of a acutely swollen limb.

1.2. Methods: 51 patients of acute limb swelling were prospectively evaluated using duplex sonogram followed by SWE. All patients were assessed for any venous disease, peripheral arterial disease, subcutaneous and dermal thickness. The SWE was performed in the anteromedial part of the mid and lower legs and Young's modulus E determined and a mean value of three readings was obtained which was plotted on a colour scale slider with a range for the common causes of limb swelling i.e., lymphedema, venous oedema, cellulitis, lipoedema and ischemic oedema and others. 10 patients with normal limbs were scanned in the above manner and normal range of values plotted. The final diagnosis was made based on duplex scan and clinical findings and MR lymphography. Statistical analysis was done for mean, median and distribution evaluation with one-way Anova test to determine the statistical significance of the E value and subcutaneous thickness between different causes of limb swelling.

1.3. Results: Patients with venous oedema 20(39%) were the commonest followed by while 17(33%) patients with lymphedema, 8(15%) had cellulitis while the other two were those with lipoedema and ischemic edema. All the groups showed a statistically significant difference ($p<0.0001$) in the E values i.e., mean E was 6.38 kPa in venous oedema patients, 3.50 kPa in lymphedema, 11.53 kPa in cellulitis patients and 15 kPa in those with ischemic limb swelling while patients with lipoedema had normal mean E of 5.25 kPa. Statistically significant differences were also seen in the subcutaneous thickness between patients with venous oedema and the others ($p<0.009$).

1.4. Conclusion: The study shows that SWE is a useful non-invasive test and combined with duplex sonography can accurately differentiate between the common causes of acute unilateral limb swelling.

2. Introduction

Limb swelling is a common prevalent problem worldwide and affects upto 30% of population. In older adults, the prevalence of limb swelling is even higher, affecting up to 50% of people over the age of 65 [1]. This is because the veins and lymphatic system in the legs tend to become less efficient with age, which can lead to fluid build-up. History and clinical examination form an important first step in the evaluation of a patient with unilateral limb oedema. The commonest causes of the unilateral limb oedema include venous, lymphatic and cellulitis and require a diagnostic testing to establish the cause. Colour Doppler examination has been the mainstay modality to rule out venous thrombosis or venous insufficiency as the cause [2,3] while for the remaining two imaging tests like magnetic resonance imaging, lymphography or computed tomography may be needed which are costly and time consuming. In routine practice CD has been used to identify patients with lymphedema and lymphedemaby excluding significant venous disease and demonstrating subcutaneous fluid accumulation, respectively. There is hence a need for an appropriate staging and evaluation tool for management and follow-up of the progression of disease in such patients.

Shear wave elastography has recently become available as a non-invasive tool to assess tissue stiffness and is used in combination with ultrasonography. Its role is well established to evaluate soft tissue stiffness of liver, breast, and thyroid diseases. We did a prospective study to evaluate role of SWE in the assessment.

patients with unilateral acute limb swelling.

3. Material and Methods

After obtaining approval from local review board a prospective study of 50 consecutive patients with acute unilateral lower limb swelling of less than 0ne month duration was done. Informed consent was obtained from all patients. After history, clinical examination and routine haematological investigations color Doppler examination of the lower limb was done for venous and arterial study on Aplio i800 system (Canon japan) using 8-14 MHz Linear probe. This was followed by SWE study for estimation of the stiffness of the subcutaneous soft tissues. The area selected was anteromedial part of the mid and lower leg. Maximum thickness of the skin, subcutaneous fat till fascia was recorded along with echotexture details. We did not compare the Stiffness of affected leg from the contralateral leg rather obtained normal soft tissue stiffness E values from a cohort of 20 volunteers with patient matched age and BMI (between 25-29 Kg/m^2). This was done to rule out any confounding factors which could influence the E values of the normal leg. The examination was done with a linear probe being placed parallel to the axis of limb with gentle pressure a routine ultrasound image was obtained. The cutaneous thickness, subcutaneous thickness (ScT) was measured. The echogenicity of the subcutaneous fat was observed for homogeneity, marbled appearance or any collection. SWE was done in the same position with a rectangular region of interest box of 15x5mm in the subcutaneous soft tissues. A round caliper of 5 mm was placed on SWE map to estimate the E which was displayed at the lower part of the elastogram. A total of three SWE maps were taken and the mean was displayed on a classifier scale using a color slider based on the E values on SWE of the subcutaneous soft tissues as shown in Figure 1. The final diagnosis of the cause of limb swelling was based on findings of color Doppler, clinical examination and MR lymphography.

All patients were then followed up after a period of two weeks and four weeks to see the post treatment results.

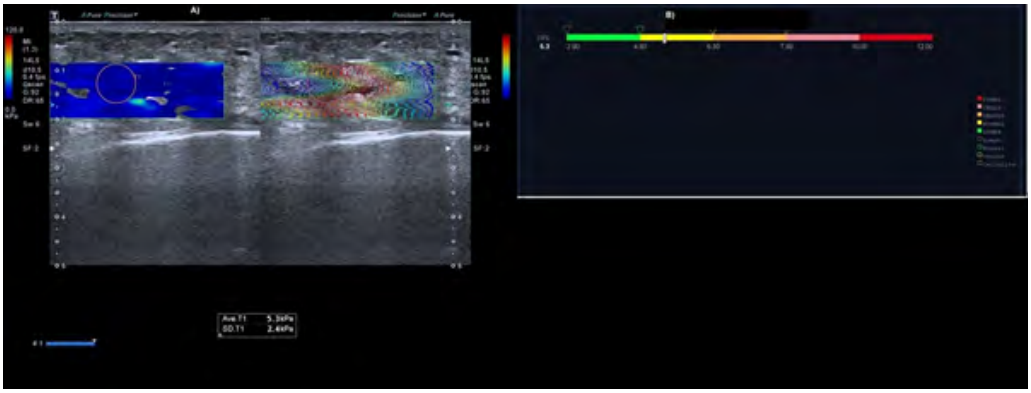


Figure 1: A) SWE in a control patient with normal E of 5.3 kPa. B) E being displayed on the color slider scale in Yellow (normal stiffness range).

3.1. Statistics: Was done using Analyse-it software (Leeds UK) and mean with standard deviation and distributions calculated for age, E values, Subcutaneous and skin thickness. One-way Anova analysis for done to determine the statistical differences between different causes and p value of <0.05 was determined as significant. Post hoc power of the study was fixed at 0.95

4. Results

The mean age of the volunteers was with a mean BMI of 27.2 Kg/m2. The mean range of E of the subcutaneous soft tissues was 5.2 kPa (range 4.8-6.3 kPa). Out of the 51 patients there were 30 males and 21 females with median age of 43.5 years (95% CI :41.5 -45.1; W 0.88).Demographic details are enlisted in (Table 1). There were 20(39%) patients with venous oedema while 17(33%) patients had lymphedema, 8(15%) cellulitis and 3(5.8%) each with lipoedema and ischemic oedema. The median cutaneous thickness was 1.2mm with no statistical difference (p=0.56) across all the categories. The SCT were 2.05 cm for venous oedema, 2.68 cm for lymphedema, 2.66 cm for cellulitis and 3.57cm for lipoedema the differences were statistically significant (p<0.0001). Pivotal table (Table 2) shows the distribution of E value determined using SWE. The Mean E value seen in patients with venous oedema was 6.38 kPa (95% CI 6.24 – 6.53) (Figures 2-3) while those with lymphedema had mean E of 3.50 kPa (95%CI 3.34-3.66) (Figures 4-5).

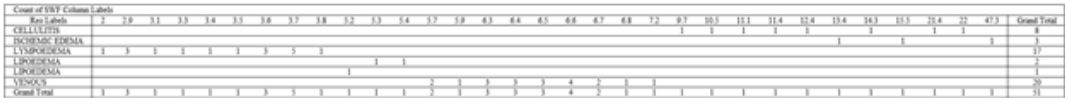
The patients with cellulitis had a mean E of 11.73 kPa (95% CI 10.04-13.41) (Figures 6-7) which overlapped with those of acute ischemic oedema 15 kPa (95% CI 11.48-18.52) (Figure 8). Patients with lipoedema had a normal E of 5.25kPa (Figure 9). One-way Anova done showed statistically significant differences p<0.001 (Table 3). Stemmer test was positive in 9 patients while lymphography was done in 7 patients which showed lymphatic obstruction.

All cases with venous oedema showed venous insufficiency with saphenofemoral incompetence in 10 patients, perforator incompetence in 7 and 3 had acute deep vein thrombosis. All patients with cellulitis had fever with leucocytosis while all patients with ischemic oedema had peripheral arterial disease on colour Doppler.

Table 1: Patient Demographics.

Sno.	DEMOGRAPHICS	Patients		Controls	
	Parameters	Mean			
1	Median Age	43.5 years	CI 41.5-45.5	44.6 years	CI 42.4-46.5
2	Sex				
	male	30		12	
	Female	21		8	
3	Mean BMI	28.5 Kg/m2	CI 26.3-30.2	27.2	CI25.8-29.5
4	Mean Duration of History	23 days	CI: 17-26		NIL
5	Positive Stemmer Sign	7			NIL
6	Mean Subcutaneous Thick	2.08cm	CI 1.8-3.2	1.5 cm	CI 1.4-2.8
7	Mean Dermal Thickness	1.1 mm			0.8mm
8	Marbled appearance	26			NIL
9	Inguinal nodes	6			NIL
10	Varicose veins	18			NIL

Table 2: Pivot table of E values on SWE in different patients in the study.



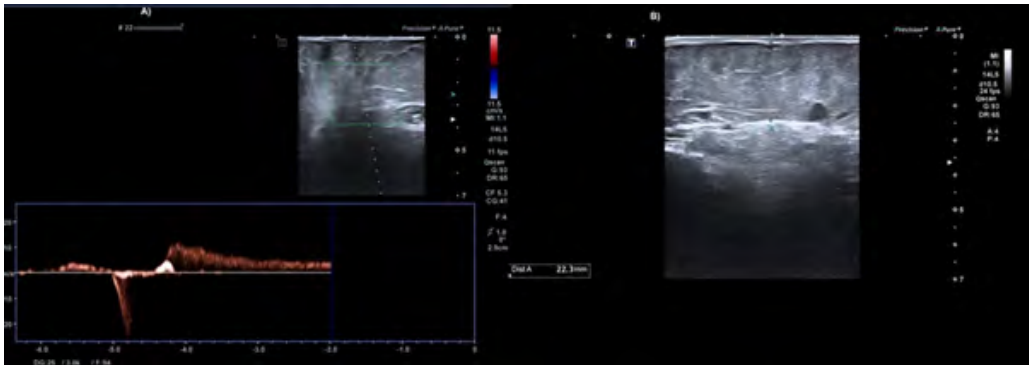


Figure 2: A) Duplex scan showing reflux in the long saphenous vein. B) Increased subcutaneous thickness (SCT) of 2.2 cm.

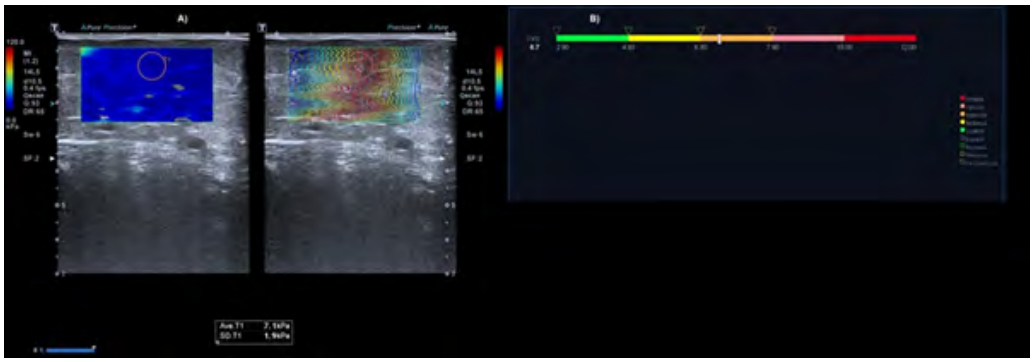


Figure 3: A) SWE map showing increased E of 7.1 kPa. B) Soft tissue slider showing E in the orange range of venous edema.

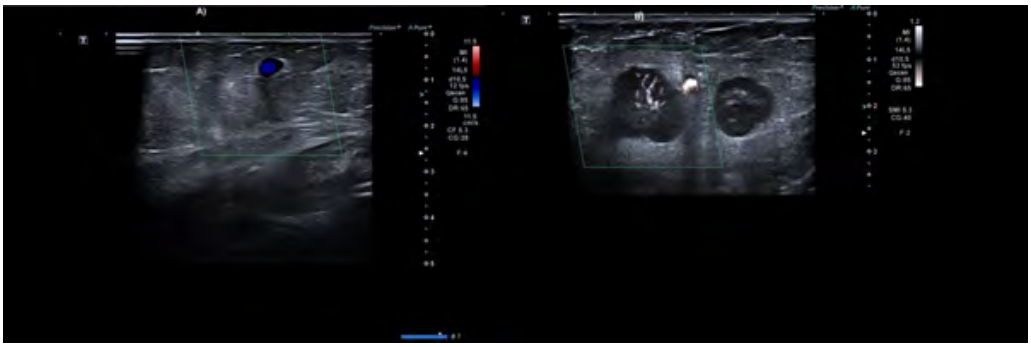


Figure 4: A). Color Doppler showing normal venous flow with increased SCT of 2.8 cm. B) Enlarged inguinal nodes with increased vascularity and surrounding echogenic fat in acute lymphangitis.

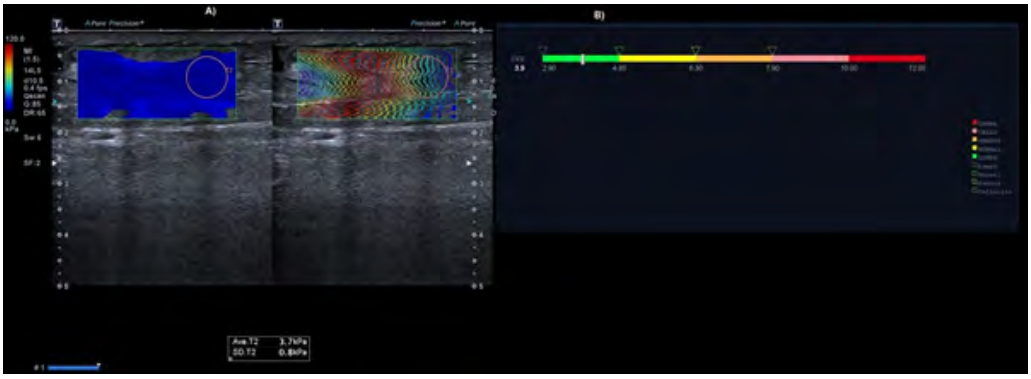


Figure 5: A). SWE maps showing reduced E of 3.7k Pa. B) Color slider showing E in the green range of lymphedema.

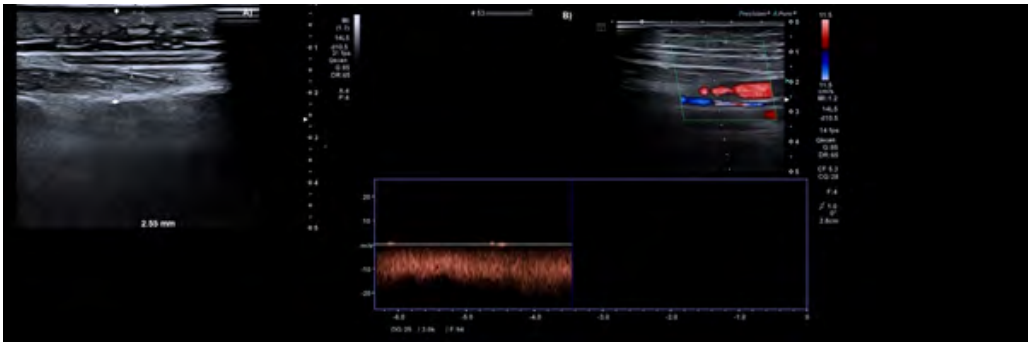


Figure 6: A) Grey scale sonogram showing increased SCT of 2.55mm. B) Normal duplex scan in the same patient.

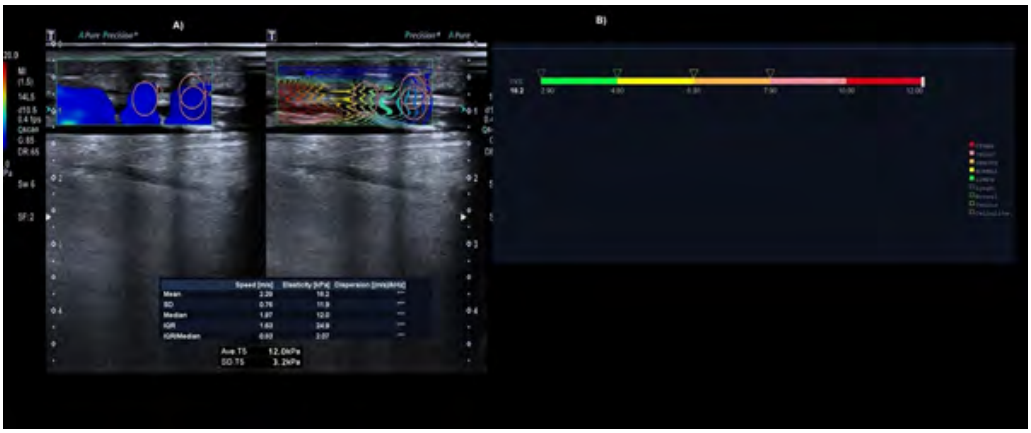


Figure 7: A) SWE map showing increased mean E of 12. kPa. B) Slider showing the above to be in the red color scale of cellulitis/others.

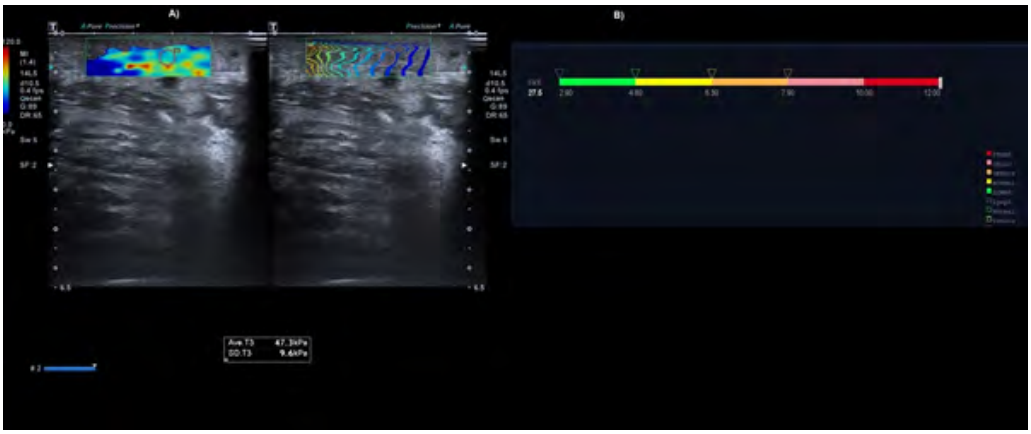


Figure 8: A) SWE map showing E of 47.3 kPa. In a patient with acute ischemic edema. B) Soft tissue slider showing it in the red color scale of cellulitis/others.

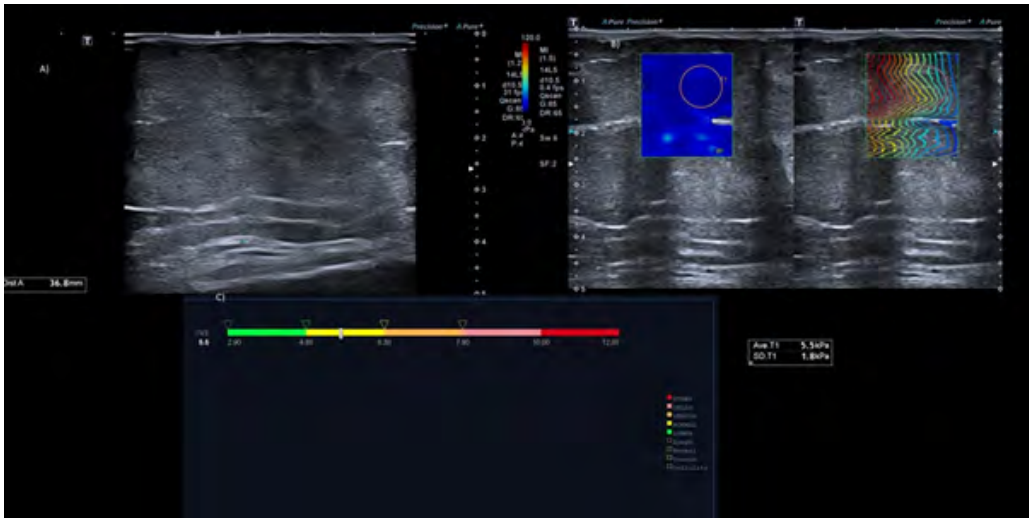


Figure 9: A) Grey scale sonogram showing increased SCT of 3.6mm B) SWE map showing E 5.5 kPa in a patient of lipoedema C) Slider scale showing E value in the normal range in orange color.

Table 3: One-way Anova analysis of comparison of E values between different categories of limb swelling.

SWE	n	Mean	SE	Pooled SE	SD
cell	8	11.73	0.714	0.311	2.02
ischemic edema	3	15	0.819	0.508	1.42
venous edema	20	6.38	0.08	0.197	0.3
lympo edema	16	3.5	0.075	0.22	0.3
lipoedema	4	5.28	0.048	0.44	0.1
Source of variation	Sum squares	DF	Mean Square	F statistic	p
SWE	582.62	4	145	187.81	<0.0001
Residual	35.7	4	0.78		
Total	618.3	50			

5. Discussion

Our study shows that it is possible to use SWE to evaluate patients with acute unilateral limb swelling with the methodology as described. SWE is based on the principle of generation and tracking of shear waves to determine the Youngs, s modulus E. The speed of the shear waves is determined which is directly linked to E [4]. Normal tissues are presumed to be non-compressible, elastic, isotropic and homogenous. Any change in these properties results in alteration of the speed of shear waves and thus alteration of E which can now be assessed. The commonest types of causes resulting in acute unilateral limb swelling have different pathogenesis and hence should have different tissue stiffness which was the hypothesis of this study. Venous insufficiency has been shown to be the most common etiology in 90% of patients of limb ede-

ma by Engelhorn et al [5]. The exact sequence of events that lead to venous edema are thought to be due to venous hypertension which triggers increased pressure in the veins and causes the fluid to leak out of the capillaries and into the soft tissues this causing limb swelling. There is a secondary exudation of fibrinogen and proteins into the interstitial space, which later produce the characteristic changes of lipodermatosclerosis [6-8]. Hence due to mixture of fluid alongwith fibrogen and proteins there is increase in the tissue stiffness and E values from the normal. Since there is still not much fibrosis in the early stage of venous insufficiency the tissue stiffness i.e., the Young's modulus changes are not very drastic as was seen in the present study and the subcutaneous thickness also did not change by more than 50%. The mean value seen in patients with venous edema of SCT was 2.05mm while E was 6.38 kPa (95% CI 6.24 – 6.53). There have been very studies done Suehiro et al [9] who studied strain patterns in patients with lymphedema but could determine the strain changes in only in late stages. Hiyashi et al [10] showed soft tissue changes using strain elastography and compared them with indocyanine green studies. They showed that strain elastography showed qualitative changes of fluid accumulation in patients of lymphedema as changes in color scale of strain elastogram. We have for the first time been able to quantify stiffness changes using SWE due to improvements in the technology. In our study patients with lymphedema showed reduced E values from normal with mean of 3.5 kPa. This is explained due to differences in the pathogenesis. In lymphedema there is hypertrophy of the adipose tissues having larger and variable size fat lobules, which are surrounded by thicker collagen matrix and lymph fluid compared to healthy adipose tissue [11]. These changes make the subcutaneous soft tissues more supple and result in lowering of the stiffness and Young's modulus E as was seen in the present study. Our study shows these differences were statistically significant and could differentiate between the two most common causes. Although there was difference in the extent of SCT between venous and lymphedema patients however these could not be used to differentiate from other causes of acute limb swelling. Lipoedema a condition where there is limb swelling due to hypertrophy of the normal subcutaneous fat lobules shows increased thickness of the fat layer with normal Young's modulus E as was seen in the patients in the current study and E value was a strong discriminator to differentiate it from lymphedema patients. It is a common practice for patients with lower limb cellulitis and swelling to rule out deep vein thrombosis by the use of duplex sonography [12]. In one study 17% of patients with clinically diagnosis of cellulitis had venous thrombosis [13]. Hence it has been a commonly asked investigation to assess and differentiate the two conditions. Studies by Leve ll et al [14] and Ko et al [15] showed that the misdiagnosis rate of cellulitis varied from 30-74% and stasis dermatitis of venous disease was the greatest mimicker. The results of the current study suggest SWE can be a useful adjunct to be used in such situations along with duplex sonography to be able to accurately solve the diagnostic dilemma even when the Doppler examination rules out venous thrombosis as the cause of acute limb swelling. Due to presence of cellular infiltrates, local tissue hyperaemia, exudation of fluid and lymphatic upregulation and tissue edema there is significant increased stiffness of subcutaneous soft tissues which result in gross increased in E value which is able to differentiate from other prior causes. The mean E value seen in the present study in patients with cellulitis was 11.73 kPa which was statistically significant. However, the current study showed an overlap of E values with patients of acute ischemic edema in patients with critical limb ischemia where clinical and other imaging findings are needed. Tang et al [16] studied the changes of arterial occlusion in rats following hind limb ischemia and suggested that there is disruption of the arteriolar network followed by inflammation and tissue loss resulting in fibrosis and atrophy of the soft tissues, similar changes soft tissue apoptosis were also observed by Tedgui et al [17] in their study. Coupled with above processes would also be secondary process of infection in such limbs which have gradual or sudden critical ischemia. All these pathological changes hence would cause increased stiffness and raise the Young's modulus E in on SWE similar to what we observed. Hence clinical background and duplex scan findings would help in differentiating it from pure cellulitis.

To summarise this is the first study to our knowledge which shows the usefulness of SWE in patients with acute unilateral limb swelling and is able to differentiate between the different commonly observed causes especially between venous edema, lymphedema and cellulitis. SWE is non-invasive and can be easily combined with routine ultrasonography and duplex color Doppler imaging to evaluate such patients.

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