HHS Public Access

Author manuscript

Bone Marrow Transplant. Author manuscript; available in PMC 2020 April 01.

Published in final edited form as:

Bone Marrow Transplant. 2019 April ; 54(4): 616–619. doi:10.1038/s41409-018-0346-7.

Objective, noninvasive measurement of sclerosis in cutaneous cGVHD patients with the handheld device Myoton: a cross-sectional study

Fuyao Chen, BE[1,2], **Laura E. Dellalana, BS**[1], **Jocelyn S. Gandelman, BS**[4], **Arved Vain, PhD**[1,5], **Madan H. Jagasia, MD, MS, MMHC**[4], **Eric R. Tkaczyk, MD, PhD**[1,2,3]

[1.]Department of Dermatology, Vanderbilt University Medical Center, Nashville, TN, USA

[2.]Department of Biomedical Engineering, Vanderbilt University, Nashville, TN, USA

[3.]Dermatology Service, Department of Veterans Affairs Tennessee Valley Healthcare System, Nashville, TN, USA

[4.]Division of Hematology and Oncology, Department of Medicine, Vanderbilt University Medical Center, Nashville, TN, USA

[5.]University of Tartu, Institute of Physics, Tartu, Estonia

Chronic Graft-versus-Host Disease (cGVHD) is the leading cause of long-term mortality and morbidity in patients after stem cell transplantation (SCT). Skin is the most commonly affected organ, involved in more than 90% of cGVHD cases[1]. Skin manifestations of cGVHD are broadly divided into two categories : erythema and sclerosis. Among patients being treated for cGVHD, 20% develop sclerosis within 3 years of transplant, leading to significant disability[2].

The current standard for monitoring sclerosis is the NIH Skin Score, ranging from 0-3 based on body surface area (BSA) and sclerotic features[3]. However, this scoring system is subjective, coarse, and unreliable[4]. Measurement of sclerosis by exam is difficult due to ill-defined borders and paucity of reliable associated visible changes. Sclerosis scores among multiple observers rarely exhibit substantial agreement, and therefore the minimal change for reliable detection is 17 to 26% BSA[5]. These limitations have impeded the assessment of disease progression and treatment response[4]. Developing a quantitative and reproducible measurement of sclerosis was deemed a top priority by the 2014 NIH Consensus on Response Criteria for cGVHD[6]. Serial skin biopsy is not a practical option for long-term follow-up to assess treatment response, and histology results are generally non-specific[7]. This has motivated an interest in imaging tools for measuring sclerotic GVHD. Previously, a magnetic resonance imaging study of 15 cGVHD patients was able to identify abnormalities in the dermis, subcutaneous tissue, and muscle[8]. Ultrasound has shown differences in

Corresponding author: Eric Tkaczyk, MD, PhD, Department of Dermatology, Vanderbilt University Medical Center, 719 Thompson Lane, One Hundred Oaks Suite 26300, Nashville, TN 37204 (eric.tkaczyk@vumc.org, 615-936-4633).

Conflict of interest disclosures: None

[4.]Competing Interests

There is no competing financial interests in relation to the work described.

normalized shear wave speed in a single study of 4 healthy controls versus 5 sclerotic cGVHD patients[9]. Neither technology has yet advanced to large studies or widespread clinical use.

In the current study, we investigated the feasibility of using an affordable tool to rapidly and directly measure cutaneous sclerosis in cGVHD patients. We employed the Myoton (Figure 1), which is a commercially available, noninvasive handheld device developed to measure biomechanical properties of muscle. It has been applied in diverse fields including neurology and sports medicine[10,11], but has not yet been used in dermal disorders. The device delivers a brief, constant mechanical impulse to which tissue responds with a damped natural oscillation. Biomechanical properties are automatically extracted from the oscillatory response curve as previously described[12].

The durometer is another handheld device that appears similar to the Myoton at first inspection. However, the underlying principle and function are in reality very different between the two devices. The durometer is an industrial tool designed for determining the hardness of a surface by measuring the amount of force required to produce an indentation. Therefore, the durometer reading is highly dependent on the amount of force applied by the individual conducting the measurement. By contrast, the Myoton applies a fixed, brief mechanical impulse, and calculates multiple biomechanical properties based on the tissue's inherent response. The durometer has been used to measure skin hardness in patients with scleroderma, but no results have been published in GVHD patients[13,14].

For our study, the Myoton was modified for enhanced selection of cutaneous tissue and reduced interrogation of the muscle tissue for which it was designed. First, a 12 mm diameter disk was attached, thereby distributing the surface impulse over a 16 fold larger surface area than the standard 3 mm testing end (probe). During measurements, the probe rests perpendicular to the skin surface. The larger contact area decreases surface power density for selection of more superficial skin tissue and also reduces the amount of residual strain imparted during the measurement process. Second, impulse delivery time (tap time) was decreased from the default 15 ms to 7 ms. Decreased tap time results in a proportional decrease of total transferred mechanical energy, which translates into a smaller effective mass of natural tissue oscillation (i.e. selection of more superficial tissue).

In this cross-sectional study, cGVHD patients (n=8) with an NIH 2014 Skin Features Score of 3 (severe sclerosis) and healthy subjects (n=10) were recruited (Table 1). For each subject, the Myoton was used to measure skin stiffness bilaterally on 9 anatomic regions (shin, dorsal forearm, upper arm, shoulder, chest, abdomen, calf, upper back, lower back), resulting in 18 total measurement sites. Generally, cGVHD patients did not have skin involvement in all sites due to the heterogeneity of the disease. When undergoing Myoton measurements, subjects were instructed to relax in a supine position. They felt a slight, painless pressure for 7 ms at a time during the mechanical impulse. Twenty measurements with one second interval per site were conducted to minimize any possible measurement variation. A single measurer, JC, operated the Myoton after 80 hours of training by AV, the inventor of the device. Each subject's measurement session lasted approximately 30 minutes.

Stiffness measurements of cGVHD patients (n=8) were compared to healthy controls (n=10) by anatomic region (Figure 1A). By a Wilcoxon rank sum test (α=.05), in 8 of the 9 measured regions (representing 16 of 18 measurement sites), cGVHD patients demonstrated significantly higher skin stiffness compared to healthy subjects ($p<.05$). The only site without statistically significant differences was the abdomen, likely because the participating patients were not affected at the periumbilical measurement location. When the average stiffness over all 9 anatomic regions was compared between patients and controls, cGVHD patients had significantly higher overall skin stiffness (657 ± 387 N/m vs. 392 ± 171 N/m, respectively, $p<0.0001$). The variation of skin stiffness measurements is generally higher in cGVHD patients compared to controls, as evidenced by the large interquartile range in Figure 2A. This reflects the heterogeneous presentation of the disease in terms of anatomic regions affected in an individual patient.

An additional analysis divided the healthy subjects into normal (<25 kg/m^2) or high (>=25 kg/m^2) body mass index (BMI) groups to investigate BMI as a potential confounder. Within these controls, no measurement sites had significant differences when stratified by normal or high BMI (Figure 2B).

Our results demonstrate that a commercially available biomechanical measurement device can objectively distinguish between healthy subjects and patients with severe cGVHD. One limitation of this preliminary study is small sample size and patient homogeneity (Caucasian, NIH score of 3), which makes it difficult to assess the generalizability of the results. While our results indicate that skin stiffness measurements are significantly greater in patients with the most severe sclerotic cGVHD when compared to healthy controls, further investigation is required to determine whether this carries over to patients with mild-moderate disease. Further study and device development are also needed to assess the degree to which the Myoton is isolating skin and subcutaneous tissue. In this study, one observer performed measurements on all patients, so the results do not speak to the interobserver reproducibility of the device. Further investigation is also necessary to answer the critical question as to whether the Myoton can distinguish meaningful longitudinal changes in sclerosis of individual patients.

We have taken the first step towards developing a new method to objectively measure sclerotic GVHD disease. Reproducibility, generalizability, and the relative contributions of different soft tissue layers to the Myoton signal remain to be determined. If prospective longitudinal studies can correlate changes in stiffness values to clinical disease progression, the Myoton can become an important tool for monitoring patient course and treatment response in sclerotic cGVHD.

Acknowledgements

Dr. Tkaczyk is grateful for support from NIH K12 CA090625. This study is also supported by Baltic-American Freedom Foundation. This study is also supported in part by Career Development Award Number IK2 CX001785 from the United States Department of Veterans Affairs Clinical Science R&D (CSRD) Service.

Funding/Support: NIH K12 CA090625, Baltic-American Freedom Foundation

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Figure 1.
Myoton, a noninvasive handheld device, modified to isolate cutaneous tissue.

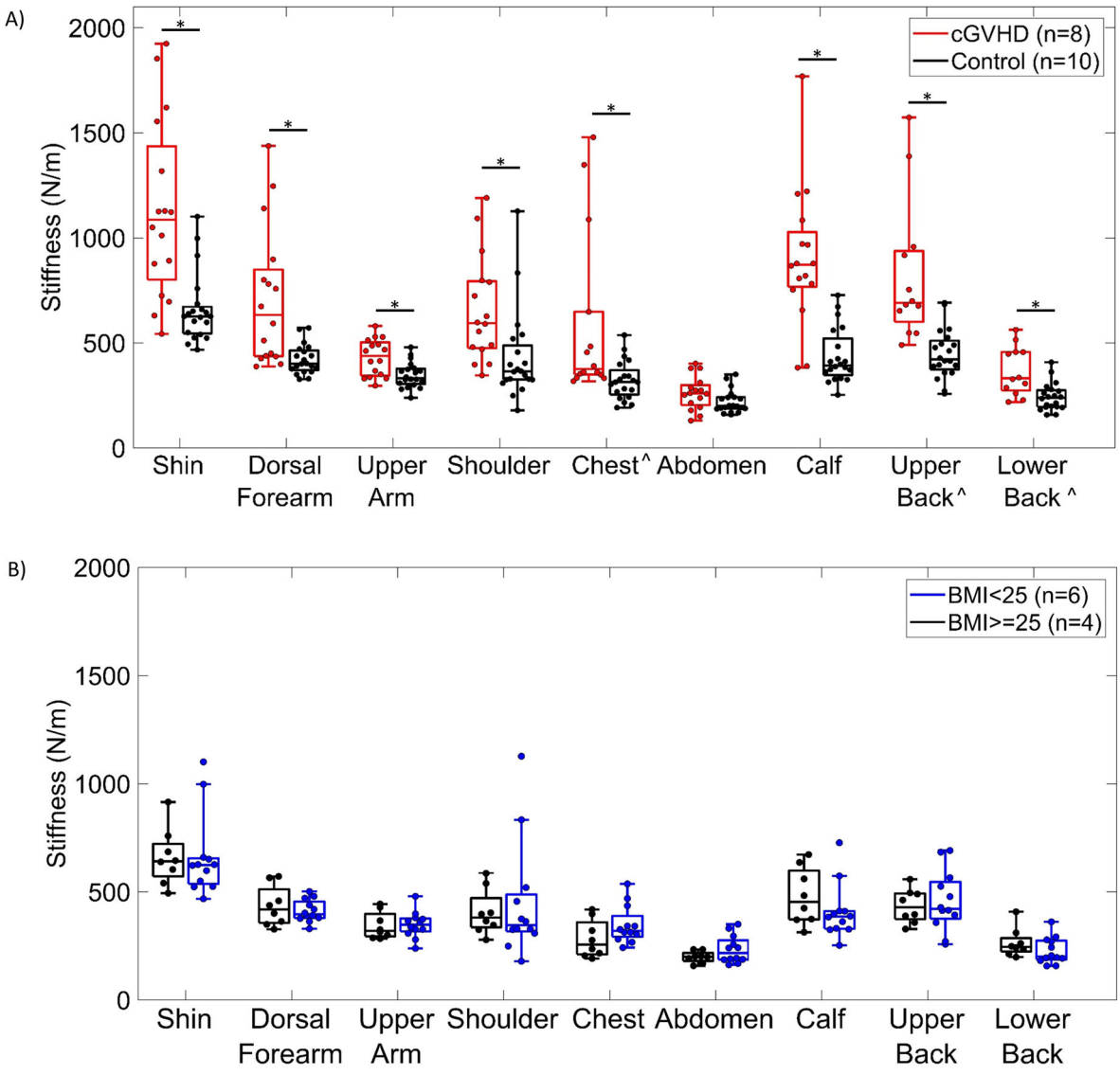

Figure 2.

A) Box-and-whisker plot of skin stiffness of 8 cGVHD patients and 10 healthy controls, measured with the Myoton device in 9 anatomic regions. *Statistically significant differences ($p<.05$). ^Only 7 cGVHD patients were measured on the chest and 6 were measured on upper and lower back for patient comfort considerations. B) Box-and-whisker plot of skin stiffness measured with Myoton in 9 anatomic regions on 10 healthy controls, divided by BMI above 25 and BMI below 25.

Table 1.

Subject Characteristics

cGVHD Subjects (n=8)	Subject Number	1	2	3	4	5	6	7	8	Summary*
Demographics &	Age	55	52	40	28	72	59	47	47	50 [45 - 56]
	Race	C	C	C	C	C	C	C	C	100% Caucasian
	Gender	M	M	M	F	M	M	M	F	25% Female
	BMI	24	24	27	14	32	17	23	34	24 [21-28]
Disease Characteristics #	Disease Histology	AL	MD	MD	MD	AL	AL	LD	AL	50% AL 38% MD 12% LD 0% Other
Transplant Characteristics $	Transplant Source	BM	PB	PB	PB	PB	PB	PB	BM	75% PB 0% CB 25% BM
cGVHD Characteristics at Study Entry	NIH Score BSA Involvement	>50%	>50%	19 - 50%	>50%	19 - 50%	>50%	1-18%	19 - 50%	1% No BSA involved 12% 1-18%BSA 38% 19-50%BSA 50% >50%BSA
	NIH Score Skin Feature %	DS	DS	DS	DS	DS	DS	DS	DS	0% No sclerotic features 0% SS 100% DS
Myoton Stiffness measurements by Sites (N/m) ^	Shin L	**878**	**1012**	631	**1318**	**892**	**1123**	**1621**	**1853**	1067 [888 - 1394]
	Shin R	**726**	**1555**	544	**1050**	**696**	**1126**	**1129**	**1924**	1088 [718 - 1235]
	Dorsal Forearm L	**674**	436	512	**1438**	426	**400**	**758**	**800**	593 [433 - 769]
	Dorsal Forearm R	**898**	451	593	**1140**	439	**388**	**781**	**1247**	687 [448 - 959]
	Upper Arm L	**488**	330	297	**462**	493	**530**	**529**	**337**	475 [336 - 502]
	Upper Arm R	**412**	331	368	**415**	514	**581**	**468**	**351**	414 [363 - 479]
	Shoulder L	**399**	790	480	**491**	598	**1093**	**725**	346	544 [460 - 741]
	Shoulder R	**471**	1191	627	**798**	555	**591**	**938**	397	609 [534 - 833]
	Chest L	**456**	332	362	**391**	649	**1088**	350	-	391 [356 - 552]
	Chest R	**361**	353	318	**1479**	484	**1348**	**334**	-	361 [344 - 916]
	Abdomen L	**312**	**274**	**179**	**152**	261	**380**	**258**	215	260 [206 - 284]
	Abdomen R	**381**	**287**	**194**	**131**	253	**402**	**275**	239	264 [228 - 310]
	Calf L	**878**	**1084**	383	**867**	878	**1210**	**971**	**808**	878 [852 - 999]
	Calf R	**754**	**1769**	390	**820**	657	**1222**	**967**	**782**	801 [729 - 1031]
	Upper Back L	-	491	682	**1388**	**677**	**1574**	**700**	-	691 [678 - 1216]
	Upper Back R	-	547	548	**918**	**754**	**958**	**653**	-	704 [575 - 877]
	Lower Back L	-	307	**563**	**261**	-	448	**328**	228	318 [273 - 418]
	Lower Back R	-	287	**457**	**516**	-	457	**336**	219	396 [299 - 457]

Control Subjects (n=10)	Subject Number	9	10	11	12	13	14	15	16	17	18	Summary*
Demographics&	Age	66	68	28	49	23	28	35	25	26	22	28 [25-46]
	Race	C	C	AA	A	C	A	A	AA	C	A	40% Calucasian
	Gender	M	M	M	F	M	F	M	M	M	F	30% Female
	BMI	31	24	29	22	22	18	25	22	29	19	23 [22-28]
Myoton Stiffness measurements by Sites (N/m)	Shin L	639	660	494	524	525	652	541	1102	686	627	632 [529-658]
	Shin R	759	627	604	468	550	623	645	998	916	598	625 [600-731]
	Dorsal Forearm L	459	330	364	377	381	471	328	392	572	480	386 [367-468]
	Dorsal Forearm R	438	420	350	403	439	502	401	363	566	390	411 [393-439]
	Upper Arm L	444	338	285	280	239	328	326	381	367	480	333 [295-377]
	Upper Arm R	429	399	301	327	309	359	288	366	315	375	343 [310-372]
	Shoulder L	586	520	404	1127	179	364	366	329	397	375	386 [364-491]
	Shoulder R	540	457	347	834	329	309	326	326	279	249	328 [313-429]
	Chest L	419	470	322	303	243	314	192	268	206	436	309 [249-395]
	Chest R	399	538	277	343	282	327	217	314	237	342	320 [278-342]
	Abdomen L	234	351	159	194	163	242	202	189	202	296	202 [190-240]
	Abdomen R	234	332	169	169	187	241	193	191	199	257	196 [188-239]
	Calf L	483	574	375	384	398	328	372	412	637	326	391 [372-465]
	Calf R	561	728	425	411	388	332	314	363	673	253	400 [340-527]
	Upper Back L	463	684	490	416	359	394	359	526	329	258	405 [359-483]
	Upper Back R	559	692	496	566	428	478	389	414	396	271	453 [401-543]
	Lower Back L	409	362	249	244	158	195	243	279	214	193	243 [200-271]
	Lower Back R	311	271	262	292	159	206	236	197	199	183	221 [198-269]

*Values are shown as Median [IQR] for continuous variables and n (%) for categorical variables.

&Demographics: C: Caucasian, , A: Asian, AA: African American, M: Male, F: Female

#Disease characteristics: AL: Acute Leukemia, MD: Myeloid Disorder (Multiple Myeloma was included in lymphoid disorders), LD: Lymphoid Disorder

$Transplant Characteristics: PB: Peripheral Blood, CB: Core Blood, BM: Bone Marrow

%NIH Score Skin Feature: SS: Superficial sclerotic feature, DS: Deep and other sclerotic feature

[-] Only 7 cGVHD patients were measured on the chest and 6 were measured on upper and lower back for patient comfort considerations.

[^] Sites affected with sclerotic cGVHD are in **bold**