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RESEARCH ARTICLE

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Fascial thickness and stiffness in hypermobile Ehlers-Danlos syndrome

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Abstract

There is a high prevalence of myofascial pain in people with hypermobile Ehlers-Danlos Syndrome (hEDS). The fascial origin of pain may correspond to changes in the extracellular matrix. The objective of this study was to investigate structural changes in fascia in hEDS. A series of 65 patients were examined prospectively—26 with hEDS, and 39 subjects with chronic neck, knee, or back pain without hEDS. The deep fascia of the sternocleidomastoid, iliotibial tract, and iliac fascia were examined with B-mode ultrasound and strain elastography, and the thicknesses were measured. Stiffness (strain index) was measured semi-quantitatively using elastography comparing fascia to muscle. Differences between groups were compared using one-way analysis of variance. hEDS subjects had a higher mean thickness in the deep fascia of the sternocleidomastoid compared with non-hEDS subjects. There was no significant difference in thickness of the iliac fascia and iliotibial tract between groups. Non-hEDS subjects with pain had a higher strain index (more softening of the fascia with relative stiffening of the muscle) compared with hEDS subjects and non-hEDS subjects without back or knee pain. In myofascial pain, softening of the fascia may occur from increase in extracellular matrix content and relative increase in stiffness of the muscle; this change is not as pronounced in hEDS.

KEYWORDS
connective tissue disorder, deep fascia, hypermobile Ehlers-Danlos syndrome, ultrasound elastography

1 | INTRODUCTION

Hypermobile Ehlers-Danlos syndrome (hEDS) is a heritable connective tissue disorder characterized by generalized joint hypermobility, joint instability, and skin changes. The hEDS population experiences a high burden of pain (Bénistan & Martinez, 2019). The pathophysiology of pain and myofascial pain, in particular, are complex. Several studies have implicated additional soft tissue structures beyond a purely muscle origin (Affaitati et al., 2011; Giamberardino et al., 2007; C. Stecco & Day, 2010; Vecchiet & Giamberardino, 1994).

Myofascial pain may correlate with increased thickness of deep fascia (A. Stecco, Meneghini, Stern, Stecco, & Imamura, 2014) with a corresponding aggregate of extracellular matrix (ECM) content (Menon, Oswald, Raghavan, Regatte, & Stecco, 2020; Menon, Raghavan, & Regatte, 2019), a phenomenon termed densification (Pavan, Stecco, Stern, & Stecco, 2014). Densification is defined as an increasing of ECM viscosity associated with alteration in gliding between fascial layers (Langevin et al., 2011) or interfaces within

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muscles, tendons, ligaments (Cowman, Lee, Schwertfeger, McCarthy, & Turley, 2015; Fourie, 2008). In addition to the fascia, there is a non-uniform increase in muscle stiffness in myofascial pain, (Müller, Aranha, & Gavião, 2015; Sikdar et al., 2009; Turo et al., 2015) associated with an increase in ECM content.

Few studies have explored the ECM in the hEDS population (Chiarelli et al., 2016; Zoppi, Chiarelli, Binetti, Ritelli, & Colombi, 2018). Understanding of how fascial stiffness and densification correlates with the clinical presentation and myofascial pain in hEDS is lacking. The objective of this study was to characterize these parameters in hEDS patients.

2 | METHODS

This IRB approved observational study involved 65 adult patients (≥18 years of age) who were examined prospectively. Twenty-seven patients had hypermobile EDS by 2017 diagnostic criteria (Malfait et al., 2017). Thirty-nine subjects without hEDS had chronic neck, knee, or back pain. All subjects consented to ultrasound examination at an outpatient Physical Medicine and Rehabilitation practice.

Three body sites, namely sternocleidomastoid muscle (SCM), the iliotibial tract (ITT), and the fascia iliaca (FI) were examined with B-mode scanning and strain elastography using the Sonimage HS-1 (Konica Minolta Corporation, Japan) and a L18-4 transducer. The patients were examined in a relaxed supine position. Strain elastography was performed via repetitive light compressions with the hand-held transducer over the areas of interest. The protocol is shown in Figure 1.

The thickness and strain ratios of the areas of interest were measured using built-in software and the strain index (SI) was calculated, as the fascia (A) to muscle (B) ratio, respectively (SI = A/B ratio) (Figure 2). Differences in SI and fascial thickness were compared using analysis of variance using XLMiner Analysis ToolPak (Frontline Systems Inc., Nevada, USA). Statistical significance was set at $p < 0.05$.

3 | RESULTS

Twenty-seven patients with hEDS (all female) and 39 controls without hEDS (54% female) were included in the analysis. Additional demographics by subgroup are shown in Table 1.

hEDS subjects had a higher mean thickness (1.8 ± 0.3 mm) in SCM deep fascia compared with non-hEDS patients with neck pain (1.5 ± 0.3 mm) and non-hEDS patients without neck pain (1.3 ± 0.2 mm). Non-hEDS subjects without neck, knee, or back pain had lower average SI (<1.00) indicating a higher level of stiffness in the fascia compared with their counterparts with neck, knee, or back pain. Non-hEDS patients with pain had a higher average SI indicating a softening of the fascia compared with a relative nonuniform stiffening of the muscle. hEDS subjects had a reduced differential in softening of the fascia compared with muscle (Table 2).

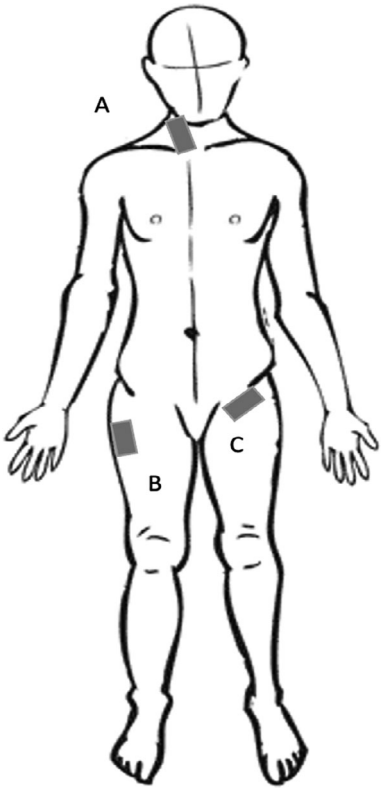

FIGURE 1 Ultrasound protocol of areas of interest. (a) Examination the SCM. The transducer was placed on the superior edge of the clavicle parallel to the SCM (A. Stecco et al., 2014). (b) Examination the ITT. The transducer was placed distally to the end of the TFL at the level of the greater trochanter in cranio-caudal direction (Flato et al., 2017). (c) Examination the FI. The transducer was placed inferior to the anterior superior iliac spine medially and parallel to the inguinal ligament (Xu et al., 2020)

4 | DISCUSSION

4.1 | Deep fascia thickness

SCM deep fascia thickness in non-hEDS subjects without neck pain (1.3 ± 0.2 mm) or with neck pain (1.5 ± 0.3 mm) were consistent with the prior report of abnormal values >1.5 mm (A. Stecco et al., 2014). hEDS patients had greater mean SCM deep fascia thickness (1.8 ± 0.3 mm) compared with non-hEDS patients with neck pain, suggesting an amplified laydown of ECM. A nonstatistically significant trend of increased thickening of the ITT and FI was seen in subjects with pain compared to subjects without pain.

The excess laydown of ECM content within fascial layers is associated with thickening of the deep fascia and the pathogenesis of myofascial pain (Hoheisel, Rosner, & Mense, 2015; Stecco et al., 2011, 2014; Vergara et al., 2020). An excess amount of ECM may increase its viscosity (Cowman et al., 2015) irritating the abundant c-fiber content of fascia (Mense, 2019), resulting in pain and dysfunction. The greater thickening of deep fascia seen in the hEDS subjects may suggest that this process is amplified in this population.

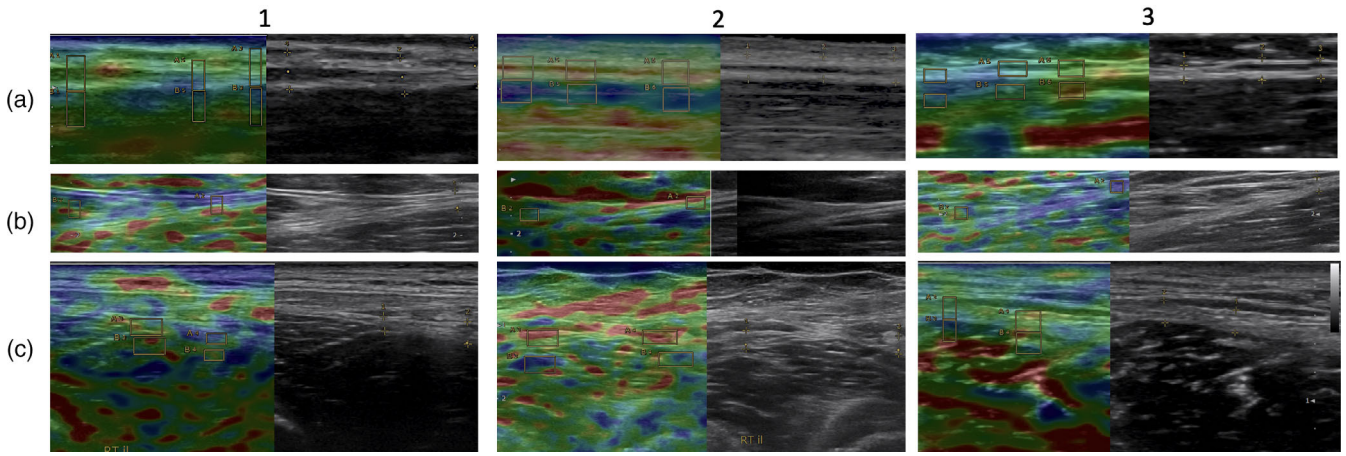

FIGURE 2 Ultrasound of areas of interest. B-mode ultrasound in black and white and strain elastography in color. Blue represents stiffer areas while red represents softer areas. Ultrasound images of subjects with 1. hEDS, 2. non-hEDS with pain, 3. non-hEDS without pain. Ultrasound image of row a. head of the SCM, row b. ITT, row c. FI. The thickness of deep fascia on the superficial SCM border was measured over three areas and the associated stiffness was measured semi-quantitatively using elastography comparing the deep fascia with the underlying muscle. The thickness of the ITT was measured where the superficial, intermediate and deep layers blended into organized fibers approximately 3 mm distal to the belly of the TFL (Flato et al., 2017). Stiffness was measured semi-quantitatively using elastography comparing the organized fibers of the ITT with the proximal TFL. The thickness of the FI was measured at two areas where it emerged from the conjoint tendon with the transversus abdominis and internal oblique abdominis and associated stiffness was measured semi-quantitatively using elastography comparing the FI with the underlying iliacus muscle. Strain ratios were measured using built-in software and the strain index (SI) was calculated, as the fascia (A) to muscle strain (B), respectively (SI = A/B ratio)

TABLE 1 Demographics of patients by subgroups

	Age (years)	Female (*n*)	Duration of pain (years)	BMI	*n*
All hEDS	35 ± 10	27	18 ± 13	21 ± 3	27
All non-hEDS	48 ± 17	21	11 ± 13	24 ± 4	39
hEDS with neck pain	35 ± 10	27	18 ± 13	21 ± 3	27
Non-hEDS with neck pain	48 ± 17	15	16 ± 14	24 ± 4	27
Non-hEDS without neck pain	47 ± 18	5	-	24 ± 5	11
hEDS with knee pain	35 ± 10	21	20 ± 13	21 ± 3	21
Non-hEDS with knee pain	54 ± 14	9	11 ± 13	26 ± 5	14
Non-hEDS without knee pain	40 ± 17	15	-	24 ± 4	17
hEDS with back pain	35 ± 10	24	18 ± 13	21 ± 3	24
Non-hEDS with back pain	49 ± 16	11	12 ± 13	23 ± 3	16
Non-hEDS without back pain	41 ± 18	1	-	25 ± 3	7

The excess laydown of ECM may occur in response to inflammation (Hoheisel et al., 2015). The phenotypic presentation of hEDS is wide and is associated with multiple inflammatory-like conditions and symptoms. Proteomic studies in hEDS showed dysregulated expression of genes involved in inflammation, pain, and immune responses in the ECM environment (Chiarelli et al., 2016, 2021). Pathologic fibroblast-to-myofibroblast transition was present and prevalent and associated with augmented levels of inflammatory mediators including metalloproteinase-9 (Zoppi et al., 2018).

4.2 | Muscle changes and palpation

Softening of the deep fascia was seen in both hEDS and non-hEDS patients with neck pain. This change was also seen in the ITT and FI and may occur from increase in ECM content that has not yet undergone increase in viscosity. A relative nonuniform increase in stiffness of the associated muscle (including its perimysium and epimysium) was seen in non-hEDS subjects with neck, knee, and back pain. This was consistent with previous sonoelastography studies of myofascial trigger points (Sikdar et al., 2009; Turo et al., 2015).

TABLE 2 Fascia thickness and strain index of areas of interest

	Fascia thickness (mm)		Strain index* (SI = A/B)	
	SCM deep fascia		A SCM deep fascia, B SCM	
hEDS with neck pain	1.8 ± 0.3	$p < 0.05$	1.32 ± 0.33	$p < 0.05$
Non-hEDS with neck pain	1.5 ± 0.3		2.35 ± 2.02	
Non-hEDS without neck pain	1.3 ± 0.2		0.88 ± 0.41	
	ITT		A ITT, B TFL	
hEDS with knee pain	2.3 ± 0.7	$p = 0.15$	1.01 ± 0.17	$p < 0.05$
Non-hEDS with knee pain	2.3 ± 0.3		1.34 ± 0.18	
Non-hEDS without knee pain	2.0 ± 0.6		0.53 ± 0.04	
	Iliac fascia		A iliac fascia, B iliacus	
hEDS with back pain	2.0 ± 0.7	$p = 0.17$	1.23 ± 0.17	$p < 0.001$
Non-hEDS with back pain	1.9 ± 0.5		2.13 ± 1.7	
Non-hEDS without back pain	1.7 ± 0.6		0.70 ± 0.06	

Abbreviations: ITT, iliotibial tract; SCM, sternocleidomastoid; TFL, tensor fascial lata.
*Higher SI indicates softening of fascia to muscle. Lower SI indicates stiffening of fascia in relation to muscle.

The muscle is a recognized source of pain in myofascial pain (Donnelly & Simons, 2019). Excess ECM with aggregation of glycosaminoglycans in the muscle itself has also been demonstrated in myofascial pain (Margalef et al., 2019). These aggregates occur in relation to connective tissue (Äärimaa et al., 2004; Kääriäinen et al., 1998) and may account for the change in stiffness seen in underlying muscle of myofascial pain points. This change is heterogeneous, but overall a stiffening is seen in the muscle (Sikdar et al., 2009; Turo et al., 2015) in relation to overall softening in areas of thickened fascia. Clinically, palpation of stiff muscle and tender points associated with myofascial pain (A. Stecco, Pirri, De Caro, & Raghavan, 2019) may be amplified by the softening of the overlying deep fascia.

In the analysis of muscle morphology, attention has to be given to the connective tissue continued within muscle such as perimysium and endomysium, both of which are composed of multiple layers of dense connective tissue with an interface filled by loose connective tissue. It cannot be excluded that muscle stiffness could be generated by an increase of the ECM (Özçakar, Ata, Kaymak, Kara, & Kumbhare, 2018; Sikdar, Shah, Gilliams, Gebreab, & Gerber, 2008) that can lead to increase of viscosity and consequent lack of gliding.

This stiffening of the underlying muscle relative to the overlying deep fascia was not as pronounced in hEDS. Previously, significant softening of the biceps brachii and brachioradialis compared to the overlying superficial fascia was seen in hypermobile spectrum disorder subjects compared to controls (Alsiri, Al-Obaidi, Asbeutah, Almandeel, & Palmer, 2019). These changes may be secondary to pathologic changes found in the ECM content and organization seen in hEDS (Chiarelli et al., 2016, 2021). Clinically, this reduced differential in stiffness between the fascia and muscle may be felt as uniform softness, making palpatory diagnosis of myofascial changes difficult in the hEDS population.

4.3 | Gliding

Deep fascia densification is also associated with alteration in gliding properties (Cowman et al., 2015; Langevin et al., 2011). A possible etiology is the alteration of hyaluronan, a high molecular weight glycosaminoglycan of the ECM. Inflammatory conditions increase the concentration of hyaluronan with macromolecular crowding, increased viscosity, and reduced lubrication and sliding movement of fascia (Cowman et al., 2015). Changes in gliding properties of fascia in hEDS may also occur from the fibroblast-to-myofibroblast transition associated with alteration in $\alpha v\beta 3$ integrin-ILK complexes in focal adhesions (Zoppi et al., 2018).

These alterations of gliding interactions may influence joint mobility and lead to impaired biomechanics, altered alignment, proprioceptive dysfunction, pain (Cowman et al., 2015; Fourie, 2008), and predisposition to future injuries (Stecco et al., 2010, 2011). The thicker ECM seen in hEDS patients suggests that this process may be amplified in hEDS and may associated with the high prevalence of joint instability (Morlino et al., 2017) and proprioceptive dysfunction (Clayton, Jones, & Henriques, 2015; Scheper et al., 2017).

4.4 | Stabilization

Hip dysfunction has been implicated in back pain (Prather, Cheng, Steger-May, Maheshwari, & Van Dillen, 2017; Sadeghisani et al., 2015). The FI thickness was not significantly different; however, there were differences in FI stiffness between groups. A significant softening of the FI compared to a relative stiffening of the underlying iliacus muscle was seen in non-hEDS subjects with back pain. The change in stiffness may reflect changes in ECM content, quality, and gliding that may contribute to pathologic hip mechanics previously reported in relationship to back pain (Sadeghisani et al., 2015). In addition, the lateral one-third of the FI gives rise to the transversus abdominis and internal oblique

abdominis forming a conjoint tendinous sheet (Cramer, Darby, & Cramer, 2014; Xu et al., 2020) and is important for the stability of the lumbar region (Fan et al., 2018). Alteration of the stiffness in the FI may contribute to instability of the lumbar region through this complex fascial relationship and contribute to back pain.

This differential in stiffness was reduced in hEDS subjects with an overall softening of both the FI and underlying iliacus. Both abdominal/pelvic girdle muscles and the associated fascia are important for stability of the lumbar region (Dufour, Vandyken, Forget, & Vandyken, 2018; Fan et al., 2018), and changes in the stiffness in hEDS may be associated with the high prevalence of back pain (67.2–75%) (Mazziotti et al., 2016; Stanitski, Nadjarian, Stanitski, Bawle, & Tsipouras, 2000). The anterior hip complex along with the muscles, tendons, and connective tissue superficial to the capsule–labral complex plays a role in the stabilization of the hip joint (Fabricant, Bedi, De La Torre, & Kelly, 2012). The softening of the FI in hEDS and the likely associated changes in the mechanics of the anterior hips (Jacobsen et al., 2018) may also be contributory to the instability seen in the hips of hEDS patients (25–29.2%) (Morlino et al., 2017).

4.5 | Strength

Alterations of the ITT are associated with knee and hip pathology (Flato et al., 2017). The ITT thickness was not significantly different between groups and consistent with the range of 1.10–3.34 mm previously reported (Fede et al., 2018). Significant softening of the ITT relative to stiffening of the TFL was seen in non-hEDS subjects with knee pain compared to their counterparts without knee pain. Prior studies of the distal ITT at the lateral femoral epicondyle have been inconsistent (Flato et al., 2017; Friede, Klauser, Fink, & Csapo, 2020) possibly because the pathology may be occurring at the proximal ITT in knee pain as this study demonstrates.

This differential in stiffness of the ITT was reduced in the hEDS subjects. Lower tendon stiffness and muscle tension is seen in hEDS/hypermobile spectrum disorder, in particular the patellar and Achilles tendons (Alsiri et al., 2019; Rombaut et al., 2012) and now the ITT. This may be associated with the high prevalence of knee pathology (17.7–26%) (Morlino et al., 2017) and pain seen in hEDS patients.

Overall, changes in the fascia, tendon, and muscle seen in hypermobile EDS may correspond to the associated 30–49% reduction in strength seen in this population (Rombaut et al., 2012; Scheper et al., 2017). Prior animal study has shown that connective tissue contained in muscle alone accounts for 30% of muscle force (Huijing & Baan, 2003). These strength changes are also associated with reduced muscle endurance and diminished functional activity, particularly walking and bending (Rombaut, Malfait, De Wandele, Taes, et al., 2012).

5 | CONCLUSION

This analysis provides insight into fascial characteristics in hEDS-stiffness and thickness changes in the muscle and fascia. hEDS patients exhibit increased deep fascia thickness compared to non-hEDS counterparts. In non-hEDS subjects, an increase of fascial thickness is recognized in symptomatic subjects; however, a softening of fascia with associated stiffening of the underline muscle infrastructure occurs with myofascial pain. Softening of the deep fascia may occur from increase in ECM content, that has not undergone change in viscosity, and relative increase in stiffness of the associated muscle infrastructure (perimysium and epimysium). This change is not as pronounced in hEDS. These changes in the deep fascia, muscle, and tendons of hEDS patients may be associated with alteration in gliding properties leading to pain, joint instability, and dysfunction.

The limitation of this study was the single-center design with low sample size at risk for type II error. Additionally, ultrasound elastography is a semi-quantitative methodology and dependent on operator experience. Nevertheless, despite the preliminary nature of our data, this study highlights important fascia characteristics in the hEDS population and possibilities for diagnosis and treatment. Assessment of stiffness and tissue glide with sonoelastography may further support diagnosis of hEDS and may guide treatment intervention. Repeated evaluation with sonoelastography after treatment may aid in the assessment of treatment efficacy.

CONFLICT OF INTEREST

None.

AUTHOR CONTRIBUTIONS

Tina J. Wang, Antonio Stecco: manuscript prepared, conceptualized, and researched; Tina Wang data research and analyzed, clinical care. All authors read and approved the final manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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