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The impact of hypermobility spectrum disorders on musculoskeletal tissue stiffness: an exploration using strain elastography

Najla Alsiri[1] · Saud Al-Obaidi[2] · Akram Asbeutah[2] · Mariam Almandeel[1] · Shea Palmer[3]

Abstract

Hypermobility spectrum disorders (HSDs) are conditions associated with chronic joint pain and laxity. HSD's diagnostic approach is highly subjective, its validity is not well studied, and it does not consider many of the most commonly affected joints. Strain elastography (SEL) reflects musculoskeletal elasticity with sonographic images. The study explored the impact of HSD on musculoskeletal elasticity using SEL. A cross-sectional design compared 21 participants with HSD against 22 controls. SEL was used to assess the elasticity of the deltoid, biceps brachii, brachioradialis, rectus femoris, and gastrocnemius muscles, and the patellar and Achilles tendon. SEL images were analyzed using strain index, strain ratio, and color pixels. Mean strain index (standard deviation) was significantly reduced in the HSD group compared to the control group in the brachioradialis muscle 0.43 (0.10) vs. 0.59 (0.24), patellar 0.30 (0.10) vs. 0.44 (0.11), and Achilles tendons 0.24 (0.06) vs. 0.49 (0.13). Brachioradialis muscle and patellar tendon's strain ratios were significantly lower in the HSD group compared to the control group, 6.02 (2.11) vs. 8.68 (2.67) and 5.18 (1.67) vs. 7.62 (1.88), respectively. The percentages (%) of red color (soft tissues) in the SEL images were significantly increased in the HSD group compared to the control group in the biceps brachii muscle, 34.72 (7.82) vs. 26.69 (3.89), and Achilles tendon, 18.14 (13.21) vs. 5.59 (8.23) ($p \leq 0.01$). The elasticity of the musculoskeletal system seems to be lower in people with HSD. SEL could be a supplementary tool for diagnosing and monitoring HSD.

Keywords Diagnosis · Hypermobility spectrum disorders · Joint hypermobility syndrome · Muscle · Strain elastography · Tendon

Introduction

"Hypermobility spectrum disorder" (HSD) refers to the conditions observed with chronic synovial joint pain and hypermobility resulting from the connective tissue deficiency [1, 2]. The term HSD was introduced in 2017 to highlight the wide heterogeneities within joint hypermobility-related conditions and to replace the terms "joint hypermobility syndrome" (JHS) and "Ehlers-Danlos syndrome hypermobility type"

(EDS-HT) [2]. JHS and EDS-HT greatly overlap as they are heritable connective tissue disorders associated with symptomatic multiple joint hypermobility in the absence of systemic inflammation [1–3]. EDS-HT additionally involves skin hyperextensibility and smoothness, velvety skin, and recurrent joint dislocations [1–3]. HSD diagnosis is likely to capture the majority of patients previously diagnosed as JHS/EDS-HT, although a discrete group of patients with more severe symptoms may meet the diagnostic criteria of "hypermobile EDS" (hEDS) [3]. The present research is specific to HSD.

Based on meta-analysis exploring joint hypermobility-related disorders, Scheper et al. (p.12) stated: "Clinicians should be aware that within these disorders, a large variability in phenotype exist" [4]. HSD considered the wide variability of joint hypermobility-related conditions; therefore, it involves four phenotypes: "localized HSD," hypermobility in one or more joints but less than five joints; "peripheral HSD," hypermobility in hands and feet; and "generalized HSD," hypermobility in five or more than five joints [2]. Joint

✉ Najla Alsiri
   dr.alsiri@outlook.com

1   Al-Razi Orthopedic and Rehabilitation Hospital, Kuwait
    City, Kuwait

2   Faculty of Allied Health Sciences, Kuwait University, Kuwait
    City, Kuwait

3   Faculty of Health and Applied Sciences, University of the West of
    England, Bristol, UK

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hypermobility reduces with age; therefore, the "historical HSD" phenotype was introduced [2, 5].

The term HSD has been newly introduced; therefore, there is a lack of research using the new criteria. However, HSD captures the previously used terms of JHS and EDS-HT. JHS had a prevalence figure of 30% of patients attending a musculoskeletal triage clinic in London [6]. JHS etiology was related to abnormalities in the genes encoding collagen, hormonal imbalance, or environmental factors [1, 7, 8]. The symptomatic manifestation of JHS varied from mild to disabling, including chronic joint pain and hypermobility, muscle weakness, proprioception impairment, recurrent injuries and dislocation, fibromyalgia, and osteoarthritis [1, 9]. JHS could be associated with cardiovascular deterioration, gastrointestinal disturbances, and psychological health decline [10]. The prevalence and disabling impact of HSD provide a remarkable rationale for optimizing strategies for its identification and diagnosis.

Despite the importance of the new diagnostic approaches for HSD, they are likely to encounter various limitations. Like the Brighton criteria (previously used for JHS), the HSD criteria are based on subjective questionings and clinical examinations (such as the Beighton score of joint mobility) [1, 11]. Therefore, the criteria are highly dependent on the examiner's skill and experience, and patient memory. Recent meta-analysis and a systematic review concluded that the diagnostic criteria are inadequate, where their validity has not been well studied [4, 12]. The current diagnostic approaches do not assess many of the most commonly affected joints in JHS such as the shoulder, 85.2% prevalence; neck, 59.3% prevalence; pelvis; hip, 66.7% prevalence; and ankle and foot, 77.8% prevalence [13]. Using the current diagnostic approach, it is easy to reach the diagnostic cutoff point of 4/9 purely with fingers and thumb hypermobility [14]. Therefore, there is a need to identify new diagnostic approaches for people with HSD.

Diagnostic imaging advances could help people with HSD. Strain elastography (SEL) is an ultrasound-based system designed to examine the elasticity of human structures by providing color-coded images [15]. Administering SEL for examining HSD may be valuable, as musculoskeletal structures could show significant laxity. The mutation identified in the genes encoding collagen in hypermobility-related disorders could reduce the mechanical rigidity of the connective tissues in the musculoskeletal system, and this laxity may be identified using SEL. Other factors could lead to significant softening of the HSD musculoskeletal system, including muscular weakness, reduced muscle-tendon stiffness, the pain-muscular inhibition cycle, and reduced activity [1, 16, 17]. Various studies have identified the impact of hypermobility-related disorders on tissue stiffness including skin extensibility, impaired Achilles tendon stiffness, and muscle activation and force production [16, 18, 19]. Other studies found no impact of

hypermobility-related disorders on skin extensibility, patellar tendon active stiffness, and hamstring muscle energy absorption [20–22]. The insignificant differences could be related to type II error due to the studies' small sample sizes, which ranged from eight to nine participants per group [20, 22]. People with HSD could lose the feature of joint hypermobility due to the condition pathological course or aging factors, which would make the diagnosis and condition monitoring more difficult. SEL could aid in providing real-time images for the elasticity degree without relying on joint hypermobility feature. Identifying significant elasticity with SEL in certain muscle groups might be important for the classification of HSD patients.

Two studies have examined the musculoskeletal elasticity in people with hypermobility-related disorders using SEL. The Achilles tendon was explored in a 10-year-old boy [23]. SEL images were analyzed qualitatively showing an increase in the green and red areas, which suggested an increase in the Achilles tendon laxity [23]. SEL feasibility was studied in ten participants with JHS against ten controls [17]. Alsiri found no significant differences between the two groups in gastrocnemius medius elasticity, which could be a type II error due to the small sample size [17]. The current study introduces a novel exploration that aims to identify the impact of HSD on musculoskeletal elasticity with SEL using a larger sample size and further anatomical sites. The study clinical importance could be enhanced by exploring the relationship of musculoskeletal elasticity with joint pain. Joint pain is a dominant feature and complaint, and an essential diagnostic element for HSD [1, 2]. Muscles and tendons are vital components in the joint stabilization system. Reduced stiffness might create deficiency in joint support which could lead to microtrauma and instability, ultimately leading to joint pain [24, 25]. It is hypothesized that joint pain would be higher with softer musculoskeletal structures. The study objective was to examine the impact of HSD on the elasticity of the musculoskeletal system.

Materials and methods

Participants

A cross-sectional research design compared musculoskeletal elasticity of a HSD group against a control group. Kuwait Ministry of Health Ethical Committee approved the study (571/2017). Patients were recruited from an orthopedic hospital using convenience sampling [26]. Four physiotherapists assessed their patients against the HSD classification, including the Beighton score. HSD subdivisions are localized, peripheral, generalized, and historical HSD [2]. The Beighton score is used to assess joint hypermobility including the fifth metacarpophalangeal joint dorsiflexion, > 90°; thumb

opposition, if reached the forearm volar aspect; elbow hyperextension, > 10°; knee hyperextension, > 10°; and spinal hypermobility [27]. A Beighton score of ≥ 5/9 was used to distinguish Generalized HSD from other HSD categories [2, 3].

Patients were identified from physiotherapy department referrals. All patients referred to the four physiotherapists were screened against the HSD subcategories [2]. The chief researcher (NA) screened all patients who attended for the outpatient orthopedic clinic. Recruitment packs were provided for identified patients. Patients who were willing to participate contacted the chief researcher. The chief investigator had more than 4-year experience in diagnosing JHS and was trained in HSD classification. Training in the HSD classification was provided to the four physiotherapists. Participants in the control group were recruited from among the staff at the Ministry of Health and their relatives through advertising emails and posters. A matching-pairs design was used to ensure homogeneity between the two groups in terms of gender and age. The examination lasted from June to December 2017 in the Radiology department. Informed consent was obtained from participants.

Women and men aged ≥ 18 years were included in the control and HSD group. Healthy adults were excluded from the control group if they had ≥ 4/9 in the Beighton score with chronic multiple joint pain or met the criteria for any of the HSD subcategories. The exclusion criteria for the two groups were upper/lower limbs' injuries during the last 3 months; upper/lower limbs' fractures or surgery in the last year; pregnancy; 1 year postpartum due to ligament laxity; other connective tissues disorders including Ehlers-Danlos Syndrome; and other conditions which might compromise muscular strength. Participants were included in the HSD group if they met the criteria for HSD [2]. Chronic multiple joint pain for longer than 3 months was the primary symptomatic manifestation for the HSD group and was self-reported by patients [6, 12]. The secondary symptomatic manifestations were recurrent injuries and dislocations.

Instrumentation

Compression SEL (Voluson E8; GE Healthcare Technologies, Milwaukee, WI, USA) was used to examine musculoskeletal structures elasticity. SEL is a clinically applicable ultrasound-based system, which measures tissues perpendicular deformation in response to mild strain induced using the examination probe [15, 28]. SEL converts the compression into strain colored images, where each color refers to a certain elasticity degree. SEL follows the mechanical law of hard tissues deforming less and soft tissues deforming more when subjected to the same force [15, 28, 29].

SEL reliability has been demonstrated for examining the biceps brachii muscle, plantar fascia, and the Achilles tendon [29–31]. An intra-rater reliability study was conducted for the

22 participants from the control group in this study, by repeating the examination twice in the same day with 1-h interval. The study showed moderate to excellent intra-rater reliability, with ICCs (type 3,1) ranging from 0.734 (95% confidence interval 0.279–0.903) to 0.950 (0.848–0.983), for examining the deltoid, biceps brachii, brachioradialis, rectus femoris, gastrocnemius medius muscles, and Achilles tendon. The same operator (NA) conducted the examination. NA has a doctorate in musculoskeletal physiotherapy, has received postgraduate training in musculoskeletal ultrasound, and has 4-year experience in performing elastography and musculoskeletal ultrasound. The piloting stage was supervised by an associate professor in radiological sciences (AA) who has 20-year experience in ultrasonography. It was not practical to blind the operator as she needed to confirm the eligibility criteria using the HSD classification. Images were saved using the participants' ID, and the analysis was performed blind to health status being entered to the relevant participant file. SEG's visual quality indicator was used to standardize the applied compression magnitude [28].

Joint pain intensity was measured using visual analogue scales (VASs). The VAS is a pain assessment tool, which is highly valid, reliable, and sensitive [32]. It is a 10-cm length line with two descriptors at the two anchors: no pain and worst possible pain. Twelve VASs were used to assess the shoulder, elbow, wrist, hip, knee, and ankle joints, bilaterally. Pain assessment was limited to a 1-week period to reduce recall error by asking, "please rate the average pain over the past week in each of the following joints."

Sample size determination

Sample size calculation was based on Lee et al.'s study who used SEL with strain ratio to examine rotator cuff tendinopathy [33]. The means (standard deviation) for grade 0, 2.92 (2.13), and grade 3, 12.3 (0.00), tendinosis were used to calculate the effect size of 0.95. An appropriate sample size was estimated to be 20 at (α) 0.05 and a power (1 − ß) of 80% [34].

Data collection procedures

After completing the demographic sheet and VASs, the dominant upper and lower limbs were examined. The dominant side was self-declared by the participant by reporting the hand used for writing and the leg used for kicking a ball [35, 36]. SEL images were recorded by applying perpendicular force to the target area using the SEL transducer through simultaneous compressions and decompressions (Fig. 1). Five muscles were examined: deltoid, biceps brachii, brachioradialis, rectus femoris, and gastrocnemius medius. Additionally, the patellar and Achilles tendons were tested. The upper and lower boundaries of the strain index were measured with the SEL (Fig. 1). The higher boundary of strain index refers to the elasticity of
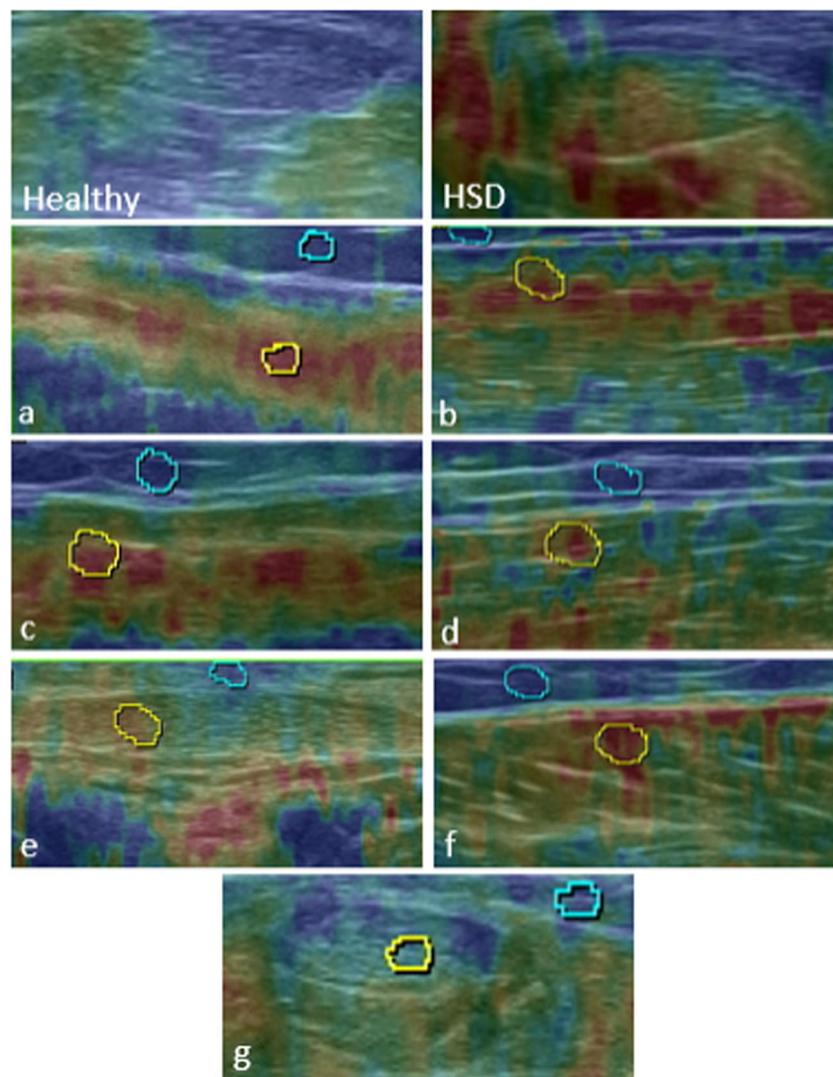
Fig. 1 Transverse strain elastography images for the Achilles tendon for a healthy participant (Healthy), and for a participant with hypermobility spectrum disorder (HSD). Red refers to soft tissues, green refers to intermittent elasticity, and blue refers to hard tissues. The size of the image box was manually adjusted to include the area of interest with adjacent subcutaneous fat as a reference. Images from **a** to **g** are for one participant with HSD, where the red color mostly dominated SEG images. The images from **a** to **g** show the tracing approach used to attain the higher and lower boundary of strain index following the manufacturer guidelines. **a** Deltoid muscle. **b** Biceps brachii muscle. **c** Brachioradialis muscle. **d** Rectus femoris muscle. **e** Patellar tendon. **f** Gastrocnemius medius muscle. **g** Achilles tendon. Following standardized procedure, the reference area selected was always superior to the area of interest but not directly above it, following the assumption proposed by the European Federation of Societies for Ultrasound in Medicine and Biology that the stress is uniformly distributed in SEL. Initially, an area encoding red pixels within the area of interest was selected to represent the higher boundary of strain index (highlighted with yellow traces). The relatively softest area was selected in cases where red pixels were not displayed, as in **g**. Then, an area encoding blue pixels was selected from the subcutaneous fat layer above the area of interest to represent the lower boundary of strain index (highlighted with blue traces) [37]. The two areas were selected to be as adjacent as possible to each other to ensure that the two areas were subjected to similar compression magnitude. Muscles and tendons are distinct structures and lack fat tissues that could serve as a reference. Using subcutaneous fat as a reference is the most applicable setup for musculoskeletal SEL, with comparable reliability to using alternative reference areas at other depth levels [37]. Representative reference tissue may be limited and sometimes difficult to obtain with comparable size and position to the area of interest; however, the size of the reference area has no significant influence on strain ratio [37]. The sizes of the two traced areas in the present investigation ranged from 0.60 to 1.00 cm^2 and were set to be as superficial as possible [37]

the target area, and the lower boundary of strain index refers to subcutaneous fat elasticity. The lower the strain index, the softer the examined structure is, and vice versa.

The upper limb structures were examined then the lower limb structures. As the examined structures were superficial a linear-array high-frequency transducer was used (6–15 MHz) as it penetrated 4–5 cm beneath the skin. The examinations were conducted by the operator in a sitting position, and the probe was maintained at a perpendicular angle to the skin. The middle fibers of deltoid muscle were examined longitudinally

in sitting, with a neutral shoulder position and supinated forearm [38]. The biceps brachii common muscle belly (5 cm above the elbow line), and brachioradialis muscles (5 cm below the elbow line laterally) were scanned longitudinally in supine, with a neutral shoulder position and elbow extension and supination [39].

In supine, with knee extension, the rectus femoris muscle was examined longitudinally (10 cm above the knee line), and the patellar tendon was examined transversely (midpoint between the inferior pole of the patella and the tibial tubercle). In prone, with knee extension and the feet in a relaxed position over the plinth edge, the gastrocnemius medius muscle was examined longitudinally (at 30% of its proximal length from the popliteal fossa midpoint to midpoint between the ankle malleoli). In the same position, the Achilles tendon was examined in a transverse plane (mid-position between the two malleoli) [40]. Each structure was examined two to three times; then, one image was saved for analysis according to the compression magnitude sufficiency examined with SEL visual quality indicator. By tracing the target area and subcutaneous fat, the SEL calculates the higher and lower boundary of strain index in real time. The strain ratio was obtained from the ratio of the strain of the target area (numerator) and subcutaneous fat (denominator) [41].

Statistical analysis

Statistical Package for Social Sciences (SPSS 23, IBM Corp., Armonk, NY, USA) was used. SEL images were analyzed semi-quantitatively through the strain index, strain ratio, and color pixel analysis with ImageJ; a Java-based image processor (U. S. National Institute of Health, Bethesda, MD, USA). ImageJ counts the pixels of the red, green, and blue color with a downloaded plugin in ImageJ; then, the percentages of each color was determined to compensate for differences in cross-sectional area between participants [17]. Data normal distribution was checked with histograms then objectively confirmed with Shapiro-Wilk tests; therefore, independent sample t tests were used. The level of p value for statistical significance was set as ≤ 0.01. The intensity of joint pain was measured and correlated with elasticity using Pearson product correlation coefficient. Only pain in joints adjacent to each anatomical structure was included in this analysis.

Results

Twenty-one participants in the HSD group were compared against 22 participants in the control group. The demographic characteristics are summarized in Table 1, indicating homogeneous groups in term of age, sex, height, weight, and body mass index. Regarding ethnicity, the HSD group included three Asian men, one Indian man, 16 Asian women, and one

Table 1 Demographic characteristics: mean (standard deviation) of the HSD and control group

	HSD group, $n = 21$	Control group, $n = 22$	p value
Age (years)	35.57 (14.89)	34.72 (7.00)	0.81
Sex	17 women, 4 men	18 women, 4 men	0.94
Height	161.11 (7.23)	162.63 (7.80)	0.51
Weight	72.66 (17.91)	74.72 (15.41)	0.68
Body mass index	27.99 (6.90)	28.06 (4.42)	0.96
Beighton score	4.71 (1.82)	0.90 (1.01)	$\leq 0.001^*$

*Statistically significant difference at $p \leq 0.01$ with independent sample t test

white British woman. The control group included four Asian men, 15 Asian women, and three Indian women. The HSD group included 14 participants with generalized HSD, six participants with localized HSD, and one participant with historical HSD [3]. Three participants in the HSD group and one participant in the control group were left side dominant. Images with artifact and tracing error were excluded: one image for the rectus femoris muscle from the HSD group, two images for the deltoid, and two images for the biceps brachii muscles from the control group. All the results present mean values.

The higher boundary of the strain index for the HSD group point toward reductions in all the examined structures except for the biceps brachii muscle (Table 2). Three of the observations were statistically significant including the brachioradialis muscle, patellar tendon, and Achilles tendon ($p \leq 0.01$) (Table 2). There were no significant differences between the two groups in the lower boundary of the strain index (Table 2). The strain ratios reveal statistically significant reduction in the elasticity of the brachioradialis muscle, and the Achilles tendon in the HSD group ($p \leq 0.01$) (Table 2).

Color pixel analysis shows a higher percentage of red color in all the examined musculoskeletal structures in the HSD group, yet two of the observations were statistically significant including the biceps brachii, and Achilles tendon ($p \leq 0.01$) (Table 3). The results of the HSD group demonstrate a reduction in the percentage of blue color in all the examined structures; however, three of the seven observations were statistically significant including the biceps brachii, brachioradialis, and the Achilles tendon ($p \leq 0.01$) (Table 3). No significant differences were noticed between the two groups in the percentages of green color (intermittent elasticity) ($p \geq 0.01$) (Table 3).

Significant differences were found between the two groups in joint pain intensity, $p \leq 0.01$ (Table 4). In the HSD group, the greatest pain was reported in the knee joint bilaterally, followed by dominant hip joint, then the shoulder joint bilaterally (Table 4). Moderate correlations were identified between the elasticity of the biceps brachii muscle and pain

Table 2 Comparison of the elasticity of the musculoskeletal structures of the hypermobility spectrum disorders group against a control group analyzed with strain index and strain ratio, mean (standard deviation)

Examined area	Lower boundary of strain index					Higher boundary of strain index					Strain ratio				
	HSD group	Control group	p value	Mean difference	95% CI	HSD group	Control group	p value	Mean difference	95% CI	HSD group	Control group	p value	Mean difference	95% CI
Deltoid muscle	0.05 (0.03)	0.05 (0.01)	0.72	−0.002	−0.01, 0.01	0.44 (0.07)	0.48 (0.09)	0.24	0.03	−0.02, 0.08	11.03 (8.95)	9.48 (2.54)	0.45	1.55	−5.75, 2.65
Biceps brachii muscle	0.06 (0.02)	0.08 (0.02)	0.05	0.01	−0.00, 0.03	0.49 (0.09)	0.45 (0.07)	0.18	−0.03	−0.09, 0.01	10.45 (10.71)	5.79 (1.19)	0.06	4.65	−9.55, 0.24
Brachioradialis muscle	0.07 (0.02)	0.07 (0.02)	0.47	−0.006	−0.02, 0.01	0.43 (0.10)	0.59 (0.24)	0.01*	0.15	0.03, 0.27	6.02 (2.11)	8.68 (2.67)	≤0.001*	2.65	1.17, 4.14
Rectus femoris muscle	0.09 (0.03)	0.08 (0.02)	0.33	−0.009	−0.02, 0.00	0.42 (0.09)	0.45 (0.09)	0.38	0.02	−0.03, 0.08	5.10 (1.68)	6.00 (1.94)	0.11	0.89	−0.23, 2.03
Patellar tendon	0.06 (0.02)	0.05 (0.01)	0.72	−0.001	−0.01, 0.00	0.30 (0.10)	0.44 (0.11)	≤0.001*	0.13	0.07, 0.20	5.18 (1.67)	7.62 (1.88)	≤0.001*	2.44	1.34, 3.53
Gastrocnemius medius muscle	0.06 (0.03)	0.06 (0.03)	0.60	0.005	−0.01, 0.02	0.48 (0.14)	0.57 (0.19)	0.11	0.08	−0.02, 0.18	10.17 (7.64)	9.70 (4.70)	0.81	0.47	−4.43, 3.48
Achilles tendon	0.05 (0.03)	0.07 (0.02)	0.18	0.01	0.00, 0.02	0.24 (0.06)	0.49 (0.13)	≤0.001*	0.25	0.19, 0.31	6.24 (5.90)	7.56 (2.33)	0.34	1.32	−1.52, 4.16

The higher boundary of strain index refers to the elasticity of the area of interest, and the lower boundary of strain index refers to the elasticity of the subcutaneous fat tissues. The softer the examined structure because the strain ratio has been calculated from the ratio of the area of interest, numerator, and adjacent subcutaneous fat, denominator

CI confidence interval

*Statistically significant difference at $p \leq 0.01$ with independent sample t test

Table 3 Comparison of the elasticity of the musculoskeletal structures of the hypermobility spectrum disorder (HSD) group against a control group analyzed with ImageJ by measuring the percentages of the color pixels: mean (standard deviation)

Examined area	Percentage of red color pixel					Percentage of green color pixel					Percentage of blue color pixel				
	HSD group	Control group	p value	Mean difference	95% CI	HSD group	Control group	p value	Mean difference	95% CI	HSD group	Control group	p value	Mean difference	95% CI
Deltoid muscle	34.04 (6.70)	28.62 (7.86)	0.02	−5.42	−10.08, −0.75	41.80 (8.06)	40.28 (3.88)	0.46	−1.52	−5.64, 2.60	24.13 (11.18)	31.07 (8.44)	0.03	6.93	0.54, 13.33
Biceps brachii muscle	34.72 (7.82)	26.69 (3.89)	≤0.001*	−8.02	−11.96, −4.08	44.05 (3.56)	43.78 (3.50)	0.80	−0.27	−2.50, 1.96	21.20 (5.99)	29.39 (4.77)	≤0.001*	8.19	4.75, 11.62
Brachioradialis muscle	34.54 (10.20)	28.22 (9.88)	0.04	−6.31	−12.50, −0.12	44.69 (4.20)	42.46 (6.08)	0.17	−2.23	−5.46, 1.00	20.75 (7.43)	29.29 (11.62)	≤0.001*	8.54	2.50, 14.58
Rectus femoris muscle	37.73 (11.41)	29.58 (10.38)	0.02	−8.14	−15.03, −1.25	41.95 (6.09)	43.73 (5.69)	0.33	1.78	−1.94, 5.50	20.29 (7.39)	26.66 (10.80)	0.03	6.36	0.48, 12.24
Patellar tendon	27.69 (16.97)	20.31 (13.05)	0.11	−7.38	−16.68, 1.91	42.94 (11.31)	43.41 (8.12)	0.87	0.47	−5.56, 6.52	29.34 (18.29)	36.25 (16.63)	0.20	6.90	−3.85, 17.66
Gastrocnemius medius muscle	34.28 (9.17)	30.38 (8.60)	0.15	−3.89	−9.37, 1.57	45.87 (4.48)	46.50 (3.81)	0.62	0.62	−1.93, 3.18	19.82 (7.88)	23.10 (7.54)	0.17	3.27	−1.47, 8.02
Achilles tendon	18.14 (13.21)	5.59 (8.23)	≤0.001*	−12.54	−19.29, −5.79	43.60 (12.29)	37.56 (19.54)	0.23	−6.04	−16.15, 4.06	38.23 (17.35)	56.82 (22.81)	≤0.001*	18.58	6.06, 31.11

The red color refers to soft structures, the green color refers to structures with intermittent elasticity and the blue color refers to hard structures

CI confidence interval

*Statistically significant difference at $p \leq 0.01$ with an independent sample t test

Table 4 The intensity of joint pain measured using visual analogue scales for the upper and lower limb joints for the hypermobility spectrum disorder group and the control group, mean (standard deviation)

	HSD group (n = 21)	Control group (n = 22)	p value	Mean difference	95% CI
Dominant shoulder pain	3.25 (3.56)	0.25 (0.81)	≤ 0.001*	− 2.99	− 4.57, − 1.42
Non-dominant shoulder pain	3.02 (3.16)	0.05 (0.27)	≤ 0.001*	− 2.91	− 4.25, − 1.58
Dominant elbow pain	2.97 (3.08)	0.13 (0.63)	≤ 0.001*	− 2.06	− 3.44, − 0.67
Non-dominant elbow pain	1.56 (3.06)	0.00 (0.00)	≤ 0.001*	− 1.56	− 2.88, − 0.24
Dominant wrist pain	2.59 (3.02)	0.00 (0.00)	≤ 0.001*	− 2.59	− 3.89, − 1.29
Non-dominant wrist pain	2.09 (2.67)	0.00 (0.00)	≤ 0.001*	− 2.09	− 3.24, − 0.93
Dominant hip pain	3.95 (4.13)	0.27 (1.04)	≤ 0.001*	− 3.67	− 5.51, − 1.84
Non-dominant hip pain	2.58 (3.30)	0.00 (0.00)	≤ 0.001*	− 2.58	− 4.00, − 1.15
Dominant knee pain	4.08 (3.70)	0.15 (0.56)	≤ 0.001*	− 3.92	− 5.53, − 2.31
Non-dominant knee pain	4.25 (3.57)	0.41 (1.33)	≤ 0.001*	− 3.83	− 5.48, − 2.19
Dominant ankle pain	2.80 (3.45)	0.00 (0.00	≤ 0.001*	− 2.80	− 4.28, − 1.31
Non-dominant ankle pain	2.37 (3.52)	0.00 (0.00)	≤ 0.001*	− 2.37	− 3.88, − 0.85

CI confidence interval

*Statistically significant difference at $p \leq 0.01$ with an independent sample *t* test

intensity at the shoulder, and elbow joints, and between knee joint pain and the elasticity of the patellar, and Achilles tendon, $r \geq 0.4$ (Table 5).

Discussion

The impact of HSD on the elasticity of the musculoskeletal system was identified. SEL images were analyzed semi-quantitatively using the strain index, strain ratio, and color pixel analysis. All analysis methods led to similar results of increased musculoskeletal elasticity in the HSD group. The results of the higher boundary of strain index point toward increased softening of the examined structures. Three of the observations were statistically significant, including the brachioradialis muscle, patellar tendon, and Achilles tendon. The deltoid, rectus femoris, and gastrocnemius medius muscles showed increased elasticity in the HSD group, but the changes have not reached statistical significance. In contrast, the higher boundary of strain index for the biceps brachii muscle was higher in the HSD group, indicating a stiffer biceps brachii muscle when compared to the control group, yet this observation has not reached statistical significance. Alternatively, the biceps brachii muscle could be stiffer in people with HSD as a compensatory mechanism adopted to control elbow hypermobility. The biceps brachii muscle is

essential for daily activities, which could increase the muscular tone. The strain ratio also demonstrated statistically significant reductions in the elasticity of the brachioradialis muscle and patellar tendon in the HSD group. Similarly, color pixel analysis showed greater elasticity and lesser stiffness in the musculoskeletal structures of the HSD group. Three observations were statistically significant including the biceps brachii muscles, brachioradialis muscles, and the Achilles tendon. The deltoid, rectus femoris, and gastrocnemius medius muscles and the patellar tendon also showed increased elasticity and reduced stiffness in the HSD group. Color pixel analysis for the biceps brachii, which showed increased elasticity, contradicting the strain index and strain ratio. However, the sample size was based on large effect size of 0.95, which might indicate that the observed differences need to be confirmed with larger sample size study.

Two studies explored musculoskeletal elasticity in hypermobility-related disorders using SEL [17, 23]. Kocyigit et al. examined a boy with generalized joint laxity and qualitatively analyzed the SEL image of the Achilles tendon [23]. An increase in the red (soft tissues) and green (intermittent elasticity) colors were reported [23], supporting the current study, where the SEL images of the HSD group showed a statistically significant increase in the red color and reduction in the blue color (hard tissues) [23]. The green color was also increased in the HSD group, but this

Table 5 Correlation between the intensity of joint pain at the dominant side and the elasticity of the musculoskeletal system measured using the higher boundary of the strain index (HSI), percentage of red and blue color pixels

Examined structure	Related joint	
Deltoid muscle	Shoulder pain	
HIS	− 0.278	
Red pixels	0.223	
Blue pixels	− 0.221	
Biceps brachii muscle	Shoulder pain	Elbow pain
HIS	− 0.009	0.138
Red pixels	0.459*	0.507*
Blue pixels	− 0.537*	−0.499*
Brachioradialis muscle	Elbow pain	Wrist pain
HIS	− 0.105	−0.249
Red pixels	0.075	0.086
Blue pixels	− 0.207	−0.212
Rectus femoris muscle	Hip pain	Knee pain
HIS	− 0.211	−0.202
Red pixels	0.320	0.335
Blue pixels	− 0.316	−0.325
Patellar tendon	Knee pain	
HIS	− 0.478*	
Red pixels	0.128	
Blue pixels	− 0.008	
Gastrocnemius medius muscle	Knee pain	Ankle pain
HIS	− 0.206	− 0.228
Red pixels	0.352	0.320
Blue pixels	− 0.322	− 0.259
Achilles tendon	Knee pain	Ankle pain
HIS	− 0.420*	− 0.345
Red pixels	0.451*	0.356
Blue pixels	− 0.440*	− 0.293

$r = 0.00$–0.19 indicates very weak correlation, $r = 0.2$–0.39 indicates weak correlation, $r = 0.40$–0.59 indicates moderate correlation, $r = 0.6$–0.79 indicates strong correlation, and $r = 0.8$–1.0 indicates very strong correlation

*Statistically significant correlation

observation was not statistically significant. A comparison with Kocyigit et al.'s study might not be appropriate as it is a case report of one boy, whereas the current study focused on adults. A feasibility study also aimed to explore the gastrocnemius medius muscle elasticity in ten adults with JHS compared to ten controls, and color pixels were used for analysis [17]. Alsiri and the current study found no significant differences between the two groups in gastrocnemius medius elasticity [17]. This could be related to type II error, as the descriptive statistics of the current study showed 4% higher gastrocnemius muscle elasticity and 4% lower gastrocnemius medius muscle hardness in the HSD group relative to the control group. The descriptive statistics of the smaller sample size of

ten participants per group [17] identified 1.51% higher gastrocnemius muscle elasticity, and no difference in muscle hardness in the JHS group. A larger sample size study could confirm the observed differences.

Previous studies on nonhypermobility-related conditions have found changes in the elasticity of certain musculoskeletal structures with SEL. Fifty-seven percent softening was identified in symptomatic Achilles tendinopathy [42]. Another study found hardening in the symptomatic Achilles tendon [43]. However, with inflammatory myositis, reduced elasticity was found in most of the cases in the thigh, leg, and arm muscles [44]. Future studies should compare HSD against other musculoskeletal system pathologies to examine the ability of the SEL to distinguish HSD.

Various reasons could explain the significant increase in musculoskeletal structures' elasticity in people with HSD. Collagen is a dominant constituent of the musculotendinous tissues, enhancing its support system and mechanical rigidity. Previous studies on hypermobility-related disorders identified mutation in the genes encoding collagen and deficiency in the collagen modification enzymes [7]. Collagen deficiency could explain the significant reduction in musculoskeletal structures' elasticity. Hypermobility-related disorders are significantly associated with muscle weakness [17], and weak muscles might reduce the resting muscular elasticity. The current study found a moderate correlation between joint pain and musculoskeletal elasticity, indicating that joint pain is associated with softer structures. The significant increase in musculoskeletal elasticity in people with HSD indicates a degree of failure in their joint dynamic support system, leading to instability, microtrauma, and pain. Alternatively, pain could lead to muscle weakness and motor inhibition [45], which could cause the significant reduction in musculoskeletal elasticity. The cause-effect relationship between pain and musculoskeletal elasticity needs to be explored in future studies.

The examiner was not blinded to the groups, yet expectation bias was partially controlled by conducting ImageJ analysis after acquiring the images. The sample size might not be sufficient for all the variables, especially the effect sizes observed were smaller than the effect size used for sample size calculation of 0.95. The observed effect sizes in the current study ranged from 0.16 to 0.77, for the rectus femoris muscle and Achilles tendon, respectively, as indicated with the higher boundary of strain index. The effect sizes ranged from 0.21 to 0.54 for the gastrocnemius medius, and biceps brachii muscles, respectively, for the red color pixels. The strain ratio was obtained from the ratio of the target area and subcutaneous fat. However, the strain index of the subcutaneous fat varies between participants, so it might not serve as an ideal reference. Therefore, a range has also been presented in the current study: lower and higher boundary of strain index. Some studies have used an external gel pad as a reference, which could be used for future studies. Heterogeneity in the reference area

elasticity might explain the large variability noticed in some structures. Spinal hypermobility is one of the major features of HSD; however, the current study did not explore the spinal musculoskeletal structures, and this area could be explored in future research.

Future research should consider inclusion of further variables to allow more advanced statistical analysis to account for potential covariates and build meaningful regression models to explore the relationships between elasticity and pain. The findings' clinical relevance need to be further explored. For example, determining the magnitude of the observe differences relative to data variability, diagnostic validity, sensitivity and specificity, and the relationships with functional outcomes are all areas for exploration. There are various strengths in the study, including establishing intra-rater reliability in a smaller study. A sample size calculation was used, and the methodological procedures were carefully standardized. The findings' clinical importance was increased by correlating the findings with joint pain.

Increased musculoskeletal system elasticity in people with HSD is evident with SEL. Using three SEL image analysis approaches, people with HSD showed significant reductions in the elasticity of muscular and tendinous structures including the biceps brachii and brachioradialis muscles, and patellar and Achilles tendons. People with HSD significantly complain of multiple joint pain which demonstrated a moderate correlation with musculoskeletal elasticity. SEL could be a supplementary tool for diagnosing, monitoring, and assessing the effectiveness of physiotherapy, strengthening programs and other management regimes provided for people with HSD.

Compliance with ethical standards

Disclosures   None.

Ethical standard   The study has been approved by the Ethical Committee of Kuwait Ministry of Health (571/2017); therefore, the study has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

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