A Novel *in Vivo* Skin Extensibility Test for Joint Hypermobility

ADAM D. FARMER, HATTY DOUTHWAITE, SAM GARDINER, QASIM AZIZ, and RODNEY GRAHAME

ABSTRACT. ***Objective.*** The stress/strain curve derived from stretching skin is not linear, but follows a J-shaped curve. An initial generous yield is followed by a steep linear phase where considerable additional force is required to achieve modest increases in deformation. The former represents the taking up of slack resulting from the alignment of dermal collagen bundles in the line of force, while the gradient of the latter represents Young's modulus for skin. Skin hyperextensibility in Ehlers-Danlos syndrome (EDS) is limited to the initial phase of taking up slack. Skin hyperextensibility and joint hypermobility (JHM) form part of the Revised 1998 Brighton diagnostic criteria for the benign joint hypermobility syndrome (BJHS), considered by many to be akin to EDS-hypermobility type. JHM may be screened for using the Beighton Score or a 5-point questionnaire. Our aim was to validate a novel method of measuring skin extensibility based on these observations in addition to revalidating the 5-point questionnaire.

Methods. 250 volunteers (131 female), median age 39 years (range 18–89 yrs), without BJHS, had their joint mobility evaluated using the Beighton Score, compared to the 5-point questionnaire. A Beighton score ≥ 4/9 was considered to represent JHM. Skin extensibility was determined by placing 2 dots on the dorsum of the right hand between the second and third metacarpals, approximately 10 mm apart, and was measured using an electronic caliper. Perpendicular to the metacarpals, a force was applied until the skin was fully taut and the increment was measured. Skin-fold thickness was measured using a Harpenden caliper. A corrected skin extensibility score (CSES) was calculated by dividing the percentage increment by skin thickness. Interobserver variability was measured in a further 50 healthy volunteers.

Results. The prevalence of JHM was 17.6%. Revalidation of the 5-point questionnaire returned a sensitivity of 0.85 and specificity of 0.85. The mean CSES was 23.84%/mm in the hypermobile group versus 13.55%/mm in the normal mobility group ($p < 0.0001$). CSES sensitivity was 0.72, specificity 0.75. The κ value for interobserver variability was 0.83.

Conclusion. The CSES is a useful and reproducible measure of skin extensibility in health. Further work is warranted to validate this test in patients with BJHS. (First Release June 15 2010; J Rheumatol 2010;37:1513–18; doi:10.3899/jrheum.091192)

Key Indexing Terms:
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The benign joint hypermobility syndrome (BJHS) is a multisystem noninflammatory disorder in symptomatic hypermobile individuals. BJHS is diagnosed according to the Revised 1998 Brighton Criteria, a major criterion of which is the presence of demonstrable joint hypermobility (JHM)[1]. Methods for determining JHM were initially proposed by Carter and Wilkinson in 1964[2] and later refined by Beighton, *et al* in 1973[3]. The Beighton score, now almost universally utilized as a measurement of JHM, assesses joint mobility across 9 joints, with a score ≥ 4/9, in adults, considered indicative of JHM. The Beighton score has excellent validity and high interobserver reproducibility[4,5]. In addition, a brief 5-point questionnaire has been developed and validated in order to rapidly screen for JHM without recourse to clinical examination. Thus, this questionnaire is particularly useful to healthcare professionals less familiar with the use of the Beighton scoring system[6].

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As Bird notes, "...although these scoring systems (the Beighton Score) set a value for the condition, they are no substitute for careful examination of each joint..."[7]. In this respect, we would concur with the need for a detailed clinical assessment, but there is a paucity of data examining paraclinical measures of skin extensibility. This is of particular importance as the central pathophysiological abnormality of BJHS is thought to exist in the collagen matrix of the dermis[8]. Grahame and Beighton evaluated the physical properties of skin in patients with Ehlers-Danlos syndrome (EDS) in comparison to healthy age and sex matched controls. A suction-cup device, applied to the back of the forearm, measured the distortion produced in response to a predetermined negative pressure to determine the elastic modulus of the skin[9]. Although the elastic modulus for patients with EDS did not differ significantly from that of controls, female skin was more elastic than male skin. In a followup study, 87 patients attending a rheumatology clinic were divided into 3 groups matched for age and symptoms whose joint mobility was stratified according to their Beighton score[10]. The presence or absence of JHM was not predictive of any demonstrable differences in skin elasticity using the suction-cup method. More recently, Remvig, *et al* evaluated the reproducibility of clinical tests for skin extensibility and consistency[11]. Six patients with EDS, 11 with BJHS, and 19 healthy controls were studied using a variation of the suction-cup device to measure skin extensibility and a soft-tissue stiffness meter test to measure skin consistency[11]. While significant differences were demonstrated between the EDS group and healthy controls in terms of skin consistency and extensibility, the intraobserver agreement was moderate. Criticism of this study included that there were no data on the ethnicity of the study groups, in that JHM demonstrates a wide racial variation[12,13], as well as skin thickness being assumed to be 1 mm, an assumption that is not necessarily justified. In EDS, dermal thickness has been reported as being normal[14] and reduced[9,15] when assessed histologically, using cross-sectional b-mode scans using a 20 MHz ultrasound system or a Harpenden caliper (Harpenden Skinfold Caliper; Baty International, West Sussex, UK), respectively. In patients with BJHS, "skin stretchiness" has only been examined in a single study, where it was estimated by lifting a skin fold on the dorsum of the hand and graded from 0 (normal) to 3 (very stretchy), where it was positively associated with the degree of JHM[16]. This maneuver represents the biomechanical "taking up of slack" phase within the connective tissue as the collagen bundles align[9]. In the hands of an experienced clinician this can be a useful sign but it remains subjective.

We aimed to address these gaps in the literature by designing and validating a novel, objective, noninvasive measurement of skin extensibility, specifically examining the aforementioned "taking up of slack" phase, as a function of skin thickness. We aimed to validate this technique, and its intraobserver variability, in healthy volunteers using instruments that are relatively inexpensive and widely available. The secondary aim of the study was to revalidate the simple 5-point questionnaire for detecting JHM.

MATERIALS AND METHODS

A total of 250 healthy volunteers were recruited for the study. Demographic data were collected on sex, age, height, weight, and ethnicity. Participants were screened for JHM using the Beighton Score and the 5-point questionnaire. Subjects who scored ≥ 4/9 on the Beighton Score, or who scored ≥ 2/5 on the 5-point questionnaire, were then evaluated for BJHS using the Revised 1998 Brighton Criteria[1]. Those who fulfilled the Brighton criteria for BJHS were excluded from the study, in addition to those with a history of skin disease or malignancy and pregnant women. The lower age limit for the study was 18 years with no upper age limit. Written informed consent was obtained from all participants and the study was approved by the Queen Mary, University of London, ethics committee (ref. QMREC2008/76) and performed in accord with the Declaration of Helsinki.

Skin extensibility. The *in vivo* skin extensibility was measured on the dorsum of the subject's right hand placed flat on a smooth surface. Between the middle third of the second and third metacarpals, 2 dots were marked using a fine-nib pen (Pilot V5 Hi-Techpoint 0.5 mm; Pilot Pen Co., Buckinghamshire, UK) approximately 10 mm apart, measured using a simple ruler. An electronic caliper (SITE digital vernier caliper, 0-150 mm model; Screwfix, Yeovil, UK) was used to measure the distance to the inner aspects of the dots (± 0.01 mm). The investigator then applied a maximal lateral stretching force, perpendicular to the metacarpals, to the dots until the skin was taut. The increase in distance between inner aspects of the dots was measured using the electronic caliper (Figure 1). This increase was recorded and transformed into a percentage increment based on the initial measurement.

Skin thickness. Skin-fold thickness was measured using Harpenden calipers[17] on the fold of skin overlying the right second and third metacarpals, i.e., between where the 2 dots had been marked when measuring skin extensibility (Figure 1). In order to derive skin thickness per se, the skin-fold thickness result was halved.

Skin extensibility as a function of skin thickness. We sought to produce a skin extensibility score, corrected for skin thickness, as skin extensibility is a function of skin thickness[18]. We therefore calculated the percentage increase in skin extensibility following the application of a lateral stretching force, and divided this result by the skin thickness in order to produce a corrected skin extensibility score (CSES), whose units are percentage increment/mm skin thickness.

Interobserver variability. In addition to the initial cohort of 250, a separate cohort of 50 volunteers were recruited to evaluate interobserver variability, here termed the "reproducibility cohort." The inclusion and exclusion criteria were identical to the first cohort. The skin extensibility test was performed by 2 observers (HD and SG), blinded to each other's results. The protocol for measuring skin extensibility and skin thickness was identical to the initial cohort. Before undertaking data collection the investigators underwent a training period in order to familiarize themselves with the technique.

Statistical analysis. Descriptive data are presented as mean ± standard error of the mean (SEM) or range as appropriate. Statistical analysis was undertaken with GraphPad Prism, Version 5 (GraphPad Inc., San Diego, CA, USA). Correlation was undertaken using 2-tailed nonparametric Spearman analysis; 2-tailed Mann-Whitney test was used to compare distribution across nonparametric variables. Paired or unpaired tests were used as appropriate. Receiver-operator characteristics (ROC) were calculated against the Beighton Score as we consider this to be the current "gold standard" method for measuring JHM. Wilcoxon signed-rank test was used to compare paired nonparametric data. A p value < 0.05 was considered to represent statistical significance.

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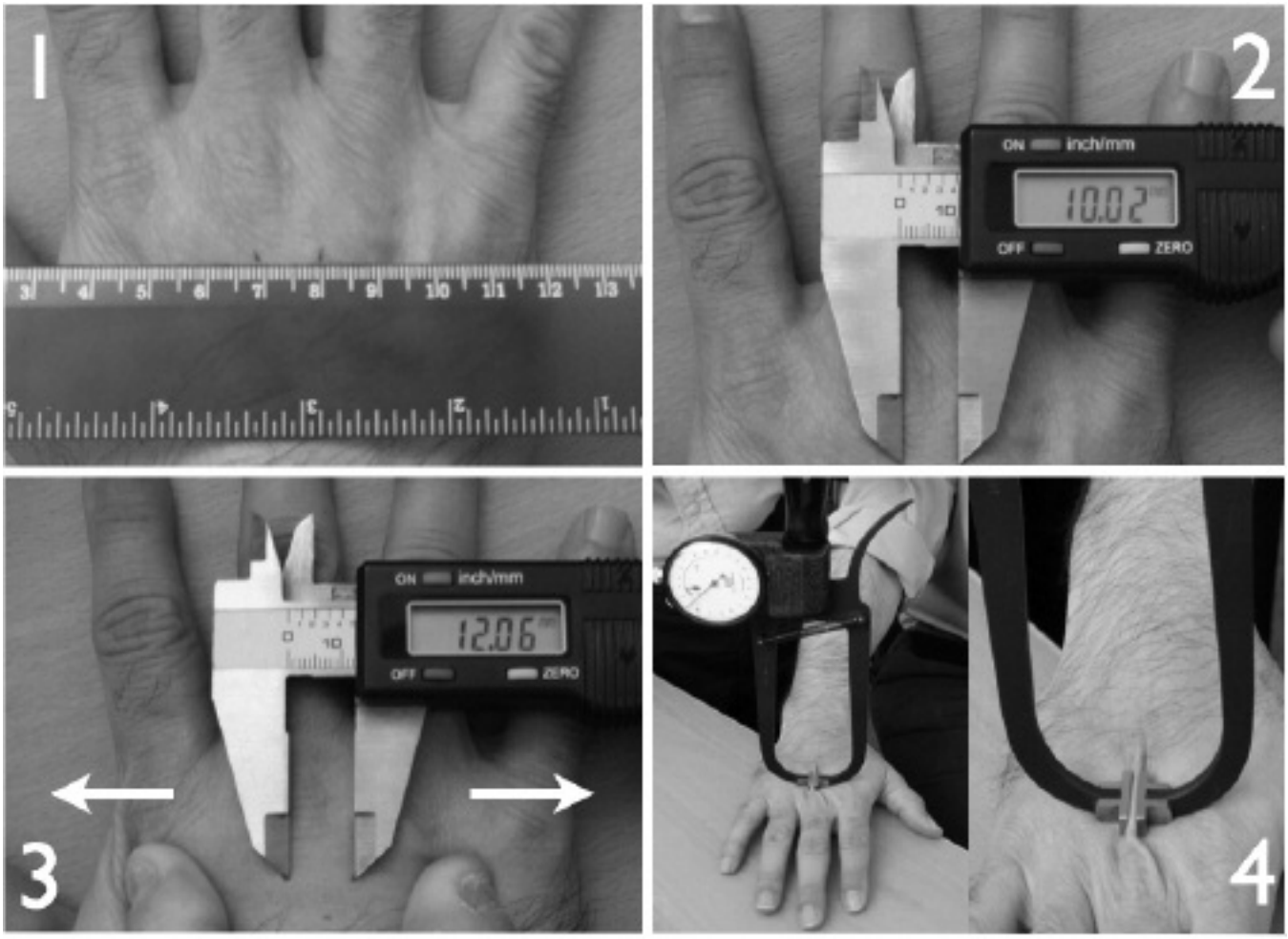

Figure 1. Skin extensibility measurements used to derive the corrected skin extensibility score. 1. On the dorsum of the right hand positioned on a flat surface, using a simple ruler, 2 dots are marked between the middle third of the second and third metacarpals 10 mm apart. 2. The distance between the inner aspects of the 2 dots is measured accurately using an electronic caliper (± 0.01 mm). 3. A maximal lateral stretching force is applied in a perpendicular fashion (arrows) to the metacarpals until the skin is taut and the increment is measured. A percentage increment can be calculated from the measurements derived in panels 2 and 3. 4. Skin-fold thickness is measured between the 2 dots using a Harpenden caliper. Skin thickness is skin-fold thickness/2.

RESULTS

In total, 250 healthy volunteers were enrolled in the study, 131 female, with a mean age of 39 years (range 18–89 yrs) and mean body mass index (BMI) 25.4 kg/m^2 (range 16.7–45.7 kg/m^2). Ethnically, 78.4% were Caucasian, 13.6% were South Asian, 5.6% were Afro-Caribbean, and 2.4% were East Asian (Japanese and Chinese). The mean Beighton score was 1.8 (range 0–8). Forty-four out of 250 (17.6%) of the cohort had a Beighton score ≥ 4. No subject fulfilled the Revised 1998 Brighton Criteria for hitherto undiagnosed BJHS.

Age, sex, skin thickness, and Beighton Score. The median skin thickness was 1.06 mm (SEM ± 0.01 mm). Skin thickness was negatively correlated with age ($r = -0.38$, $p < 0.0001$). Beighton Score was negatively correlated with age ($r = -0.27$, $p = 0.01$). Women had significantly thinner skin than men ($p = 0.01$) with a trend toward higher Beighton scores, although the latter did not reach statistical significance.

Beighton Score and ethnicity. South Asians and East Asians had significantly higher Beighton scores in comparison to Afro-Caribbeans and Caucasians ($p < 0.05$, ANOVA with Tukey test; Figure 2).

Percentage increment in skin extensibility. The Beighton Score was positively correlated with percentage increment in stretch ($r = 0.47$, $p < 0.0001$). Dividing groups based on whether they were hypermobile or not, as defined by a Beighton score ≥ 4, the median percentage increase was 12.96% (SEM ± 0.30) in the normal mobility group compared to 20.93% (SEM ± 0.56) in the hypermobile group ($p < 0.0001$).

Skin extensibility as a function of skin thickness. Skin extensibility was corrected for skin thickness by dividing the percentage increase in skin stretch by skin thickness to produce a CSES. The median CSES was 14.58 (SEM ± 0.43). CSES was positively correlated with Beighton Score ($r = 0.45$, $p < 0.0001$). There was considerable "skewing" of CSES to the

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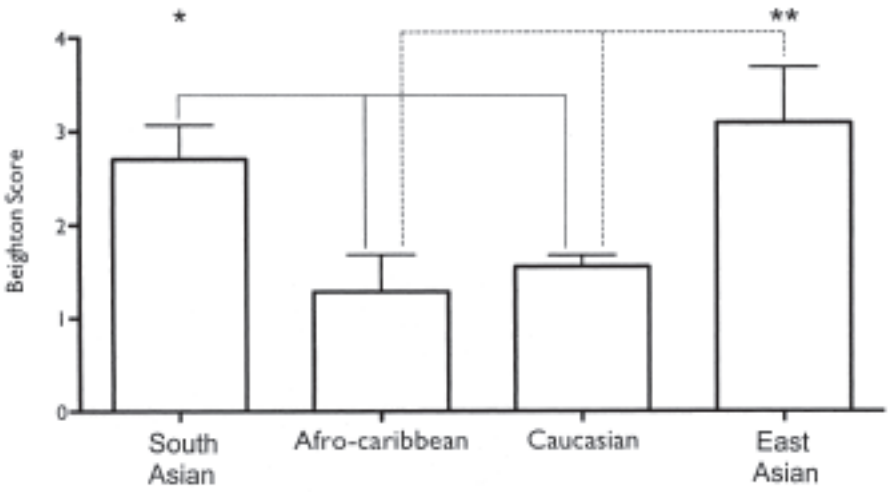

Figure 2. Median Beighton scores of the ethnic groups tested. ANOVA reveals that South Asians (*; solid line) and East Asians (**; broken line) had significantly higher Beighton scores than Afro-Caribbeans and Caucasians ($p < 0.05$).

right as Beighton Score increased (Figure 3A). Dividing groups based on whether they were hypermobile or not, as defined by a Beighton score ≥ 4, the median CSES in the hypermobile group was 21.76 (SEM ± 0.82) versus 12.94 (SEM ± 0.38) in the normal mobility group ($p < 0.0001$; Figure 3B). Specificity and sensitivity for CSES are given in Table 1. The ROC curve is shown in Figure 3C and the area under the curve (AUC) was 0.86 (95% CI 0.81–0.91).

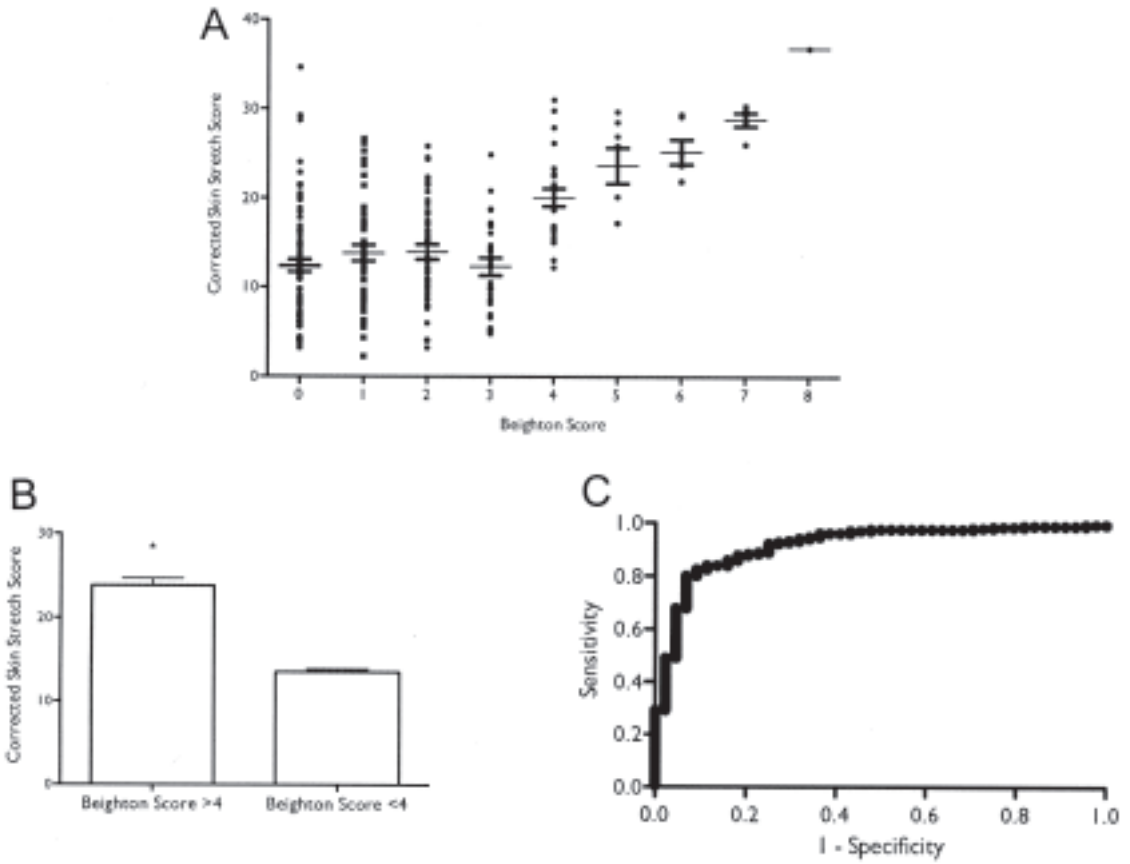

Figure 3. A. Scatter plot (mean ± SEM) shows corrected skin extensibility score (CSES) by Beighton Score, demonstrating that subjects with scores ≥ 4 have higher CSES. Panel B shows these data by hypermobile and normal mobility grouping (*$p < 0.0001$). C. The ROC for the skin stretch test corrected for skin thickness. AUC for the ROC is 0.86 (95% CI 0.81–0.91).

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Interobserver variability. Table 2 details the differences between the initial cohort and the reproducibility cohort. Using ≥ 17.0%/mm as the cutoff between a positive and negative test, the interobserver agreement was 0.94 (SEM ± 0.094) and Cohen's κ reliability coefficient was 0.83 (95% CI 0.65–1.0). There was no statistical difference between the observers in terms of the initial measurement between the dots placed approximately 10 mm apart, the percentage increment following the application of force until the skin was taut or skin thickness (Wilcoxon signed-rank test, p = 0.09, p = 0.17, p = 0.88, respectively).

Revalidation of the 5-point questionnaire for detecting joint hypermobility. The median score on the 5-point questionnaire was 1.0 (range 0–4). Table 3 details the sensitivity, specificity, and negative and positive predictive values, considering a Beighton Score ≥ 4 as positive result. Calculating the ROC, the AUC for this test is 0.90 (95% CI 0.84–0.96).

DISCUSSION

We evaluated a relatively large number of healthy volunteers. There was a good age range among the study participants, especially with respect to the older age group. We sought to evaluate our test using an inclusive, rather than exclusive, population. The prevalence of JHM was 17.6%, in accord with previous epidemiological studies, which have shown a prevalence of 0.6%–31.5% depending on variables such as age, race, and ethnicity[3,19-22]. In line with these studies, we found that hypermobility was negatively associated with age but positively associated with female sex, although the latter did not reach statistical significance. The differences in hypermobility between ethnic groups in our study demonstrated that Orientals and Asians were more hypermobile than Caucasians or Afro-Caribbeans. In this respect, these results are in broad agreement with Seow, *et al*, who showed in a group of 306 subjects from Singapore that the most hypermobile subjects were Malays, followed by Asians and Chinese[22]. While we did not attempt to subclassify the Oriental ethnic group, these subjects composed the most hypermobile group although we acknowledge that they represented only a small proportion of the study population (2.4%). In contrast to Beighton's findings[3], we found no difference between Afro-Caribbeans and Caucasians in terms of their hypermobility scores, possibly reflecting the different geographical locations (rural village location in South Africa vs urban location in England, respectively)[3].

We found that the median skin thickness was 1.06 mm (SEM ± 0.01 mm), which may have important implications for studies whose methodologies are based on the assumption of skin thickness being 1.0 mm. As expected, we found that age and female sex were negatively associated with skin thickness. We were surprised to find that, in contrast to the majority of the published literature, those who were hypermobile had skin thickness similar to those with normal mobility. This may reflect our study design, with a population of exclusively normal healthy persons, rather than a case-control study.

We found that the percentage increment in skin stretch correlated well with Beighton Score, suggesting that subjects who are hypermobile have greater skin extensibility. Further, when percentage increment in skin stretch was stratified according to the presence of hypermobility or not, the hypermobile group had significantly more extensible skin. When the percentage increment was transformed into a function of skin thickness, i.e., to give a CSES, the area under the ROC curve was 0.86, indicating moderate accuracy of the test. An AUC ≥ 0.8 is considered to be a useful test[23]. Using a value of ≥ 17.0%/mm as the threshold for a positive result, we observed clinically useful sensitivity and specificity.

Table 1. Sensitivity, specificity, negative predictive value (NPV), and positive predictive value (PPV) data for various levels of cutoff values for the corrected skin stretch. With a threshold level of ≥ 17%/mm for a positive test, it returns the most satisfactory balance between sensitivity and specificity.

Positive Results Cutoff Level, %	Sensitivity, %	Specificity, %	NPV	PPV
≥ 14.0	95.4	59.7	0.33	0.98
≥ 16.0	86.4	70.8	0.39	0.96
≥ 17.0	72.7	75.2	0.40	0.94
≥ 18.0	68.2	80.1	0.42	0.92
≥ 20.0	63.6	85.4	0.44	0.90

Table 2. Demographic comparison between the initial cohort and the reproducibility cohort, demonstrating that the cohorts were similar.

Variable	Cohort I, n = 250	Reproducibility Cohort, n = 50	p
Female, %	52.4	56	0.64
Median age, yrs	39 (± 1)	41 (± 2.2)	0.34
Median BMI, kg/m^2	25.4 (± 0.29)	26.11 (± 0.7)	0.28
Ethnicity, %	Caucasian 78.4, South Asian 13.6, Afro-Caribbean 5.6, East Asian 2.4	Caucasian 76, South Asian 14, Afro-Caribbean 10	NA
Median Beighton Score	1.8 (± 0.1)	1.6 (± 0.26)	0.36
JHM prevalence, % (n)	17.6 (44/250)	16 (8/50)	0.56

BMI: body mass index; JHM: joint hypermobility; NA: not applicable.

Table 3. Revalidation of the 5-point questionnaire; answering 2 or more questions positively on the questionnaire gives a sensitivity of 85.3% and specificity of 85% for detecting joint hypermobility.

Positive Results Cutoff	Sensitivity, %	Specificity, %	NPV, %	PPV, %
1 question positive	95.2	46.3	26.2	97.6
2 questions positive	85.3	85	51.4	97
3 questions positive	55.8	99	92.3	91.5

NPV: negative predictive value; PPV: positive predictive value.

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The interobserver variability for the test was reasonable, the observed agreement being 0.96 with a κ reliability coefficient of 0.83. The κ reliability coefficient assesses the degree of agreement between 2 dichotomous variables and it is considered that a κ reliability coefficient ≥ 0.8 is required for a test to be reproducible. Therefore, we can consider our test has reasonable interobserver reproducibility[24].

In terms of our secondary objective, we aimed to revalidate the simple 5-point questionnaire for detecting JHM. First developed in 2003 as an adjunct to assessment of patients with diffuse musculoskeletal pain, the study reported that across 2 cohorts, of a total of 489 subjects who had BJHS/JHM or who were normal, the sensitivity was 84% and 84% and specificity was 89% and 80%, respectively[6]. We have demonstrated similar results and concur that the simple 5-point questionnaire is a useful screening tool for detecting JHM that can be self-reported by subjects, reducing the need for healthcare professionals to undertake a formal Beighton Score.

Study limitations. One methodological difficulty for a study of this kind is definition of the "gold standard" test to which others are compared. We chose to use the Beighton Score because of its reported good internal and external validity[5]. However, the Beighton Score only measures hypermobility across 5 joint groups, and as such has its own limitations in evaluation of generalized JHM. While we sought to obtain a homogenous cohort, we did not take into account sun-induced or occupational skin changes that may alter the physical properties of the skin. A further limitation relates to the lateral stretching force applied to the dorsum of the subject's right hand, in that this force could potentially vary between investigators and therefore influence the percentage increase in skin extensibility. However, in the reproducibility cohort there was no statistically significant difference between the 2 observers in percentage increment following application of the lateral stretching force. This demonstrates that the force needed to stretch the skin until taut was similar between observers. Finally, we would stress that our study was conducted in normal healthy subjects, so we would advocate caution in applying these findings to patients with BJHS or EDS.

We have validated a novel, objective, and noninvasive measurement of skin extensibility and thickness in a group of healthy volunteers using instruments that are inexpensive and widely available. The CSES represents a useful paraclinical adjunct in the clinician's resources for evaluating skin extensibility in JHM. The CSES provides an objective measure of skin extensibility corrected for skin thickness with good sensitivity, specificity, and interobserver reproducibility. Further work is now warranted to validate this test in a cohort of patients with BJHS and EDS.

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