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Department of Dermatology and Venereology

A Diagnostic Skin Score for Patients with Ehlers-Danlos-Syndromes

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Background

Together with joint hypermobility (HM), cutaneous manifestations provide important clues for the diagnosis of Ehlers-Danlos-Syndromes (EDS). As HM is only rarely syndromic, skin signs may guide the decision of molecular testing in patients with HM.[1,2] However, skin signs are often subjective (e.g. “skin hyperextensibility”, “soft, velvety skin”) and non-specific (e.g. “piezogenic papules”, “easy bruising”). Even patients with the monogenetic EDS undergo a long diagnostic journey, which may take decades and results in high morbidity despite high healthcare utilization.[3]

To support clinical assessment in patients with generalized HM, we developed a standardized skin score based on predefined features (included as diagnostic criteria in the current 2017 Classification).[1]

Methods

We developed a standardized skin score (Fig. 1) and examined its applicability in healthy controls, dancers with presumed asymptomatic generalized HM and patients with the most common EDS subtypes (classical EDS (cEDS); hypermobile EDS/hypermobility spectrum disorder (hEDS/HSD). We recruited two cohorts, an exploratory development cohort (n=42; controls, dancers, hEDS/ HSD, classical EDS) and an independent validation cohort (n=25; hEDS/ HSD, cEDS) (Fig. 2). The exploratory cohort was assessed as part of the prospective MYPER study, comparing clinical signs and muscle mechanics in healthy controls vs cEDS vs hEDS/ HSD vs dancers. Predictive performance of the Skin Score was evaluated using multinominal logistic regression, cut-point estimation and ROC analysis.

Item	Points
Skin Texture ① soft skin texture ② doughy, extremly soft skin texture	⓪ ① ②
Skin Hyperextensibility ① > 1,5 cm (over volar forearm and dorsal hand) ② > 3,0 cm (over volar forearm, dorsal hand, neck, elbows, knees)	⓪ ① ②
Atrophic scars ① ≤ 5 scars at presentation ② hemosiderotic scars or low-impact wounds or spontaneous wounds or > 5 atrophic scars at presentation	⓪ ① ②
Molluscoid pseudotumors or subcutaneous spheroids	⓪ ②
Increased venous visibility ① on the legs or extensive spider veins ② unusual localisation or acrogeria	⓪ ① ②
Striae distensae ① any striae present ② not explained by pregnancy/weight changes or unusual localisation	⓪ ① ②
Hematoma ① low-impact or ≤ 5 at presentation ② unusual localisation or > 5 at presentation	⓪ ① ②
Bilateral piezogenic nodules	⓪ ①
Standardized dermatologic scoring system assessing predefined cutaneous manifestations associated with hypermobility disorders, as shown in clinical images.	**Total Points:**



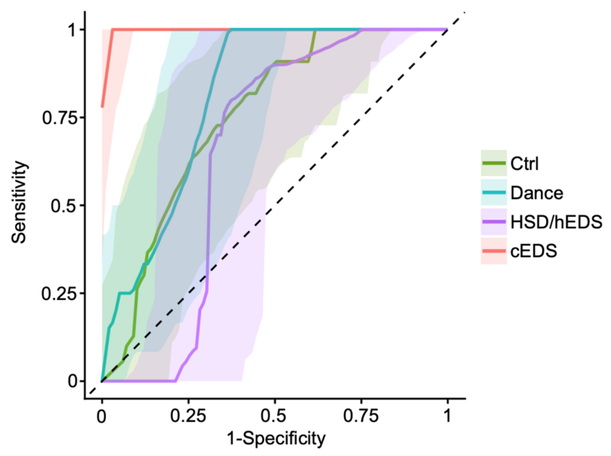
Result 1: Predicted probabilities for group membership by development cohort

SkinScore	Ctrl	Dance	HSD/hEDS	cEDS
0	0.81 (0.56–0.95)	0.16 (0.05–0.36)	0.03 (0.01–0.10)	0.00 (0.00–0.02)
1	0.64 (0.38–0.83)	0.29 (0.12–0.50)	0.07 (0.02–0.18)	0.01 (0.00–0.04)
2	0.41 (0.21–0.62)	0.43 (0.22–0.62)	0.15 (0.06–0.31)	0.02 (0.00–0.07)
3	0.21 (0.10–0.38)	0.45 (0.23–0.64)	0.30 (0.14–0.50)	0.04 (0.01–0.13)
4	0.09 (0.03–0.21)	0.34 (0.15–0.52)	**0.49 (0.25–0.70)**	0.08 (0.02–0.22)
5	0.04 (0.01–0.12)	0.19 (0.07–0.36)	**0.59 (0.31–0.80)**	0.18 (0.07–0.38)
6	0.02 (0.00–0.07)	0.09 (0.02–0.23)	**0.53 (0.27–0.75)**	0.36 (0.17–0.60)
7	0.01 (0.00–0.04)	0.04 (0.01–0.14)	0.36 (0.14–0.60)	**0.59 (0.31–0.83)**
8	0.00 (0.00–0.02)	0.02 (0.00–0.08)	0.20 (0.05–0.46)	**0.78 (0.49–0.94)**
9	0.00 (0.00–0.01)	0.01 (0.00–0.05)	0.10 (0.01–0.30)	**0.89 (0.66–0.98)**
10	0.00 (0.00–0.01)	0.00 (0.00–0.03)	0.05 (0.00–0.19)	**0.95 (0.79–1.00)**

An ordinal logistic regression model was fitted in the development cohort to evaluate the relationship between cumulative skin score and diagnostic group assignment. Predicted probabilities were calculated across the full score range.

Result 2: Diagnostic performance of the skin score

	Development cohort				Validation cohort	
Variable	**Ctrl**	**Dance**	**HSD/hEDS**	**cEDS**	**HSD/hEDS**	**cEDS**
Sensitivity	0.27	0.75	0.7	1	0.43	0.91
Specificity	0.9	0.73	0.94	0.97	0.91	1
PPV	0.5	0.53	0.78	0.9	0.86	1
NPV	0.78	0.88	0.91	1	0.56	0.93
Balanced accuracy	0.59	0.74	0.82	0.99	0.67	0.96
Accuracy	0.74	0.74	0.88	0.98	0.64	0.96
Kappa	0.21	0.43	0.66	0.93	0.32	0.92
p-value (Acc>NIR)	0.58	0.44	0.04	<0.001	0.28	<0.001



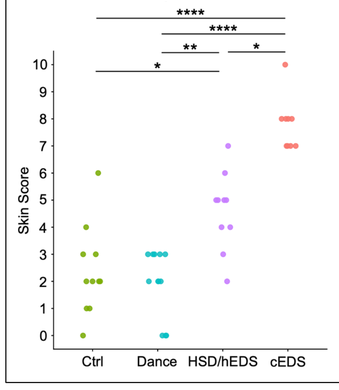
Diagnostic performance of the cumulative skin score was evaluated using receiver operating characteristic (ROC) analysis with one-versus-rest comparisons in the development cohort and independent validation in routine clinical data.
The score demonstrated very good discrimination for cEDS, with high sensitivity, specificity, balanced accuracy, and Cohen’s kappa across both cohorts, while discriminatory performance for HSD/hEDS remained moderate.

Patient characteristics

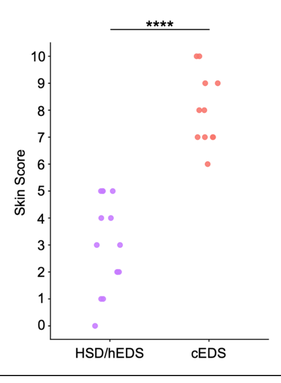
Development cohort				
Variable	**Ctrl** (n = 11)	**Dance** (n = 12)	**hEDS** (n = 10)	**cEDS** (n = 9)
Age (years), mean (SD)	32.0 (8.7)	32.2 (8.4)	34.6 (13.4)	33.2 (10.8)
Sex (f/m), n	11 / 0	12 / 0	10 / 0	9 / 0
BS, mean (SD)	1.7 (1.4)	4.9 (0.9)**	6.1 (1.3)***	5.8 (1.1)***

Validation cohort		
Variable	**hEDS** (n = 14)	**cEDS** (n = 11)
Age (years), mean (SD)	37.4 (10.9)	44.4 (16.9)
Sex (f/m), n	14 / 0	9 / 2
BS, mean (SD)	5.1 (0.3)	6.7 (1.1)###

Development cohort



Validation cohort



Clinical characteristics of the development and validation cohorts, including controls (Ctrl), dancers, HSD/hEDS and cEDS individuals. Beighton scores (BS) and skin scores increased progressively across groups, with highest values observed in cEDS patients. ** p < 0.01, *** p < 0.001 vs. Ctrl (development cohort), Kruskal–Wallis test; ### p < 0.001 vs. hEDS (validation cohort), two-sided unpaired Mann–Whitney U test.

Summary

- The developed Skin Score demonstrated very good discrimination for cEDS (≥ 7), with high sensitivity, specificity, balanced accuracy, and Cohen’s kappa across both cohorts.
- Patients with the non-monogenetic HSD/hEDS showed a higher score than the healthy controls, including dancers. However, discriminatory performance remained moderate, probably reflecting the mildness of skin manifestations in these patients and the high degree of subjectivity on clinician’s behalf.
- Thus, the developed Skin Score provides an easily applicable tool to improve diagnostic confidence – also for non-dermatologists - and prioritize patients for molecular testing.
- Our study suggests that the usefulness of cutaneous manifestations as diagnostic criteria for hEDS/HSD needs to be critically re-evaluated.

Clinical summary

Group	Skin Score Range
Ctrl/Dance	< 4
HSD/hEDS	4–6
cEDS	≥ 7

Outlook

- Prospective validation of the skin score in larger, multicenter cohorts including additional monogenic EDS subtypes.
- Correlation of cutaneous scores with genetic, biomechanical, and systemic disease manifestations to refine phenotypic stratification in EDS.

References:
1) Malfait F et al., Am J Med Genet. 2017;175(1):8-26.
2) Damseh N et al. Am J Med Genet A. 2022 May;188(5):1376-1383.
3) Rauterberg J, Hock M et al. Orphanet J Rare Dis. 2025;20(1):1-10.