THE EUROPEAN SOCIETY OF MEDICINE
Medical Research Archives, Volume 13 Issue 2

RESEARCH ARTICLE

Biomechanical alterations of the spine correlated with the severity of dermatitis and calcitonin gene-related peptide levels

Danial Khorsandi[1], Mackarena Ccoicca[1], Alex Ruiz[1], Miguel Angel Tejero[2], Angela Olaru[3,4], Ignacio Umbert[1, 4*]

[1]Umbert Institute of Dermatology, Corachan Clinic, Plaza Manuel Corachán 4, 08017 Barcelona, Spain.
[2]Diagnostic Imaging Department, Corachan Clinic, Plaza Manuel Corachán 4, 08017 Barcelona, Spain.
[3]Biomedical Vertix, Integrative Medicine and Chiropractic Health Center, Sant Cugat del Valles, Barcelona, Spain.
[4]Co-senior authors
*Email: info@idermumbert.com

OPEN ACCESS

PUBLISHED
28 February 2025

CITATION
Khorsandi, D., Ccoicca, M., et al., 2025. Biomechanical alterations of the spine correlated with the severity of dermatitis and calcitonin gene-related peptide levels. Medical Research Archives, [online] 13(2). https://doi.org/10.18103/mra.v13i2.6283

DOI
https://doi.org/10.18103/mra.v13i2.6283

ISSN
2375-1924

ABSTRACT

Background: Intrinsic atopic dermatitis is a chronic cutaneous inflammatory disease with pruritus and eczematous lesions of skin. A long-lasting cycle of itch-scratch roots results in substantial morbidities and discomfort. Treatment of patients with moderate to severe dermatitis is a challenge.

Objectives: A) To characterize the relationship between spinal biomechanical alterations, the severity of intrinsic atopic dermatitis, and the blood levels of calcitonin gene-related peptide (CGRP) and B) to determine whether chiropractic spinal manipulative therapy can be an effective complementary treatment.

Materials and Methods: In this prospective study, 33 patients with severity index (EASI) score less than 7 were compared with 40 patients with EASI score greater than 7. The severity level of spine biomechanical alterations (spinal biomechanical alterations) was quantified using full spine radiographic descriptions. The expression of CGRP was determined in blood using ELISA tests. All patients were prescribed the same anti-inflammatory topical cream. Of the 73 patients, 51 choose to be also treated by chiropractic and the 22 others were used as control. Data were analyzed before and after the treatment.

Results: A strong correlation was found between overall spinal biomechanical modifications, altered skin status and CGRP levels. The EASI scores were correlated with the different segments of the spine. Although the EASI score of the patients in the control group decreased after 2 weeks of using the anti-inflammatory cream, 3 months later the dermatitis symptoms flared up again and the EASI scores returned to baseline values. In contrast, both the EASI scores and the CGRP levels of treated patients by chiropractic remained low after 3 months.

Conclusions: This study shows that the severity of intrinsic dermatitis is related to that of spinal biomechanical alterations, and that CGRP levels may serve as a valuable pathological marker. Chiropractic proved to be a valuable complementary therapeutic tool.

Keywords: Chiropractic, CGRP, Column, Dermatitis, Dermatology, Spine.

Introduction

Atopic dermatitis (AD) is a chronic inflammatory skin disease with exclusive clinical manifestations through age, race or ethnicity groups. It is an important public health problem, with a lifetime prevalence of 10–20% in children, and 1–3% in adults[1]. Intensive pruritus and eczematous lesions of skin are the main symptoms[2]. In most patients with AD, a long-lasting cycle of itch-scratch roots results in substantial morbidities and discomfort. Etiologically, AD is multifactorial with genetically, environmental and immunological interacting factors[3]. Similar to many other dermatological diseases, a psychosomatic component might be involved in the development of AD[4]. The clinical phenotype of AD is characterised as the product of several interactions including susceptible genes, environment, defective cutaneous barrier function, and the immunologic diversity of the immune responses. A simple classification divides AD into two groups: extrinsic and intrinsic. The extrinsic group is characterised by high immunoglobulin (Ig) E levels and impaired barriers. The intrinsic group, which comprises 20% of the patients, is defined by normal IgE levels and preserved barriers[1,5].

Several studies have shed light on the role of the nervous system in the pathogenesis of AD[6-8]. The nervous system is critical for disease progression through an irregular expression of neuropeptides in the affected skin[6,7]. Neurogenic inflammation occurs during cutaneous inflammatory reactions. The nerve endings secrete neuropeptides, such as calcitonin gene-related peptide (CGRP) and substance P, which induce the release of inflammatory mediators (cytokines and neuropeptides) by immune cells increasing inflammation[9].

Several studies attempted to determine the bone mineral density in AD patients. These studies showed a relationship between AD and a decrease in bone mineral density that could explain the increase in bone fractures of these patients[10,11]. Based on these findings, a prospective study was designed to explore the relationship between spinal biomechanical alterations and intrinsic AD. Understanding this relationship may help optimise approaches used to control some of the pathological mechanisms in AD and thus contribute to the development of effective treatments.

Materials and Methods:

PATIENTS:

All study participants were patients of the 'Umbert Institute of Dermatology' Corachan Clinic, Barcelona, Spain. Patients were aged between 20 and 70 years of both sexes (48 females and 25 males) with confirmed atopic dermatitis (American Academy of Dermatology Consensus Criteria)[12] with moderate-to-severe disease activity and affected body surface area 10% or higher at both screening and baseline, with documented history (within 1 year) of inadequate response to topical medications. In any of the patients no significant high levels of IgE were observes. Patients with diagnosis of dermatitis along with other dermatological conditions or other systemic diseases were excluded from the study. The studies were reviewed on 2021/02/23 and approved by the ethics committee, Hospital group Quiron Salud-Catalunya with protocol number INCV-001. All patients gave written informed consent to participate in this study.

CLINICAL EVALUATION:

For the clinical evaluation the following areas: scalp, forehead, eyes, ears, face, chin, neck, trunk, arms, and hands, legs, genital area, and feet were photographed at each visit. The revision of the photographs was used to quantitatively assessed the degree of disease's severity using "The Eczema Area and Severity Index" (EASI) system[13-15].

FULL-SPINE X-RAY VIEW (SPINOGRAPHIC TELEMETRY):

To calculate the severity score of spinal biomechanical alterations full spine x-rays (scoliogram) were taken for each patient. X-ray analysis was performed by a team of MD radiologists and in double blind they quantified the scoliogram according to literature-based criteria[16-23] in different areas of the spine: cervical[23],

thoracic[17], lumbar[20] and sacrum[22]. In order to allow statistical analysis a numerical score was assigned to each radiological finding as described in Table S1.

Table S1

Antero-posterior (AP) and AP transoral cervical spine X-ray view.

AT-AX1. Atlas-axis relationship 1 [37,39]. Parameters evaluated:
1. Preserved atlanto-odontoid relationship: score 0.
2. Atlanto-odontoid relationship with asymmetry (rotational subluxation) Right> Left or Left > Right: score 1.

AT-AX2. Atlas-axis relationship 2. Parameters evaluated:
1. Preserved bilateral atlanto-axial joint: score 0.
2. Mechanical changes of the articular surfaces of the bilateral atlanto-axial joint: score 1.
3. Degenerative changes of the articular surfaces of the bilateral atlanto-axial joint: score 2 for incipient changes, score 3 for moderate changes, and score 4 for severe changes.

CC1. Parameters evaluated:
1. Preserved uncoapophyseal and interapophyseal joints: score 0.
2. Generalised mechanical changes of the uncoapophysial and interapophyseal joints of the cervical spine: score 1.
3. Generalised degenerative changes of the uncoapophysial and interapophyseal joints of the cervical spine: score 2 for incipient changes, score 3 for moderate changes, and score 4 for severe changes.

CC2. C7-T1 spinal transition anomaly. Parameters evaluated:
1. C7-T1: Unilateral/bilateral mega transverse processes of C7: score 0.
2. C7-T1: Unilateral/bilateral mega transverse processes of C7 with articulated/fused ossicles (discrete supernumerary ribs of C7): score 1.
3. C7-T1: Unilateral/bilateral mega transverse processes of C7 with cervical ribs (true supernumerary ribs of C7): score 2.

CC3. Closure defect in the posterior arch with absence of union in the spinous process (occult spina bifida). Parameters evaluated:
1. Preserved closure: score 0.
2. Closing defect: score 1.

Lateral cervical spine X-ray view [40]

CC4. Anterior Atlantodental Interval (ADI). Parameters evaluated:
1. Preserved atlanto-odontoid joint. Anterior ADI distance 2-3 mm: score 0.
2. Degenerative changes of the atlanto-odontoid articular surfaces with preserved joint space: score 1 for anterior ADI distance 2-3 mm, and score 2 for anterior ADI distance < 2 mm.
3. Degenerative changes of the atlanto-odontoid articular surfaces with a slight decrease in joint space, anterior ADI distance > 3 mm: score 3.

CC 5. Cervical lordosis. Parameters evaluated:
1. Cervical lordosis angle C1-C7 (value "-" = lordosis; value "+" = kyphosis).
2. C2-C7 cervical lordosis angle (N between -25º and -40º) (<-25º= rectification / > -40º = hyperlordosis).
2.1. Preserved: score 0 (Physiological Lordosis between -25º and -40º).
2.2. Rectification: score 1 (value between 0º and -25º).
2.3. Rectification with kyphotic inversion: score 2 (value +).

CC 6. Interbody space of global segment C2-C7:
1. Preserved space: score 0.
2. Decreased space: score 1.

CC 6-1. Interbody spaces of the proximal segment C2-C4:
1. Preserved space: score 0.
2. Decreased space: score 1.
3. Decreased space with signs of degenerative disc disease: score 2.
4. Decreased space with signs of degenerative disc disease and anterior/posterior marginal osteophytosis: score 3.

CC 6-2. Interbody spaces of the distal segment C4-C7:
1. Preserved space: score 0.
2. Decreased space: score 1.
3. Decreased space with signs of degenerative disc disease: score 2.
4. Decreased space with signs of degenerative disc disease and anterior/posterior marginal osteophytosis: score 3.

CC 7. Parameters evaluated: Facet joints of the cervical rachis.
1. Preserved: score 0.
2. Mechanical changes: score 1.
3. Incipient degenerative changes: score 2.
4. Degenerative changes: score 3.

CC 8. Cervical instability global segment C2-C7:
1. No signs of segmental instability observed in relation to the sagittal alignment of the posterior vertebral walls: score 0.
2. Signs of segmental instability in relation to the sagittal alignment of the posterior vertebral walls:
2.1. Instability sagittal alignment of the posterior vertebral walls, < or = 2mm, (anterolisthesis vs retrolisthesis): score 1.
2.2. Instability sagittal alignment of the posterior vertebral walls > 2 mm (anterolisthesis vs retrolisthesis): score 2.

CC 8-1. Cervical instability proximal segment C2-C4:
1. No signs of segmental instability observed in relation to the sagittal alignment of the posterior vertebral walls: score 0.
2. Signs of segmental instability in relation to the sagittal alignment of the posterior vertebral walls:
2.1. Instability sagittal alignment of the posterior vertebral walls, < or = 2mm, (anterolisthesis vs retrolisthesis): score 1.
2.2. Instability sagittal alignment of the posterior vertebral walls > 2 mm (anterolisthesis vs retrolisthesis): score 2.

CC 8-2. Cervical instability distal segment C4-C7:
1. No signs of segmental instability observed in relation to the sagittal alignment of the posterior vertebral walls: score 0.
2. Signs of segmental instability in relation to the sagittal alignment of the posterior vertebral walls:
2.1. Instability sagittal alignment of the posterior vertebral walls, < or = 2mm, (anterolisthesis vs retrolisthesis): score 1.
2.2. Instability sagittal alignment of the posterior vertebral walls > 2 mm (anterolisthesis vs retrolisthesis): score 2.

Antero-posterior (AP) full-spine X-ray view (scoliogram).

AP 1. Parameters evaluated: lower extremities (EEII) dysmetria, femoral head height difference.
1. Preserved: score 0.
2. Dysmetria: score 1 (1 cm).
3. Dysmetria: score 2 (1.5 cm and 3 cm).
4. Dysmetria: score 3 (> 3 cm).

AP 2. Parameters evaluated: clavicle height difference.
1. Preserved: score 0.
2. Asymmetry: score 1.

AP 3 [41]. Parameters evaluated: Coronal Spinal Balance (CSB) and Coronal Balance Distance (CBD) (CBD: N = 0 mm with deviation of +/- 20 mm):
1. Neutral CSB: C7 plumb line (C7PL) located in the same vertical plane as central sacral vertical line (CSVL) considered as a normo-axated spine (CBD: distance between the C7PL and CSVL. CBD = 0 mm).
2. Negative CSB: C7PL located to the left of CSVL (value "-").
2.1. Negative CSB: CBD between -1 mm and -20 mm (within the normal range): score 1.

2.2. Negative CSB: CBD between -20 mm and -30 mm (value greater than normal range): score 2.
2.3. Negative coronal imbalance: CBD > -30 mm = Coronal Imbalance: score 3.
3. Positive CSB: C7PL located to the right of CSVL (value "+").
3.1. Positive CSB: CBD between +1 mm and +20 mm (within the normal range): score 1.
3.2. Positive CSB: CBD between +20 mm and +30 mm (value greater than normal range): score 2.
3.3. Positive coronal imbalance: CBD > +30 mm = Coronal Imbalance: score 3.

AP 4. Parameters evaluated: Scoliotic attitude. Scoliosis.
1. Normoaxade (normal curve): score 0.
2. Scoliotic attitude (main curve value < 11º): score 1.
3. Mild scoliosis (main curve value < 20º): score 2.
4. Moderate scoliosis (main curve value between 20º and 40º): score 3.
5. Moderate/severe scoliosis (main curve value between 40º and 50º): score 4.
6. Severe scoliosis (main curve value > 50º): score 5.

AP 5. Parameters evaluated: Vertebral bodies and posterior elements of the thoracic and lumbar spine [42].
1. Preserved: score 0.
2. Mechanical changes: score 1.
3. Degenerative changes (incipient degree): score 2.
4. Degenerative changes (moderate degree): score 3.
5. Degenerative changes (severe degree): score 4.

AP 6. Parameters evaluated: Bilateral sacroiliac joint and pubic symphysis [42].
1. Preserved: score 0.
2. Incipient mechanical changes: score 1.
3. Mechanical changes: score 2.
4. Degenerative changes: score 3.

AP 7. Parameters evaluated: Bilateral femoroacetabular (FA) joint [42].
Preserved femoroacetabular joint: score 0.
1. FA joint with incipient mechanical changes: score 1.
2. FA joint with mechanical changes: score 2.
3. FA joint with incipient degenerative changes (coxarthrosis): score 3.
4. FA joint with moderate degenerative changes (coxarthrosis): score 4.
5. FA joint with severe degenerative changes (coxarthrosis): score 5.

AP 7-1. Parameters evaluated: Femoroacetabular impingement (FAI), CAM type hump deformity, Pincer type or mixed [42].
1. Conserved sphericity: score 0.
2. Femoroacetabular impingement (FAI): score 1.
3. FAI: CAM type hump deformity (pistol grip deformity) [43]: score 1.
4. FAI: Pincer type (acetabular over coverage of the femoral head): score 1.
5. FAI Mixed: CAM and Pincer: score 2.

Lateral full-spine X-ray view (spinographic telemetry):

LAT 1. Parameters evaluated: Sagittal Spinal Balance (SSB) and Sagittal Vertical Axis (SVA) (SVA: N = 0 mm with deviation of +/- 30 mm):
1. Neutral SSB: C7 plumb line (C7PL) located in the same vertical plane as posterior-superior corner S1 (SVA: distance between the C7PL and the posterior-superior corner of S1. SVA = 0 mm): score 0.
2. Positive SSB: C7PL located in front of the posterior-superior corner S1 (value "+"):
2.1. Positive SSB: SVA between +1 mm and +30 mm (within the N range): score 1.
2.2. Positive SSB: SVA between +30 mm and +50 mm (value greater than N range): score 2.

2.3. Positive Sagittal Imbalance (SI):
2.3.1. Moderate SI: SVA between +50 mm and +95 mm: score 3.
2.3.2. Severe SI: SVA > +95 mm: score 4.
3. Negative SSB: C7PL located behind posterior-superior corner S1 (value "-"):
3.1. Negative SSB: SVA between -1 mm and -30 mm (within the N range): score 1.
3.2. Negative SSB: SVA between -30 mm and -50 mm (value greater than N range): score 2.
3.3. Negative Sagittal Imbalance (SI):
3.3.1. Moderate SI: SVA between -50 mm and -95 mm: score 3.
3.3.2. Severe SI: SVA > -95 mm: score 4.

LAT 2. Parameters evaluated: Main physiological thoracic kyphosis angle T4-T12 (value "+").
1. Preserved T4-T12 thoracic kyphosis: N range between +20º and +40º: score 0.
2. Tendency to thoracic hyperkyphosis T4-T12: value between +40º and +50º: score 1.
3. Hyperkyphosis of thoracic spine T4-T12: value > +50º: score 2.
4. Thoracic hypokyphosis T4-T12: value < +20º (value < +10º = flat back): score 3.

LAT 3. Parameters evaluated: Transitional kyphosis angle T10-L2 (value "+")
1. Preserved T10-L2 transitional physiological kyphosis: N < +20º: score 0.
2. Lordotic inversion of transitional kyphosis T10-L2: value "-": score 1.
3. Rectification of thoracolumbar transitional kyphosis T10-L2: value 0º: score 2.
4. Hyperkyphosis of the thoracolumbar transition T10-L2: value > +20º: score 3.

LAT 4. Parameters evaluated: Lumbar Lordosis angle (LL = L1-S1) (value "-").
1. Preserved LL (N between -40º and -70º): score 0.
2. Hypolordosis (LL < -40º): score 2.
3. Hyperlordosis (LL > -70º): score 1.

LAT 5. Parameters evaluated: Lordosis Distribution Index (LDI) (L4-S1/L1-S1 x 100 = %).
1. Aligned and offset distribution: 50%-80%: score 0.
2. Hyperlordotic maldistribution: > 80%: score 1.
3. Moderate hypolordotic maldistribution: 40%-49%: score 2.
4. Severe hypolordotic maldistribution: > 40%: score 3.

LAT 6. Parameters evaluated: Interbody spaces of the thoracic spine.

LAT 6-1. Interbody spaces of the thoracic spine main segment T4-T12.
1. Preserved space: score 0.
2. Decreased space: score 1.

LAT 6.2. Interbody spaces of the thoracic spine middle segment T4-T9.
1. Preserved space: score 0.
2. Decreased space: score 1.

LAT 6-3. Interbody spaces of the distal segment thoracic spine T9 -T12.
1. Preserved space: score 0.
2. Decreased space: score 1.

LAT 7. Parameters evaluated: Interbody spaces of the lumbar spine L1-S1.

LAT 7-1. Interbody spaces of the lumbar spine L1-L3 (proximal segment).
1. Preserved space: score 0.
2. Decreased space: score 1.
3. Decreased space with signs of degenerative disc disease: score 2.
4. Decreased space with signs of degenerative disc disease and anterior/posterior marginal osteophytosis: score 3.

LAT 7-2. Interbody spaces of the lumbar spine L3-S1 (distal segment).

1. Preserved space: score 0.
2. Decreased space: score 1.
3. Decreased space with signs of degenerative disc disease: score 2.
4. Decreased space with signs of degenerative disc disease and anterior/posterior marginal osteophytosis: score 3.

LAT 8 (Global column). Parameters evaluated: Assessment of vertebral bodies and posterior arches of the spine.

LAT 9 (Thoracic spine). Assessment of vertebral bodies, posterior arches and interbody spaces of the thoracic spine.
1. Preserved vertebral bodies and posterior elements of the thoracic spine: score 0.
2. Mechanical changes: score 1.
3. Degenerative changes (incipient degree): score 2.
4. Degenerative changes (moderate degree): score 3.
5. Degenerative changes (severe degree): score 4.

LAT 10 (Lumbar spine). Assessment of vertebral bodies, posterior arches and interbody spaces of the lumbar spine.

LAT 10-1 (Distal segment L3-S1). Assessment of vertebral bodies, posterior arches and interbody spaces of the lumbar spine.
1. Preserved vertebral bodies and posterior elements of the lumbar spine: score 0
2. Mechanical changes: score 1.
3. Degenerative changes (incipient degree): score 2.
4. Degenerative changes (moderate degree): score 3.
5. Degenerative changes (severe degree): score 4.
6. Degenerative changes with signs of degenerative disc disease: score 5.
7. Degenerative changes with signs of degenerative disc disease + anterior/posterior marginal osteophytosis: score 6.

LAT 11 (Instability). Lumbar Spine (L1-S1): Sagittal alignment of the posterior vertebral walls.
1. Preserved: score 0.
2. Instability: score 1.

LAT 11-1 (Instability). Lumbar Spine (L1-S1): Retrolisthesis.
1. Preserved: score 0.
2. Retrolisthesis: score 1.

LAT 11-2 (Instability). Lumbar Spine (L1-S1): Anterolisthesis.
1. Preserved: score 0.
2. Anterolisthesis:
2.1. G1: Low-grade spondylolisthesis with displacement < or = 25% according to Meyerding's classification [44]: score 1.
2.2. G2: Low-grade spondylolisthesis with displacement between 26% and 50% according to Meyerding's classification: score 2.
2.3. G3: High-grade spondylolisthesis with displacement between 51% and 75% according to Meyerding's classification: score 3.
G4: High-grade spondylolisthesis with displacement between 76% and 100% according to Meyerding's classification: score 4.

STUDY DESIGN:

Seventy-three patients (48 females and 25 males) suffering from AD and with no significant high IgE levels participated in this study. Due to the difficulty in recruiting patients without spinal biomechanical alterations, in the first part of the study patients were divided into two groups according to their dermatitis severity measured using the EASI score (see above): patients with EASI score equal to or lower than 7 units (n=33) and patients with EASI score higher than 7 units (n=40). The male/female and age ratios were similar in both groups. Following diagnosis, patients were treated with a topical compound anti-inflammatory cream, 3 times a day for 15 days. The composition of the cream was as follows: beeler C.S.P. 100 g, pentoxifylline 3%, gentamicin 0.1%, triancenalon acetonide 0.1%, despantenol 5%, aloe vera 15%, vitamin E 5%, nicotinamide 5%, glycerin 15%, melatonin 1%, and indomethacin 3%[24].

In the second part of the study, 51 patients voluntarily chose to be treated through chiropractic spinal manipulative therapy (SMT), a current treatment for biomechanical problems of the spine[25,26]. The remaining 22 patients were used as control group.

The following data were analyzed in all patients: a. dermatological examination once a month with quantification of the EASI score; b. radiographic description and quantification of the spinal biomechanical alterations (SBA) severity; and c. once a month measurement of plasma CGRP levels.

DETERMINATION OF CALCITONIN GENE-RELATED PEPTIDE:

Blood calcitonin gene-related peptide (CGRP) levels were determined in duplicate using a commercial Elisa kit, EAI kit (K-015–09, Phoenix Pharmaceuticals).

CHIROPRACTIC SPINAL MANIPULATION TREATMENT:

Patients that chose to be treated by chiropractic spinal manipulation treatment (SMT) underwent 12 sessions of chiropractic treatment as follows: twice a week for 3 weeks, once a week for 4 weeks, and twice a month for one month. The duration of the chiropractic treatment was 3 months. The chiropractors aimed to detect and treat with specific manual techniques, called "adjustments", also known as SMT[27,28], any alteration in the normal dynamic, anatomical or physiological joint relationships of adjacent structures in the spine to restore proper spinal biomechanics and physiological balance. Two types of techniques were used: high-velocity, low amplitude (HVLA)-diversified technique[29] and activator technique[30].

DATA ANALYSIS:

To compare non-parametric variables U-Mann Whitney test was performed for group comparison. In addition, non-parametric linear Gaussian test was performed to find correlations between the levels of variables. To study correlations, only the most severe patients with EASI>7 group were used. All statistics analyses were conducted using GraphPad Prism® version 10, GraphPad Software, San Diego, California, USA. The results are shown as the mean ± SD.

Results:

THE SEVERITY OF DEGENERATIVE CHANGES INDUCED BY SBA CORRELATED WITH THE SEVERITY OF DERMATITIS AND THE CGRP LEVELS:

The scores assigned to the different parts of the spine of a patient were then summed, thereby calculating a total spine SBA severity score for that patient. None of the 73 patients participating in this study was free of radiographically evidenced spinal biomechanical alterations and, they were divided into two groups according to the severity of the dermatitis, based on the EASI score. As expected, difference in EASI scores between the EASI≤7 group and the EASI>7 group was statistically significant (Figure 1a). Difference in the total spine severity score of the two groups was also statistically significant (Figure 1b). A good correlation (R= 0.76) between the severity of AD and the total spine severity score (Figure 1c) was observed. Interestingly, CGRP levels were also higher in the EASI>7 group (Figure 1d) and they correlated with EASI scores (R= 0.70, Figure 1e) and the spine severity scores (R= 0.70, Figure 1f).

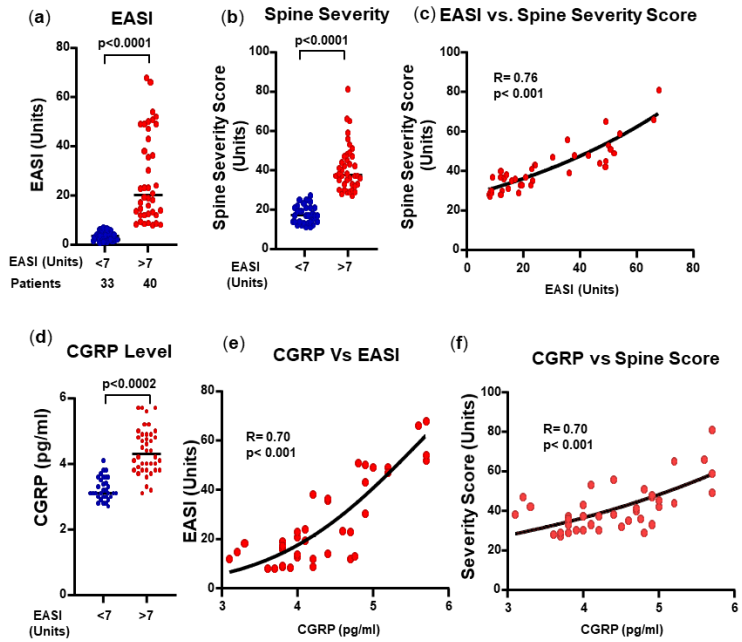


Figure 1. Correlation between the severity of dermatitis (EASI), the spinal condition and CGRP. (a) EASI score in the two groups. (b) Total spine severity score. (c) Correlation between total spine severity scores and EASI scores. (d) CGRP levels. (e) Correlation between CGRP levels and EASI scores. (f) Correlation between CGRP levels and total spine severity scores.

DEGENERATIVE CHANGES IN THE CERVICAL SPINE:

The study then determined which areas of the spine were responsible for the correlation between SBA severity and the dermatological anomalies. For this purpose, the spinal severity score was calculated starting from the upper (C1-Atlas) to the lower spinal section (Sacral section) separately. This calculation aimed at establishing which specific area of the spine (i.e., cervical, thoracic, lumbar, and sacro-coccygeal, including sagittal balance) could be associated with dermatitis.

When comparing the severity score of the cervical spine (C1 to C7), a significant difference was observed between the EASI≤7 and the EASI>7 group (Figure 2a). A good correlation was observed between the spine severity and the EASI (R= 0.73, Figure 2b) or the CGRP levels (R= 0.74, Figure 2c). The different segments of the cervical spine were analysed in more detail in Supplementary Figures.

ALTERATIONS IN THE SAGITTAL BALANCE OF THE SPINE

The sagittal balance of the spine refers to the physiological spinal alignment in the sagittal plane. Muscular forces maintain this balance. During walking and vertical movements, this balance is constantly challenged by single-foot support. The pelvic prevalence is persistent, and the sacral slope in addition to the pelvic angle are positional. The cervical boundaries are the superior (O–C2), lower cervical curve (C2–C7), the slope of C7, the vertical cervical balance, and the spinal-cranial position. Apart from the cervical lordosis, the thoracic and lumbar spine are kyphosis and lordosis, respectively[31,32].

In order to analyse the sagittal balance of the spine radiographic lateral views of the patients' spine were evaluated. There was a statistically significant difference in the thoracic spine total severity score between patients with EASI≤7 and those with EASI>7s (Figure 2d). Nevertheless, the correlations of the severity scores of the sagittal balance and the importance of cutaneous involvement were borderline significant (Figure 2e), as well as with the CGRP levels (Figure 2f).

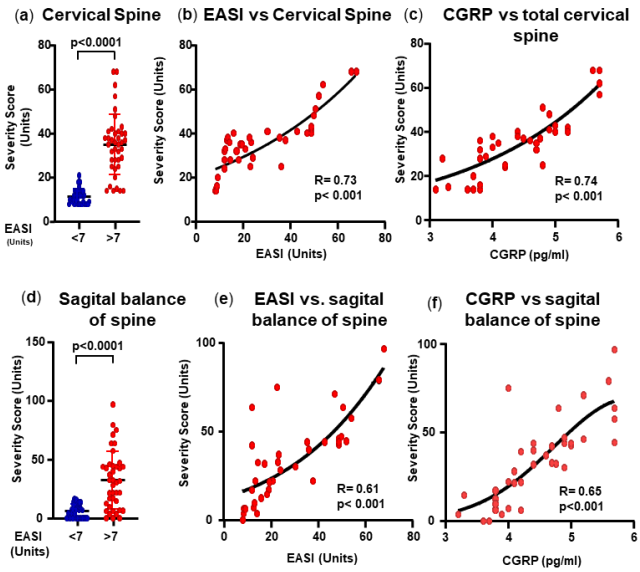


Figure 2. Cervical spine and sagittal balance of the spine. (a) Cervical spine severity score. (b) Correlation between cervical spine severity scores and EASI scores. (c) Correlation between cervical spine severity scores and CGRP levels. (d) Levels of sagittal balance of the spine. (e) Correlation between the levels of sagittal balance of the spine and EASI scores. (f) Correlation between the levels of sagittal balance of the spine and CGRP levels.

THORACIC SPINE SEVERITY SCORE:

These scores were calculated by reviewing the lateral X-ray images of the patients' spine. There was a statistically significant difference in thoracic spine total severity score between patients with EASI≤7 and those with EASI>7 (Figure 3a). While there was a reduced correlation between the severity of spinal degeneration and that of dermatitis (Figure 3b), there was a good correlation with the CGRP levels (Figure 3c).

LUMBAR SPINE SEGMENTS SEVERITY SCORE:

The lumbar spine segments are located at the bottom of the spine, between the thoracic and the sacral segments. It consists of five separate vertebrae that are the largest vertebrae in the human spine. The lumbar segments help the spine to support its structure. Concerning the lumbar spine, there was a statistically significant difference between the EASI≤7 group and the EASI>7 group (Figure 3d). Moreover, the correlation between the EASI score and the lumbar spine severity score was R=0.63, which was close to significance (Figure 3e). However, there was an excellent correlation (R= 0.88) between the spine severity scores and the CGRP levels (Figure 3f).

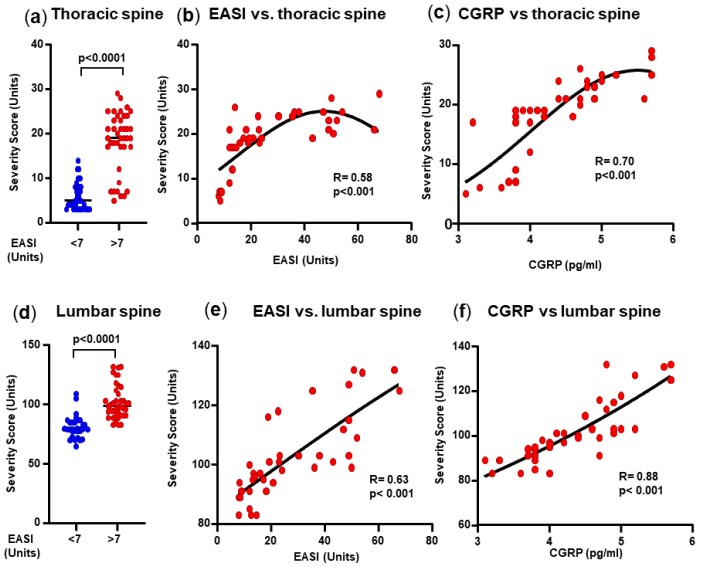


Figure 3. Thoracic spine and lumbar spine. (a) Thoracic spine severity score. (b) Correlation between thoracic spine severity scores and EASI scores. (c) Correlation between thoracic spine severity scores and CGRP levels. (d) Lumbar spine severity score. (e) Correlation between lumbar spine severity scores and EASI scores. (f) Correlation between lumbar spine severity scores and CGRP levels.

SACRAL AND COCCYX SCORE AREA:

The sacrum is a large and flat bone located below the last lumbar vertebra (L5) and the coccyx is located under the sacrum. The sacrum consists of 5 vertebrae (S1-S5) while the coccyx is made up by 3 to 5 small bones. Both help in supporting the human weight and are essential for walking, standing, and sitting. There was a difference between the two EASI groups (Fig 4(a)). The correlation between the severity score and EASI level was significant (Fig 4(b)), as well with the CGRP values (Fig 4(c)).

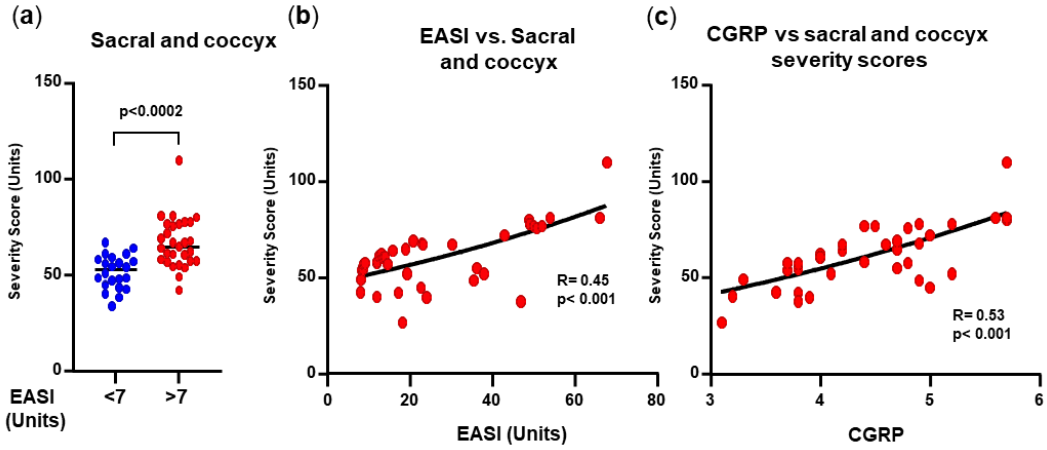


Figure 4. Coccyx and sacral spine. (a) Coccyx and sacral spine severity score. (b) Correlation between coccyx and sacral spine severity scores and EASI scores. (c) Correlation between coccyx and sacral spine severity scores and Calcitonin Gene-Related Peptide (CGRP) levels.

THE AGE OF THE PATIENTS CORRELATED WITH THE SEVERITY OF DERMATITIS:

Aging causes important cutaneous modifications. With age the stratum corneum and epidermis becomes thicker, the papillary dermis contains less collagen than the reticular dermis and is more fragmented and clustered, epidermal rete edges and the dermal/epidermal junction dermal papillae become flat due to the retraction of villi. In addition, in the stratum basale, keratinocytes proliferate less and fibroblasts have a lower ability to migrate, due to the fragmented extracellular matrix[33].

Aging in patients with AD has been reported to exhibit unique clinical phenotypes and immunologic endotypes[34-36]. Hence, the effect of age in relation to the importance of dermatological lesions was evaluated in all patients. An excellent correlation was found between the age of the patients and the EASI score (R= 0.81, Figure 5a), thus suggesting that age is associated with more severe clinical presentation of AD. Age was also associated with spinal damage severity score, but with a limited value of R= 0.61 (Figure 5b), and with the GCRP levels (R= 0.59, Figure 5c).

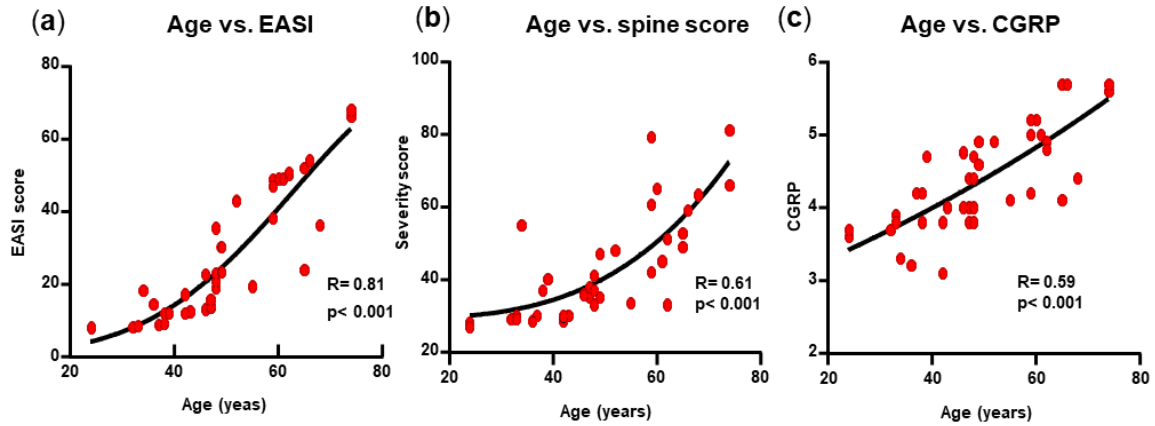


Figure 5. Correlation between patient age and atopic dermatitis. (a) Correlation between patient age and EASI scores. (b) Correlation between patient age and CGRP levels. (c) Correlation between patient age and total spine severity scores.

CHIROPRACTIC SPINAL MANIPULATIVE THERAPY AS COMPLEMENTARY THERAPEUTIC TOOL:

All 73 patients were treated with a topical anti-inflammatory cream 3 times a day for 15 days as soon as dermatitis was diagnosed 51. Patients chose to be treated by the chiropractic spinal manipulative therapy (SMT). The 22 patients who chose not to undergo chiropractic treatment were used as control group. The chiropractic SMT consisted of 12 sessions during 3 months distributed as follows: twice a week for 3 weeks, once a week for 4 weeks, and twice a month for one month.

Before chiropractic SMT, the spine severity scores, the EASI scores and the CGRP levels of the treatment and control groups were similar (Figures 6a, 6b and 6c). In the control group treated only with the cream, the EASI score decreased significantly after 2 weeks ($p < 0.005$, Figure 6d). However, after 3 months, the EASI score increased again ($p < 0.02$, Figure 6d). No significant differences were found between the EASI score before cream treatment and after 3 months (Figure 6d). After 3 months of chiropractic SMT, the EASI scores and the CGRP levels decreased significantly ($p < 0.0001$, Figures 6e and 6f). When we compared the effect of chiropractic treatment in relation to the group untreated, both the levels of EASI and CGRP levels were significantly reduced ($p < 0.0001$, Figures 6g and 6h).

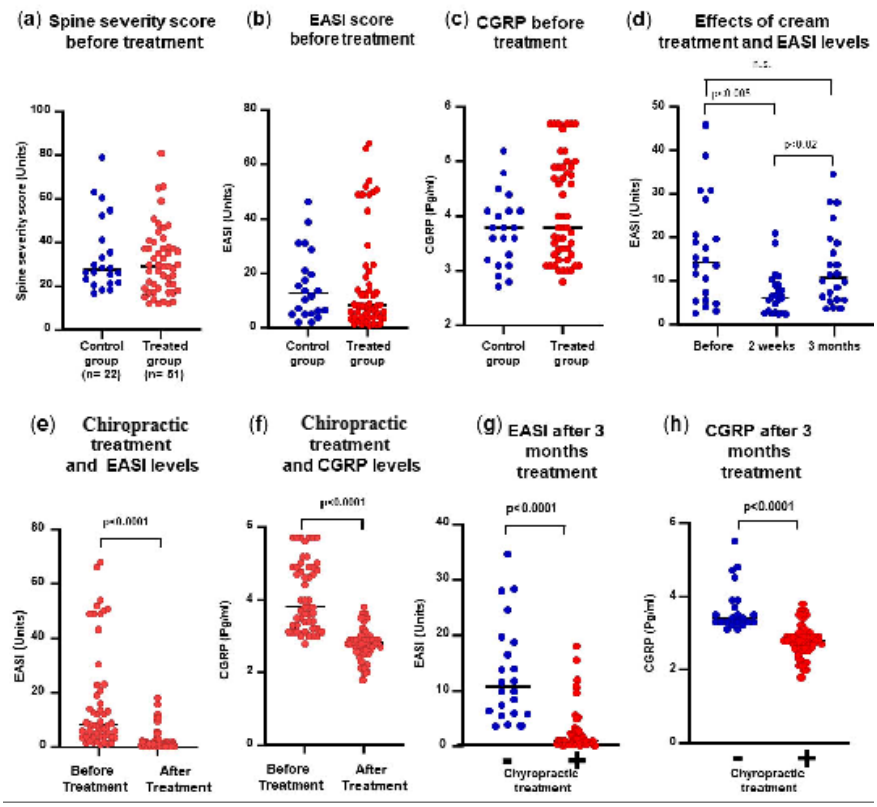


Figure 6. Effect of chiropractic Spinal ManipulationTreatment (SMT) on the EASI scores and (CGRP levels. (a) Total spine severity score before treatment. (b) EASI score before treatment. (c) CGRP level before treatment. (d) Effects of cream treatment on the EASI scores. (e) Effects of chiropractic SMT on the EASI scores. (f) Effects of chiropractic SMT on the CGRP levels. (g) EASI score after 3 months of treatment. (h) CGRP level after 3 months of treatment.

Moreover, the EASI scores before and after treatment correlated with the CGRP levels before and after treatment ($R = 0.70$, Figure 7a), suggesting a close relationship between both parameters. Finally, the decrease of CGRP levels before and after treatment correlated negatively with the patients' age ($R = 0.73$, Figure 7b). This may be related to the different spinal biomechanical alterations associated with aging[37-39].

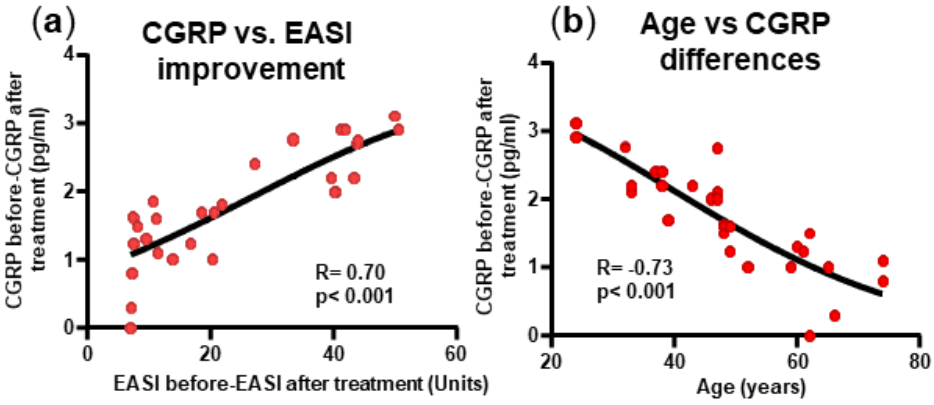


Figure 7. Improvement of clinical parameters after chiropractic SMT correlated with amelioration of the CGRP values a) Correlation between CGRP level and EASI score improvements after chiropractic SMT. (b) After chiropractic SMT, the figure shows the correlation between CGRP level improvement and age of patients.

Discussion:

The results obtained in this study showed a strong correlation between the altered biomechanics of spine and the extent of dermatological lesions of intrinsic AD. Regarding the different spinal segments, the EASI scores of patients suffering from AD were well correlated, particularly with SBAs in the cervical spine as well as in the sagittal balance of the spine. In the upper cervical spine (C1-C2 and C3-C7 segments), a good correlation was found between SBAs and EASI scores (R=0.79 and R=0.64). Remarkably, in this study patients with manifestation of dermatitis on the arms and hands showed more severe SBAs in the C3-C7 segment where the nervous fibres directly affect the epithelial cell in the chest, shoulders, arms, and hands[40]. Of note, both measurements are related areas of high spinal mobility and are probably caused by modern habits, such as the use of smartphones[41,42].

Regarding the thoracic column, no correlations were found between the EASI scores and the radiographic alterations in the T1 to T9 column area. However, alterations in the T10 vertebrae correlated with the EASI scores (R= 0.81), as well as with the CGRP levels (R= 0.78). This may be related to the different biomechanical behaviour with greater mobility of this area in relation to the rest of the thoracic spine[43,44].

The lumbar spine is one of the most injured areas because it bears the most pressure when holding and pushing, hence resulting in more damage and injury[45,46]. In this study, a correlation was found between the lumbar severity scores and the EASI scores (R= 0.63) and the CGRP levels (R= 0.88).

The spinal nerves of the sacrum and coccyx can directly affect epithelial cells in the sacral area, legs, feet, anus, and genital parts, resulting in dermatitis of the vagina (vaginitis), penis and scrotum[40]. Neurogenic inflammation caused by altered biomechanics of the sacrum has also been reported to correlate with inflammatory diseases in the genital area[47].

However, concerning the sacral and coccyx area, the results of this study did not indicate a good correlation between the EASI scores and the severity of spinal biomechanical alterations (R= 0.45).

Interestingly, this study found a strong correlation between the cutaneous disease involvement, the SBA and the CGRP levels. Peptide CGRP is released by sensory neurons and is one of the main components involved in neurogenic inflammation regulating pruritus in AD[48]. By using degenerated intervertebral discs from patients with low back pain and healthy, painless ones from human organ donors, cultured *ex vivo*, researchers observed a greater release of tumor necrosis factor (TNF)-α, interleukin-1β, nerve growth factor (NGF) and brain derived neurotrophic factor (BDNF), both associated with inflammation and chronic low back pain. Furthermore, factors released by degenerating intervertebral discs such as NGF increased neurite growth and CGRP expression[49].

These interactions may be triggered by the activation of Toll-like receptors by endogenous

alarmins such as fragmented extracellular matrix proteins found in degenerating discs or cartilage that produce NGF[50]. The role of CGRP depends on its localisation. In the dorsal horn, skin-mediated central pruritus causes neuroinflammation, neurogenic vasodilation, and modulation of cutaneous and immune cell function[48]. To amplify neuroinflammation, both immune cells, and keratinocytes release CGRP.

Of note, the CGRP levels before and after chiropractic treatment decreased with the age of the patients. This may be explained because despite its recognised benefit in elderly people[51], physical activity is much reduced[52]. This reduced mobility may also border on the correlation between chronic dermatitis and low bone mineral density associated with a high prevalence of osteopenia of the spine and hip[53].

The treatment of AD is based on reducing itch symptoms. As a primary anti-inflammatory drug, topical corticosteroids are the first-line therapy for acute flares of eczema[54]. In this study, treatment with topical anti-inflammatory compounds reduced to normal values the EASI scores and the CGRP levels of all patients. However, evidence suggests a limited effect for topical and systemic targeted neural therapies[55]. Given our clinical observation of the presence of spinal biomechanical alterations in all patients with AD, we decided to treat the patients with chiropractic SMT for 3 months[27,28]. In accord with a review study about the usefulness of CAM (Complementary Alternative Medicine) in treating AD, our results showed that chiropractic can be valid a supportive treatment[56].

Conclusions:

This study was undertaken because there are emerging evidences suggesting a role for neuro-immune interactions in dermatological diseases. However, at the present, no guideline-based method is available for treating dermatitis and the pathogenesis of intrinsic atopic dermatitis remains unknown. This comprehensive study of the spine reveals for the first time several items: a) There is a strong correlation between the severity of spine biomechanical alterations and the intensity of atopic dermatitis (EASI score). b) The levels of calcitonin gene-related peptide (CGRP) correlated with both the severity of spinal biomechanical alterations and with the EASI score. c) The treatment with anti-inflammatory drugs reduced the EASI score and the CGRP levels, but both increased again after 3 months. However, these parameters remained low after chiropractic spinal manipulation therapy. The implication of this study is that spinal biomechanical alterations (SBA) are one of the main causal factors of the pathophysiology of atopic dermatitis and neurogenic inflammation may be the bridge linking spine biomechanical alterations and the intensity of atopic dermatitis since both are correlated with CGRP levels. Finally, complementary alternative therapies such as chiropractic may be beneficial for patients with atopic dermatitis.

Conflict of Interest:

Authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Funding Statement:

None.

Acknowledgements:

We would like to thank the patients for their time and support in this study.

Data availability statement:

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

Disclosure Summary:

The authors have nothing to disclose.

Ethical Approval:

The study was reviewed on 2021/02/23 and approved by the ethics committee research with medications (CEIm), Hospital group Quiron Salud-Catalunya with protocol number INCV-001.

All patients gave written informed consent to participate in this study.

Author contribution:

Danial Khorsandi: Data curation, Formal analysis, Methodology, Investigation, Resources, Validation, Visualization, Writing Original Draft. Mackarena Ccoicca: Data curation, Investigation, Resources. Alex Ruiz: Formal analysis. Miguel Angel Tejero: Data curation, Investigation, Resources. Angela Olaru: Conceptualization, Project administration, Supervision, Validation, Writing, Review & Editing. Ignacio Umbert: Conceptualization, Investigation, Data curation, Methodology, Project administration, Supervision, Validation, Visualization, Writing, Review & Editing.

Consent for publication:

All the co-authors have consented to the publication of the study results.

References:

1. Leung DY, Bieber T. Atopic dermatitis. *Lancet* 2003; 361: 151-60.

2. Langan SM, Irvine AD, Weidinger S. Atopic dermatitis. *Lancet* 2020; 396: 345-60.

3. Kader HA, Azeem M, Jwayed SA *et al.* Current Insights into Immunology and Novel Therapeutics of Atopic Dermatitis. *Cells* 2021; 10.

4. Roguedas AM, Machet L, Fontes V *et al.* [Atopic dermatitis: which are the diagnostic criteria used in medical literature?]. *Ann. Dermatol. Venereol.* 2004; 131: 161-4.

5. Tokura Y, Hayano S. Subtypes of atopic dermatitis: From phenotype to endotype. *Allergol Int* 2022; 71: 14-24.

6. Misery L. Atopic dermatitis and the nervous system. *Clin Rev Allergy Immunol* 2011; 41: 259-66.

7. Fan J, Mishra SK. The emerging role of neuroimmune interactions in atopic dermatitis and itch. *FEBS J* 2022; 289: 2723-35.

8. Zhang Y, Zhang H, Jiang B *et al.* Current views on neuropeptides in atopic dermatitis. *Exp. Dermatol.* 2021; 30: 1588-97.

9. Marek-Jozefowicz L, Nedoszytko B, Grochocka M *et al.* Molecular Mechanisms of Neurogenic Inflammation of the Skin. *Int. J. Mol. Sci.* 2023; 24.

10. Garg NK, Silverberg JI. Eczema is associated with osteoporosis and fractures in adults: a US population-based study. *JACI* 2015; 135: 1085-7 e2.

11. Lowe KE, Mansfield KE, Delmestri A *et al.* Atopic eczema and fracture risk in adults: A population-based cohort study. *JACI* 2020; 145: 563-71 e8.

12. Bieber T. Atopic dermatitis. *NEJM* 2008; 358: 1483-94.

13. Leshem YA, Hajar T, Hanifin JM *et al.* What the Eczema Area and Severity Index score tells us about the severity of atopic dermatitis: an interpretability study. *BJD* 2015; 172: 1353-7.

14. Hanifin JM, Thurston M, Omoto M *et al.* The eczema area and severity index (EASI): assessment of reliability in atopic dermatitis. EASI Evaluator Group. *Exp. Dermatol.* 2001; 10: 11-8.

15. Silverberg JI, Lei D, Yousaf M *et al.* What are the best endpoints for Eczema Area and Severity Index and Scoring Atopic Dermatitis in clinical practice? A prospective observational study. *BJD* 2021; 184: 888-95.

16. Harrop JS, Vaccaro AR, Hurlbert RJ *et al.* Intrarater and interrater reliability and validity in the assessment of the mechanism of injury and integrity of the posterior ligamentous complex: a novel injury severity scoring system for thoracolumbar injuries. *J. Neurosurg. Spine* 2006; 4: 118-22.

17. Lee JY, Vaccaro AR, Lim MR *et al.* Thoracolumbar injury classification and severity score: a new paradigm for the treatment of thoracolumbar spine trauma. *J. Orthop. Sci.* 2005; 10: 671-5.

18. Kotil K, Alan MS, Bilge T. Medical management of Pott disease in the thoracic and lumbar spine: a prospective clinical study. *J. Neurosurg. Spine* 2007; 6: 222-8.

19. Kaale BR, Krakenes J, Albrektsen G *et al.* Whiplash-associated disorders impairment rating: neck disability index score according to severity of MRI findings of ligaments and membranes in the upper cervical spine. *J. Neurotrauma* 2005; 22: 466-75.

20. Hasegawa K, Kitahara K, Shimoda H *et al.* Facet joint opening in lumbar degenerative diseases indicating segmental instability. *J. Neurosurg. Spine* 2010; 12: 687-93.

21. Lotz JC, Haughton V, Boden SD *et al.* New treatments and imaging strategies in degenerative disease of the intervertebral disks. *Radiology* 2012; 264: 6-19.

22. Garg A, Kapellusch JM. Applications of biomechanics for prevention of work-related musculoskeletal disorders. *Ergonomics* 2009; 52: 36-59.

23. Anderson PA, Moore TA, Davis KW *et al.* Cervical spine injury severity score. Assessment of reliability. *J. Bone Joint Surg. Am.* 2007; 89: 1057-65.

24. Umbert I, Sans G, Valls J *et al.* EP2311454 treatment for atopic dermatitis: therapeutic efficiency in patients and anti-inflammatory in vitro. *Clin. Dermatol.* 2017; 5: 5-11.

25. Trager RJ, Bejarano G, Perfecto RT *et al.* Chiropractic and Spinal Manipulation: A Review of Research Trends, Evidence Gaps, and Guideline Recommendations. *J. Clin. Med.* 2024; 13.

26. Young KJ, Leboeuf-Yde C, Gorrell L *et al.* Mechanisms of manipulation: a systematic review of the literature on immediate anatomical structural or positional changes in response to manually delivered high-velocity, low-amplitude spinal manipulation. *Chiropr. Man. Ther.* 2024; 32: 28.

27. Rubinstein SM, de Zoete A, van Middelkoop M *et al.* Benefits and harms of spinal manipulative therapy for the treatment of chronic low back pain: systematic review and meta-analysis of randomised controlled trials. *BMJ* 2019; 364: l689.

28. Qaseem A, Wilt TJ, McLean RM *et al.* Noninvasive Treatments for Acute, Subacute, and Chronic Low Back Pain: A Clinical Practice Guideline From the American College of Physicians. *Ann. Intern. Med.* 2017; 166: 514-30.

29. Haavik H, Kumari N, Holt K *et al.* The contemporary model of vertebral column joint dysfunction and impact of high-velocity, low-amplitude controlled vertebral thrusts on neuromuscular function. *Eur. J. Appl. Physiol.* 2021; 121: 2675-720.

30. Bussieres AE, Stewart G, Al-Zoubi F *et al.* Spinal Manipulative Therapy and Other Conservative Treatments for Low Back Pain: A Guideline From the Canadian Chiropractic Guideline Initiative. *J Manipulative Physiol Ther* 2018; 41: 265-93.

31. Le Huec JC, Thompson W, Mohsinaly Y *et al.* Sagittal balance of the spine. *Eur. Spine J.* 2019; 28: 1889-905.

32. Ling FP, Chevillotte T, Leglise A *et al.* Which parameters are relevant in sagittal balance analysis of the cervical spine? A literature review. *Eur. Spine J.* 2018; 27: 8-15.

33. Blair MJ, Jones JD, Woessner AE *et al.* Skin Structure-Function Relationships and the Wound Healing Response to Intrinsic Aging. *Adv. Wound Care* 2020; 9: 127-43.

34. Williamson S, Merritt J, De Benedetto A. Atopic dermatitis in the elderly: a review of clinical and pathophysiological hallmarks. *Br. J. Dermatol.* 2020; 182: 47-54.

35. Tanei R. Atopic Dermatitis in Older Adults: A Review of Treatment Options. *Drugs Aging* 2020; 37: 149-60.

36. Wang S, Zhu R, Gu C *et al.* Distinct clinical features and serum cytokine pattern of elderly atopic dermatitis in China. *JEADV* 2020; 34: 2346-52.

37. Coskun Benlidayi I, Basaran S. Comparative study of lumbosacral alignment in elderly versus young adults: data on patients with low back pain. *ACER* 2015; 27: 297-302.

38. Jinkins JR. Acquired degenerative changes of the intervertebral segments at and suprajacent to the lumbosacral junction. A radioanatomic analysis of the nondiskal structures of the spinal column and perispinal soft tissues. *Radiol Clin North Am* 2001; 39: 73-99.

39. Galbusera F, van Rijsbergen M, Ito K *et al.* Ageing and degenerative changes of the intervertebral disc and their impact on spinal flexibility. *Eur. Spine J.* 2014; 23 Suppl 3: S324-32.

40. Stecco C, Pirri C, Fede C *et al.* Dermatome and fasciatome. *Clin. Anat.* 2019; 32: 896-902.

41. Park JHM, Kang SYP, Lee SGP *et al.* The effects of smart phone gaming duration on muscle activation and spinal posture: Pilot study. *Physiother. Theory Pract.* 2017; 33: 661-9.

42. Rodriguez-Sanz J, Carrasco-Uribarren A, Cabanillas-Barea S *et al.* Validity and reliability of two Smartphone applications to measure the lower and upper cervical spine range of motion in subjects with chronic cervical pain. *J Back Musculoskelet Rehabil* 2019; 32: 619-27.

43. Burgos J, Barrios C, Mariscal G *et al.* Non-uniform Segmental Range of Motion of the Thoracic Spine During Maximal Inspiration and Exhalation in Healthy Subjects. *Front. Med.* 2021; 8: 699357.

44. Morita D, Yukawa Y, Nakashima H *et al.* Range of motion of thoracic spine in sagittal plane. *Eur. Spine J.* 2014; 23: 673-8.

45. Liyew WA. Clinical Presentations of Lumbar Disc Degeneration and Lumbosacral Nerve Lesions. *Int. J. Rheumatol.* 2020; 2020: 2919625.

46. Brooks BK, Southam SL, Mlady GW *et al.* Lumbar spine spondylolysis in the adult population: using computed tomography to evaluate the possibility of adult onset lumbar spondylosis as a cause of back pain. *Skelet. Radiol.* 2010; 39: 669-73.

47. Wesselmann U. Neurogenic inflammation and chronic pelvic pain. *World J. Urol.* 2001; 19: 180-5.

48. Steinhoff M, Ahmad F, Pandey A *et al.* Neuroimmune communication regulating pruritus in atopic dermatitis. *JACI* 2022; 149: 1875-98.

49. Krock E, Rosenzweig DH, Chabot-Dore AJ *et al.* Painful, degenerating intervertebral discs up-regulate neurite sprouting and CGRP through nociceptive factors. *J Cell Mol Med* 2014; 18: 1213-25.

50. Krock E, Currie JB, Weber MH *et al.* Nerve Growth Factor Is Regulated by Toll-Like Receptor 2 in Human Intervertebral Discs. *J. Biol. Chem.* 2016; 291: 3541-51.

51. Pahor M, Guralnik JM, Ambrosius WT *et al.* Effect of structured physical activity on prevention of major mobility disability in older adults: the LIFE study randomized clinical trial. *JAMA* 2014; 311: 2387-96.

52. Keadle SK, McKinnon R, Graubard BI *et al.* Prevalence and trends in physical activity among older adults in the United States: A comparison across three national surveys. *Prev. Med.* 2016; 89: 37-43.

53. Haeck IM, Hamdy NA, Timmer-de Mik L *et al.* Low bone mineral density in adult patients with moderate to severe atopic dermatitis. *BJD* 2009; 161: 1248-54.

54. Tadicherla S, Ross K, Shenefelt PD *et al.* Topical corticosteroids in dermatology. *JDD* 2009; 8: 1093-105.

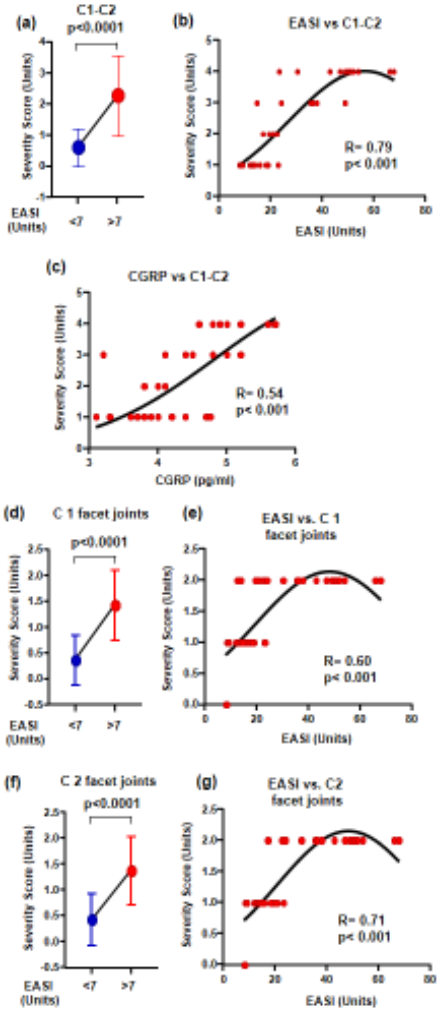
55. Elmariah SB. Adjunctive Management of Itch in Atopic Dermatitis. *Dermatol. Clin.* 2017; 35: 373-94.

56. Vieira BL, Lim NR, Lohman ME *et al.* Complementary and Alternative Medicine for Atopic Dermatitis: An Evidence-Based Review. *Am. J. Clin. Dermatol.* 2016; 17: 557-81.

Supplementary Figures:

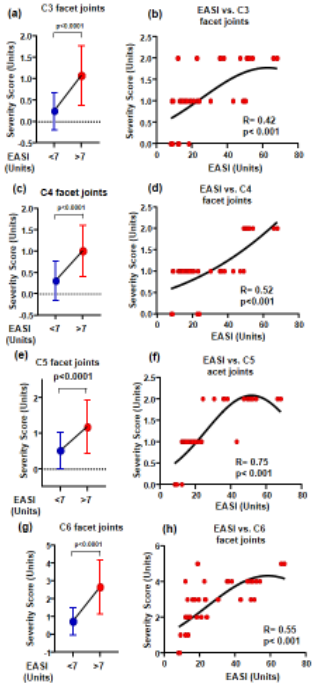
Anteroposterior and open mouth views of the cervical spine

The C1 (atlas)-C2 (axis) relationship showed that the spine severity score in patients with EASI>7 was almost 4-times higher than in patients with EASI≤7 (Figure S1a). Therefore, there was a high correlation between the severity of spine alterations and that of skin involvement (Figure S1b, R= 0.79). However, the correlation with the CGRP levels was limited (Figure S1c, R= 0.54). The C1 and C2 vertebra preservation of its zygapophyseal or facet joints was also measured. These are synovial joints between the superior articular process of one vertebra and the inferior articular process of the vertebra directly above or below it. There are two facet joints in each spinal motion segment. A statistically significant difference in the C1 facet degeneration (p<0.0001) was observed between the two EASI groups (Figure S1d). However, the correlation between the C1 segment damage and the dermatitis magnitude was limited (R= 0.60, Figure S1e). Regarding the C2 facet degeneration, the difference between the two EASI groups was also statistically significant (p< 0.0001, Figure S1f), and there was a good correlation between the EASI scores and the facet degeneration (R= 0.71, Figure S1g).

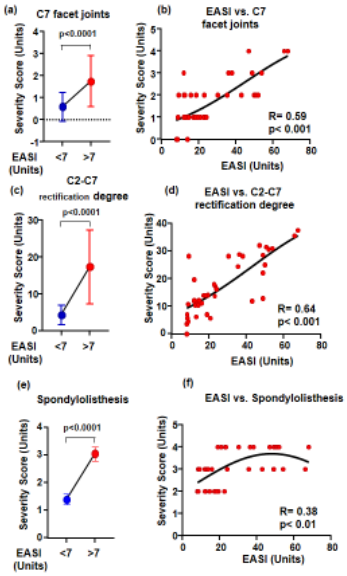


Figures S1. C1-C2 relationship of cervical spine and C1 and C2 facet joints. (**a**) Levels of C1-C2 relationship severity score. (**b**) Correlation between C1-C2 relationship severity score and EASI. (**c**) Correlation between the levels of the C1-C2 relationship severity score and CGRP. (**d**) Levels of C1 facet joints of the spine. (**e**) Correlation between the levels of C1 facet joints of the spine and EASI. (**f**) Levels of C2 facet joints of the spine. (**g**) Correlation between the levels of C2 facet joints of the spine and EASI.

The cervical vertebral segments C3 - C4 - C5 – C6 – C7, the zygapophyseal joints and uncoapophyseal joints (also called 'Lushka joints') [31] were examined The C3 segment facilitates the bending and rotation of the neck, therefore, this cervical segment may be subject to mechanical disorders by work-related activities such as reading, writing, typing, etc. There was a statistically significant difference ($p<0.0001$) in the C3 severity score between the two EASI groups (Figure S2a). However, the correlation between the EASI score and the C3 severity score in the EASI>7 group was limited (R=0.42) (Figure S2b). Segments C4, C5, C6 and C7, differences according to the EASI score were found in all cases (Figures S2c, S2e, S2g, and S3a). The values of the EASI score and the severity score for C4, C6, and C7 were correlated (R= 0.52, R= 0.55, and R= 0.59, Figures S2d, S2h, and S3b, respectively) and a better correlation was found for C5 (R= 0.75, Figure S2f). The lateral views of cervical spine radiographs were also evaluated. The C2–C7 angle was defined as the angle between the lines parallel to the inferior end plate of C2 and C7 vertebral bodies (Cobb's method) (*Harrison DE, Harrison DD, Cailliet R et al. Cobb method or Harrison posterior tangent method: which to choose for lateral cervical radiographic analysis. Spine 2000; 25: 2072-8*). The value of C2–C7 angles indicated a lordosis at the measured segments. The rectification angle in the 73 patients varied from 0 to 38. There was a statistically significant difference between patients with low and high EASI scores (Figure S3c) and a moderate correlation between the EASI score and the spine severity scores (R= 0.64; Figure S3d). Spondylolisthesis, the slippage of vertebra forwards or backwards,was diagnosed in almost 87% of the patients in the study. The spondylolisthesis was graded according to Meyerding classification (*Meyerding HW. Spondylolisthesis; surgical fusion of lumbosacral portion of spinal column and interarticular facets; use of autogenous bone grafts for relief of disabling backache. Journal of the International College of Surgeons* 1956; 26: 566-91). There was a statistically significant difference ($P<0.0001$, Figure S3e) between the severity of spondylolisthesis in patients with EASI≤7 and those with EASI>7. No correlation between the EASI scores and the spondylolisthesis severity scores was found (R= 0.36, Figure S3f).



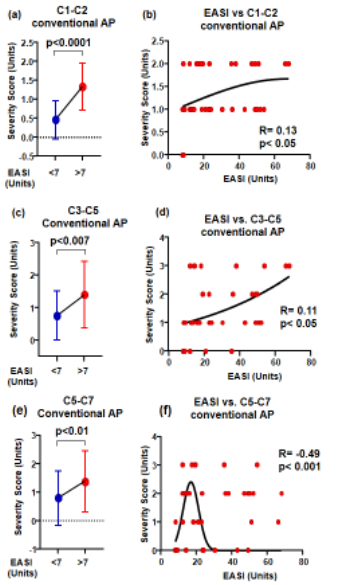
Figures S2. C3, C4, C5 and C6 facet joints of cervical spine. (**a**) Levels of C3 facet joints of the spine. (**b**) Correlation between the levels of C3 facet joints of the spine and EASI. (**c**) Levels of C4 facet joints of the spine. (**d**) Correlation between the levels of C4 facet joints of the spine and EASI. (**e**) Levels of C5 facet joints of the spine. (**f**) Correlation between the levels of C5 facet joints of the spine and EASI. (**g**) Levels of C6 facet joints of the spine. (**h**) Correlation between the levels of C6 facet joints of the spine and EASI.



Figures S3. C7 facet joints of cervical spine and levels of rectification degree of the spine (**a**) Levels of C7 facet joints of the spine. (**b**) Correlation between the levels of C7 facet joints of the spine and EASI. (**c**) Levels of rectification degree of the spine. (**d**) Correlation between the levels of rectification degree of the spine and EASI. (**e**) Levels of spondylolisthesis of the spine. (**f**) Correlation between the levels of spondylolisthesis of the spine and EASI.

Analysis of the conventional anterior-posterior view of the cervical spine

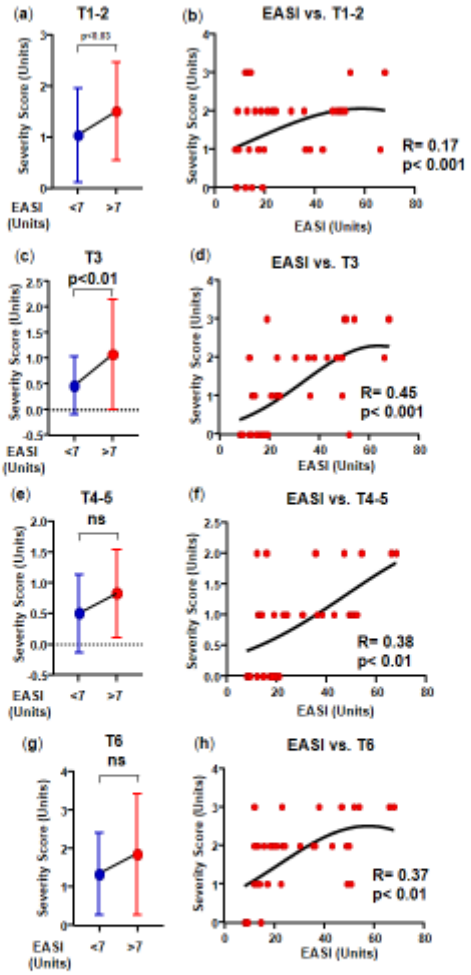
The cervical spine was divided into three sections: C1-C2, C3-C5, and C5-C7. The conventional anterior-posterior open mouth X-ray of the cervical spine revealed a significant difference between the severity score in patients with EASI≤7 and those with EASI>7 (Figures S4a, S4c and S4e). Conversely, no correlations were found between the spine severity scores and the EASI scores (Figures S4b, S4d and S4f).



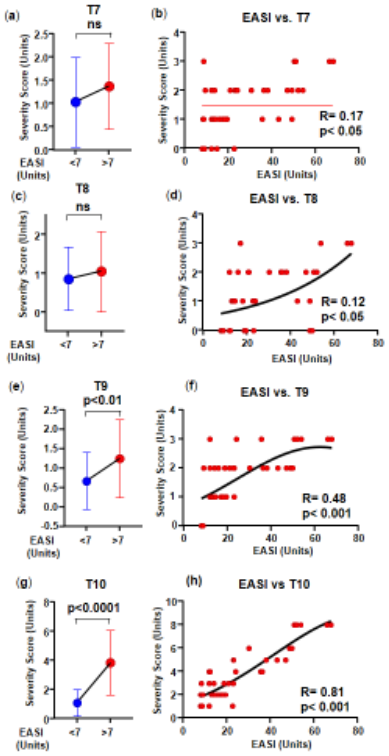
Figures S4. Conventional antero-posterior (AP) view of the spine. (**a**) Levels of C1-C2 conventional AP. (**b**) Correlation between the levels of C1-C2 conventional AP and EASI. (**c**) Levels of C3-C5 conventional AP. (**d**) Correlation between the levels of C3-C5 conventional AP and EASI. (**e**) Levels of C5-C7 conventional AP. (**f**) Correlation between the levels of C5-C7 conventional AP and EASI.

Thoracic spine analyzed in detail

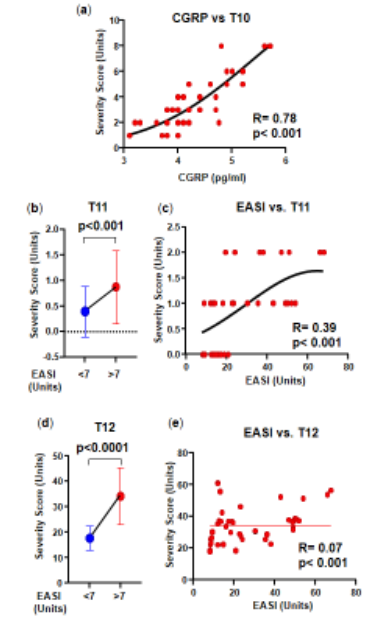
When the thoracic spine was analyzed in detail, a small but statistically significant difference was found in T1-2 and in T3 (Figures S5a and S5c) between the EASI≤7 group and the EASI>7 group. No differences between the two groups were found in T4-5, T6, T7 and T8 (Figures S5e, S5g, S6a and S6c). Conversely, in the lower part of the dorsal spine (T9, T10, T11, and T12), a statistically significant difference was found between the two groups (Figures S6e, S6g, S7b and S7d). No correlations were found in most of the cases between the severity scores of the different thoracic spines and the severity of dermatitis (Figures S5b, S5f, S5h, S6b, S6d, S7c and S7e). This correlation was found in the T3 and T9 segments (Figures S5d and S6f). Finally, T10 showed a strong correlation, not only between the spine severity scores and the EASI scores (R= 0.81, Figure S5h), but also with the CGRP levels (R= 0.78, Figure S7a).



Figures S5. Thoracic spine. (**a**) Levels of T1-T2. (**b**) Correlation between the levels of T1-T2 and EASI. (**c**) Levels of T3. (**d**) Correlation between the levels of T3 and EASI. (**e**) Levels of T4-T5. (**f**) Correlation between the levels of T4-T5 and EASI. (**g**) Levels of T6. (**h**) Correlation between the levels of T6 and EASI.



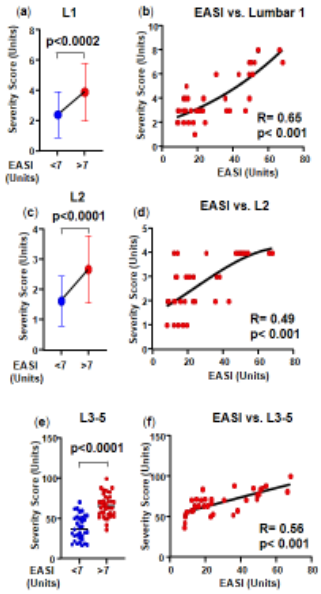
Figures S6. Thoracic spine T7, T8, T9 and T10. (**a**) Levels of T7. (**b**) Correlation between the levels of T7 and EASI. (**c**) Levels of T8. (**d**) Correlation between the levels of T8 and EASI. (**e**) Levels of T9. (**f**) Correlation between the levels of T9 and EASI. (**g**) Levels of T10. (**h**) Correlation between the levels of T10 and EASI.



Figures S7. Thoracic spine T11 and T12. (**a**) Correlation between the levels of T10 and CGRP. (**b**) Levels of T11. (**c**) Correlation between the levels of T11 and EASI. (**d**) Levels of T12. (**e**) Correlation between the levels of T12 and EASI.

Lumbar segments

To facilitate the analysis, the lumbar segments were divided into three segments: L1, L2 and L3-L5. A statistically significant difference in all three segments was found between the EASI≤7 group and the EASI>7 group (Figures S8a, S8c and S8f). Nevertheless, only L1 showed a correlation between the spine severity score and the EASI score (R= 0.65, Figure S8b). Both L2 and L3-L5 showed poor correlation (R= 0.49 and R= 0.56, respectively; Figures S8e and S8f).



Figures S8. Coccyx and sacral (lumbar) spine. (**a**) Levels of L1. (**b**) Correlation between the levels of L1 and EASI. (**c**) Levels of T2. (**d**) Correlation between the levels of T2 and EASI. (**e**) Levels of T3. (**f**) Correlation between the levels of T3 and EASI.

Graphical Abstract Image