Spinal Biomechanical Alterations, Neurogenic Inflammation (CGRP), Dermatitis

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Alteration of the Spine, Neurogenic inflammation (CGRP), and Dermatitis

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Human beings are members of a whole,
In creation of one essence and soul,
If one member is afflicted with pain,
Other members uneasy will remain,
If you've no sympathy for human pain,
The name of human you cannot retain.

Saadi Shirazi

Acknowledgement

This thesis becomes a reality with the kind support and help of many individuals. I would like to extend my sincere thanks to all of them.

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" تقدیم به مادر بزرگ عزیزم برای عشقی که در وجودش نهفته است و از آن عشق به ما هر آنچه که بوده را ارزانی داشته است."

I would like to direct this thesis to my grandma. She is the one who I missed the most.

The one who her prayers and kindness saved me from mistakes and darkness.

May God bless her!

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Abbreviations

AARF	Atlantoaxial Rotatory Fixation
ANS	Autonomic Nervous System
AP	Anteroposterior
AT	Atlas
Atv	Activator Technique
AV	Anterior Vertebral
Ax	Axis
BMD	Bone Mineral Density
C	Cervical
CCI	Cervical Curvature Index
CG	Control group
CGRP	Calcitonin Gene- Related Peptide
CNS	Central Nervous System
Co	Coccygeal
CSTS	Cervical Spine Total Severity score
CSVL	Central Sacrum Vertical Line
CT	Computer Tomographic
CVB	Coronal Vertebral Balance
DC	Doctor of Chiropractic
DT	Diversified Technique
EASI	Eczema Area and Severity Index
HVLA	High-Velocity, Low-Amplitude
IAD	Incontinence-Associated Dermatitis
IFN	Interferon
IgE	Immunoglobulin E
IL	Interleukin
L	Lumbar
LAT	Lateral
LBP	Low Back Pain
LL	Lumbar Lordosis

MSDs	Musculoskeletal disorders
NGF	Nerve Growth Factors
NK	Neurokinin receptor
OA	Osteoarthritis
OD-HA	Odontoid Hip Axis Measurement
PI	Pelvic Incidence
PL	Plumb Line
PT	Pelvic Tilt
PV	Posterior Vertebral
S	Sacral
SBA	Spinal Biomechanical Alterations
SBS	Sagittal Balance of the Spine
SL	Spinolaminar lines
SMT	Spinal Manipulative Therapy
SP	Substance P
SpSS	Spine Severity Score
SS	Sacral Slope
SVA	Sagittal Vertical Axis
T	Thoracic
TDT	Toggle Drop Technique
TG	Treatment Group
TP	Transverse Process
TTP	Thompson Terminal Point
VSB	Vertebral Sagittal Balance

Summary (English)

Dermatitis is a chronic inflammatory skin disease, described by intensive pruritus and eczematous lesions of skin. In most of the patients with Dermatitis, a long-lasting cycle of itch-scratch roots produces substantial morbidities and discomforts. For instance, sleeping problems, compromised quality of life, and psychosocial problems, as well as appearance-related complications including skin infections resulting to a loss of self-confidence. The purpose of treatment in dermatitis is to decrease symptoms, cure superinfection, avoid exacerbations, lessen the risk of treatment, and bring back the integrity of the skin. In most patients with mild Dermatitis, treatment goals can be accomplished with topical therapies, however, in patients with moderate to severe Dermatitis, treatment is still a challenge.

At present, a guideline-based method for treating Dermatitis is lacking and the pathogenesis of Dermatitis remains unknown. However, there is evidence that neuropeptides such as Calcitonin gene- related peptide (CGRP) influence the development and course of Dermatitis. Likewise, there are studies investigating spinal neurotransmitters in accordance with itching in dermatitis and it is reported that a species of neuropeptides is released from chloroquine-sensitive pruriceptors within the spine to arbitrate histamine-independent itch in Dermatitis. Moreover, a correlation between spine biomechanical alteration and Dermatitis is reported in numerous studies.

Therefore, the main objective of this work is to carry out a prospective study to determine the relationship between alterations in the spine and

Dermatitis by focusing on the level of CGRP in patients' plasma. Furthermore, in this study we set out to investigate whether chiropractic can be an effective treatment for dermatitis.

73 patients suffering from dermatitis participated in this study. 51 of these patients were randomly assigned to the treatment group and 22 patients were also randomly assigned to the control group. All patients in both, treatment and control groups, were prescribed a topical compound cream, containing emollient corticosteroid-indomethacin, and antioxidants. However, only patients in the treatment group underwent chiropractic treatment while patients in the control group only received the above-mentioned topical treatment. In order to accomplish our objectives, the following data was analyzed in patients of the treatment group: *(1)* Dermatological examination quantified using the Eczema Area and Severity Index (EASI) score method, *(2)* Radiographic description and quantification of the severity level of spinal biomechanical alterations (SBA), hereinafter referred to as (spinal) severity score. *(3)* Biological data including blood tests and measurement of plasma calcitonin gene-related peptide (CGRP) level in all the patients and *(4)* chiropractic spinal examination and treatment (SMT) and on a 3-month weekly plan. All data was compared and analyzed before and after the treatment in the 73 study patients.

The results presented in this study would be indicative of a correlation between the altered biomechanics of different spinal segments and the altered state of the skin. In this study we found that the EASI levels in the patients suffering from Dermatitis were significantly correlated with SBA in the Atlas- Axis (AT- AX) ($p< 0.001$; $r=0.82$), in the cervical spine ($r=0.91$), in the sagittal balance of the spine (SBS) ($p< 0.001$; $r=0.88$), in

Spondylolisthesis ($p < 0.001$; $r=0.85$), in Thoracic 10 ($p < 0.001$; $r=0.87$), in Lumbar 1 ($p < 0.001$; $r=0.81$), and Lumbar 2 ($p < 0.001$; $r=0.70$).

Overall, the results of this study indicated that improvement in the plasma CGRP level correlates with the improvement in the EASI level and the improvement in the SBA severity score. It suggests that spinal biomechanical alterations may contribute to the release of neuropeptides, including CGRP, from sensory nerves endings. Increase of plasma CGRP results in neurogenic inflammation of the skin and contributes to dermatological disorders such as dermatitis.

In addition, our results indicated a significant reduction in the CGRP level in patients of the treatment group (who underwent chiropractic spinal treatment) and following that a significant reduction in EASI scores (improvement of skin´s situation). On the other hand, although the EASI level of the patients in control group decreased after 2 weeks of using compound cream, the CGRP level remained altered and consequently, the dermatitis symptoms showed up in those patients after 3 months.

As a conclusion, the result of our study suggesting that there may be a strong correlation between the spine biomechanical alteration, CGRP level, and neurogenic inflammation of skin (in the form of Dermatitis of the skin). We also strongly suggest further investigations with bigger sample population.

Resumen (Castellano)

La dermatitis es una enfermedad inflamatoria crónica de la piel, descrita por prurito intensivo y lesiones cutáneas eccematosas. En la mayoría de los pacientes con dermatitis, un ciclo prolongado de raíces con picazón y rascado produce morbilidades y malestares sustanciales. Por ejemplo, problemas para dormir, calidad de vida comprometida y problemas psicosociales, así como complicaciones relacionadas con la apariencia, incluidas infecciones de la piel que provocan una pérdida de la confianza en uno mismo. El propósito del tratamiento de la dermatitis es disminuir los síntomas, curar la superinfección, evitar las exacerbaciones, disminuir el riesgo del tratamiento y devolver la integridad de la piel. En la mayoría de los pacientes con dermatitis leve, los objetivos del tratamiento se pueden lograr con terapias tópicas, sin embargo, en pacientes con dermatitis moderada a grave, el tratamiento sigue siendo un desafío.

En la actualidad, se carece de un método basado en directrices para el tratamiento de la dermatitis y se desconoce la patogenia de la dermatitis. Sin embargo, existe evidencia de que los neuropéptidos como el péptido relacionado con el gen de la calcitonina (CGRP) influyen en el desarrollo y el curso de la dermatitis. Asimismo, hay estudios que investigan los neurotransmisores espinales de acuerdo con la picazón en la dermatitis y se informa que una especie de neuropéptidos se libera de los pruriceptores sensibles a la cloroquina dentro de la columna vertebral para arbitrar la picazón independiente de histamina en la dermatitis. Además, en numerosos estudios se informa de una correlación entre la alteración biomecánica de la columna y la dermatitis.

Por tanto, el principal objetivo de este trabajo es realizar un estudio prospectivo para determinar la relación entre las alteraciones de la columna y la dermatitis centrándose en el nivel de CGRP en el plasma de los pacientes. Además, en este estudio nos propusimos investigar si la quiropráctica puede ser un tratamiento eficaz para la dermatitis.

En este estudio participaron 73 pacientes que padecían dermatitis. 51 de estos pacientes fueron asignados al azar al grupo de tratamiento y 22 pacientes también fueron asignados al azar al grupo de control. A todos los pacientes de los grupos de tratamiento y control se les prescribió una crema compuesta tópica que contenía corticosteroide-indometacina emoliente y antioxidantes. Sin embargo, solo los pacientes del grupo de tratamiento se sometieron a un tratamiento quiropráctico, mientras que los pacientes del grupo de control solo recibieron el tratamiento tópico mencionado anteriormente. Para lograr nuestros objetivos, se analizaron los siguientes datos en pacientes del grupo de tratamiento: (1) Examen dermatológico cuantificado mediante el Índice de Severidad y Área de Eczema
(EASI) método de puntuación, (2) Descripción radiográfica y cuantificación del nivel de gravedad de las alteraciones biomecánicas espinales (SBA), en lo sucesivo denominado puntuación de gravedad (espinal). (3) Datos biológicos que incluyen análisis de sangre y medición del nivel de péptido relacionado con el gen de calcitonina en plasma (CGRP) en todos los pacientes y (4) examen y tratamiento espinal quiropráctico (SMT) y en un plan semanal de 3 meses. Todos los datos se compararon y analizaron antes y después del tratamiento en los 73 pacientes del estudio.

Los resultados presentados en este estudio serían indicativos de una correlación entre la biomecánica alterada de diferentes segmentos

espinales y el estado alterado de la piel. En este estudio encontramos que los niveles de EASI en los pacientes que padecían Dermatitis se correlacionaron significativamente con SBA en el Atlas-Eje (AT-AX) ($p < 0{,}001$; $r = 0{,}82$), en la columna cervical ($r = 0{,}91$), en el balance sagital de la columna SBS ($p < 0.001$; $r = 0.88$), en Espondilolistesis ($p < 0.001$; $r = 0.85$), en T10 ($p < 0.001$; $r = 0.87$), en L1 ($p < 0.001$; $r = 0{,}81$) y L2 ($p < 0{,}001$; $r = 0{,}70$).

En general, los resultados de este estudio indicaron que la mejora en el nivel de CGRP en plasma se correlaciona con la mejora en el nivel de EASI y la mejora en la puntuación de gravedad de la SBA. Sugiere que las alteraciones biomecánicas espinales (SBA) pueden contribuir a la liberación de neuropéptidos, incluido el CGRP, de las terminaciones de los nervios sensoriales. El aumento de CGRP en plasma da como resultado una inflamación neurogénica de la piel y contribuye a trastornos dermatológicos como la dermatitis. Además, nuestros resultados indicaron una reducción significativa en el nivel de CGRP en los pacientes del grupo de tratamiento (que se sometieron a tratamiento espinal quiropráctico) y luego una reducción significativa en los puntajes EASI (mejora de la situación de la piel). Por otro lado, aunque el nivel de EASI de los pacientes del grupo de control disminuyó después de 2 semanas de uso de la crema compuesta, el nivel de CGRP permaneció alterado y, en consecuencia, los síntomas de dermatitis aparecieron en esos pacientes después de 3 meses.

Como conclusión, el resultado de nuestro estudio sugiere que puede haber una fuerte correlación entre la alteración biomecánica de la columna, el nivel de CGRP y la inflamación neurogénica de la piel (en forma de dermatitis de la piel). También recomendamos encarecidamente que se realicen más investigaciones con una muestra de población más grande.

CHAPTER 1:
INTRODUCTION

1.1 Dermatitis

Dermatitis is a chronic inflammatory skin disease, described by intensive pruritus and eczematous lesions of skin. [1] In most of the patients with Dermatitis, a long-lasting cycle of itch-scratch roots produces substantial morbidities and discomforts. For instance, sleeping problems, compromised quality of life, and psychosocial problems, as well as appearance-related complications including skin infections resulting to a loss of self-confidence. In addition, dermatitis is one of the first evidence of disease in early childhood, with possible evolution of the march of asthma, food allergies, and allergic rhinitis in young patients resulting to additional discomforts and morbidities. [2,3] On the other hand, many studies relate Dermatitis to some nonallergic conditions, providing a chance for systemic and multiorgan infections [4], in addition to some cardiovascular diseases [5], and neuropsychiatric conditions such as depression [6], anxiety [7], and hyperactivity disorders. [5]

From the etiological point of view, Dermatitis is very complicated and multifactorial with genetical, environmental and immunological interacting factors. [8] According to the levels of immunoglobulin E (IgE), which are the antibodies against common environmental allergens, there are two characteristic forms of Dermatitis: extrinsic and intrinsic. [9]

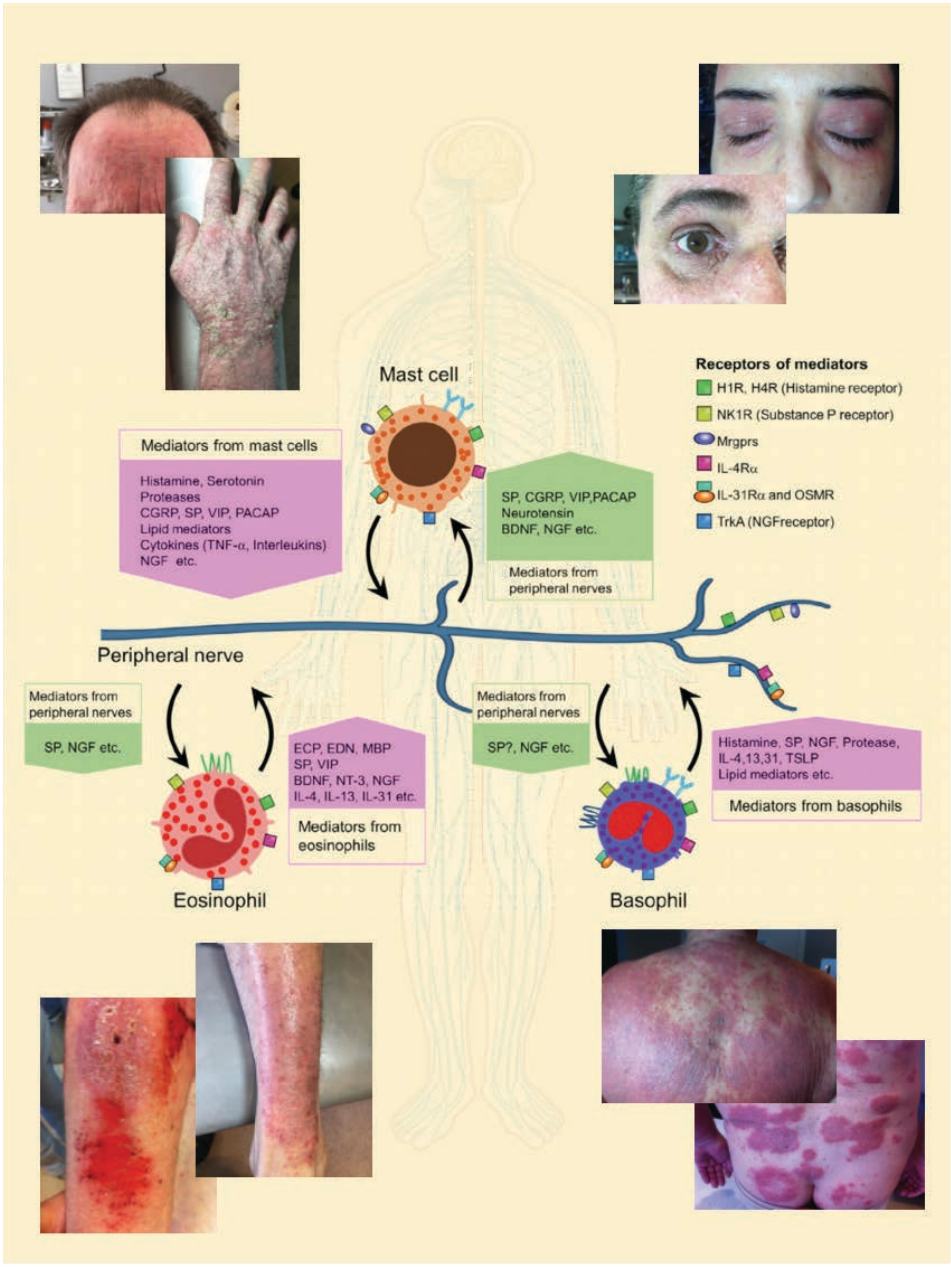


Figure 1- Dermatitis- The communications between peripheral nerves and mast cells, eosinophils, and basophils in addition to some clinical pictures of dermatitis appearance. Schematic is reprinted with permission from. [10] *Clinical pictures are original from our study patients. All patients have signed an informed consent for the case to be published (including images, case history and data)*

About 25 years ago, the histological connection between mast cells and peripheral nerve cells was explained. [11] Since then, many studies indicated mast cells in close proximity to Calcitonin gene-related peptide (CGRP) peripheral nerves in the skin. The communications between peripheral nerves and mast cells, eosinophils, and basophils is shown in Figure 1. This correlation and linkage between mast cells and peripheral nerves, is found enhanced in the pathological conditions such as dermatitis and psoriasis. In addition, numerous neuromediators such as amines, neuropeptides (CGRP, substance P, VIP and PACAP), cytokines (tumour necrosis factor-α [TNF-α], Interleukins [ILs]) and growth factors are released from mast cells. Release of these mediators by activated mast cells results in the direct sensitization of nociceptors on peripheral nerves and leading to inflammations, redness, and itching on the skin.[12,13]

Besides, the European Academy of Allergology and Clinical Immunology has classified dermatitis to nonallergic and allergic types. [14] Both allergic and nonallergic types share similar clinical features, however, different immunological factors are involved.

The common necessity for treatment of this disease makes significant financial and mental pressures on patients and/or their families. The treatment of Dermatitis has developed gradually, initiating from early 1930s by using topical lotions to 1960s by using topical steroids. By the beginning of the new century (2000s) calcineurin inhibitors have emerged, and currently, in addition to compound cream designed by dermatologists, many biologic agents such as anti–interleukin (IL) 4/IL-13 antibodies are available to be used in different forms. [15]

The purpose of treatment in dermatitis is to decrease symptoms, cure superinfection, avoid exacerbations, lessen the risk of treatment, and bring back the integrity of the skin. [16] In most patients with mild Dermatitis, treatment goals can be accomplished with topical therapies, however, in patients with moderate to severe Dermatitis, treatment is still a challenge. Education, elimination of worsening factors, improving hydration and skin barrier function, and healing the inflammation are some of the general principles of dermatitis therapy. [17]

In clinical procedure, there are different tactics to cure Dermatitis, and wide-ranging recommendations are given to patients by both primary care clinicians and specialists. This variation of methods in treating Dermatitis and lack of a precise and defined treatment procedure causes confusion and anxiety and discomfort for patient and their relatives while dealing with this chronic condition. [18,19]

Dermatitis is a hard and challenging disease. There are many patients every day who do not achieve any improvement by using vigorous, topical anti-inflammatory therapies. As yet, the treatment choices are limited to systemic immunomodulatory agents, phototherapy, and immunotherapy, which are not data- based and are limited due to their reported side effects [20]. Currently, there are many new other therapeutics compounds, containing small molecule agents and anticytokine proteins being studied for treatment of dermatitis, as presented in Table1 .

As more new and promising therapeutics become available, some hard question need to be answered: *(1) Are these new treatments likely to be effective in all types of dermatitis or only certain* dermatitis *phenotypes? (2) How to choose a certain biologic agent for a patient? (3) Are there any*

good biomarkers or clinical markers to guide treatment? (4) What is the long-term safety and effectiveness? (5) What is the risk of severe outcomes? (6) What is the safety/ efficacy of treatments/ drugs in younger children in whom the disease is more widespread? (7) How long is the treatment period, and what is the probability of decline after the treatment is stopped? (8) What is the effect on other allergic diseases, such as asthma? (9) When will these drugs be available in the market, and how about coverage by insurance payers? All in all, there is no specific answer yet for any of these questions covering all Dermatitis cases as a general answer. Thus, Dermatitis remains a challenging inflammatory disease. In addition, current available treatments usually provided temporary relief, and their effectiveness varies from one patient to another.

Target	Compound	Trial Phase, Clinicaltrials.gov Identifier
Topical Agents		
AhR	Tapinarof/Benvitimod	2a, NCT02466152/NCT02564055
PDE4	Roflumilast	2a
JAK1, JAK3	Tofacitinib	2a, stopped
JAK1, JAK3	LEO 124249/JTE-052	2a
S aureus	*Roseomonas mucosa* bacteria	1/2 antecubital AD
S aureus	Coagulase-negative *Staphylococcus*	1/2 ventral arm AD
PDE4	Crisaborole	Clinical use
Biologics		
IL-4	Pitrakinra	2a
IL-5	Mepolizumab	2a
IL-12/23P40	Ustekinumab	2a, NCT01806662
IL-13	Tralokinumab	2 completed, NCT02347176
IL-13	Lebrikizumab	2 completed, NCT02340234
IL-4/1L-13R	Dupilumab	Approved for clinical use 2017
IL-17	Secukinumab	2, NCT02594098
IL-22	Fezakinumab (IV)	2, NCT01941537
IL-31R	Nemolizumab	2 complete, NCT01986933
IL-31	BMS-981164	1, NCT01614756
TSLP	Tezepelumab	1 complete, NCT00757042
TSLP-R	MK-8226	1, NCT01732510
IgE	QGE031/ligelizumab	2 complete, NCT01552629

Table1 - New investigational agents for treatment of moderate to severe dermatitis. Data obtained from clinicaltrials.gov and Vakharia et al.[21]

The pathogenesis of Dermatitis remains unknown. [22] However, there is evidence that neuropeptides such as Calcitonin gene- related peptide (CGRP) influence the development and course of Dermatitis [23–26]. Likewise, there are studies investigating spinal neurotransmitters in accordance with itching in dermatitis and it is reported that a species of neuropeptides is released from chloroquine-sensitive pruriceptors within the spine to arbitrate histamine-independent itch in Dermatitis [23,24,27–30]. Also, in various studies indicated the relationship between spinal problems

and pathogenesis of Dermatitis [31–35]. A summary of itching process in Dermatitis has been presented in Figure 2.

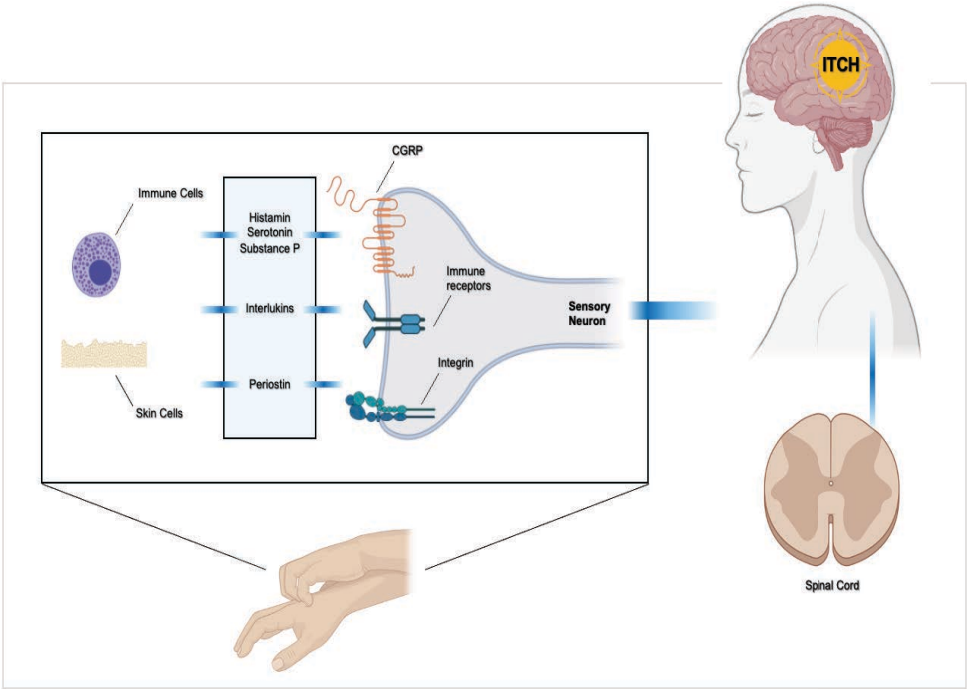


Figure 2- Itching process. Mediators and neuropeptides signalling the cortex in the brain to trigger itch through the spinal cord. Reprinted and modified from.[36]

Therefore, we designed a study to investigate the dermatitis from neuronal/ spinal point of view. Our aim is to understand this chronical inflammatory disease from the point of its onset and the involvement of neuropeptides in the pathway through a complex biological event identified as "the neurogenic inflammation".

1.2 Neurogenic inflammation, sensory nerve, and neuropeptides

Neurogenic inflammation is a type of inflammation initiated by stimulation of peripheral nerve, the fibre C neurons [37]. The neuronal activity operates

through neuropeptide release and inflammation at locations different from the original stimulus. In humans, some of the neuropeptides and many different chemicals can cause an irritant effect by stimulating these c-fibers. There is an individual variation in the susceptibility to the chemical reactivity of their c-fibers [38–40].

This inflammation is produced by the discharge of neuropeptides such as SP, CGRP, and NGF. [41–43]

1.2.1 Neuropeptides

Neuropeptides are small proteins that are used to communicate between neurons [44]. Neuropeptides act on the surface receptors of neurons. Many neuropeptides and their receptors are widely distributed in the central nervous system. In the brain, more than 100 active neuropeptides have been identified that are biologically unique [45]. The effects of many peptides are induced by several receptor subtypes on different areas of the brain. In fact, the discovery of new peptides and receptor subtypes has broadened our understanding of the role of these peptides in the functioning of the central nervous system [46]. The pharmacological, molecular, and genetic approaches are pioneering our understanding of the role of neuropeptide systems in psychiatric disorders today [47,48]. Neuropeptides have been implicated in regulating a variety of physiological and behavioural processes including temperature regulation, water and food consumption, sexual activity, sleep, locomotor activity, memory learning, stress and pain response, emotion, and social cognition. These systems may be involved in the symptoms and behaviours of major psychiatric illnesses such as psychotic disorders, mood disorders, mental retardation, and spectrum

disorders. [49–52] Neuropeptides may act as neurotransmitters (nerve-media), nerve regulators, or nerve hormones. [53] Neurotransmitters are usually secreted from axonal terminals into the synapse. Neuropeptide release is not limited to synapses or axonal terminals but may occur throughout the axon or even in dendrites. [53,54] The most important peptides playing a significant role in the onset of neurogenic inflammation are described below.

(i) Substance P

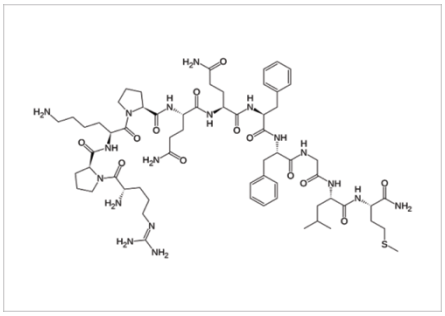


Figure 3- Molecular Structure of Substance P

Substance P (SP) is a peptide structured by 11 amino acids (See Figure 3). This peptide initially was isolated from intestinal extracts. Its capability to generate hypotension was primarily reported in the 1930s. [55] Substance P circulated in the central, intestinal, and peripheral nervous systems of various species. [56] The function of the substance P in the CNS is as neurotransmitter. SP and its neurokinin receptor (NK) are localized in regions of the brain that are important in influencing both chemical and neurological behaviour, as well as the response to both mental and physical stress. [57] SP may also coordinate the stress response by interacting with the HPA axis and the sympathetic nervous system. [58,59] In addition, substance P is involved in the sensory pathways and, most importantly, the pain. On

the periphery, substance P has been identified at the end of type C sensory nerves throughout the body. Substance P is present in inflammatory sites and inflammation can enhance its expression. The nerves containing SP are abundant in the mucosa and are found in the ganglion, spinal cord, brain, airways, and skin and around the blood vessels [56,57]. SP is stored in the vesicles and released from the sensory nerves in response to various stimuli such as leukotrienes, prostaglandins and histamine. [60] In addition, substance P can be produced and distributed from immune cells, for instance, macrophages and eosinophils, particularly during diseases. [61]

(ii) CGRP

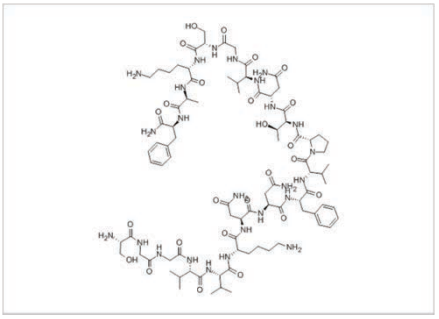


Figure 4- An example of CGRP´s molecular structure

Besides SP, the creation of neurogenic inflammation is dependent on release of CGRP. [62] This peptide was first reported in 1982 and forms the calcitonin-related peptide family along with calcitonin, amylin, adrenomedullin, and the calcitonin receptor-stimulating peptide. [63] It is a combination of a single intermolecular ring structure and a fused C-terminus that is shared by family members (See Figure 4). CGRP is synthesized and released from the sensory nerves in the central nervous system and digestive tract. So far 4 different types of receptors have been reported for this peptide. [64]

(iii) Nerve Growth Factors

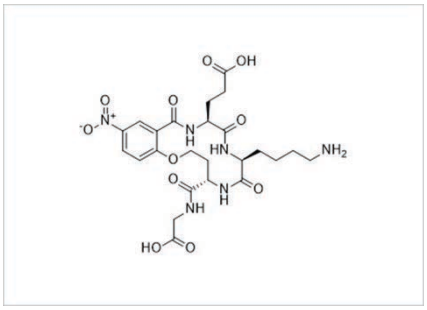


Figure 5- Molecular Structure of NGF

In addition to SP and CGRP, there are some findings about the role of nerve growth factors (NGF) in generating of neurogenic inflammation. [65–68] NGF represents the best known and studied trophic factor, acting on the sensory and sympathetic neurons of the peripheral nervous system and on the frontal basal brain and striated cholinergic neurons of the central nervous system (See Figure 5). [69] The specificity and trophic actions of NGF on these neuronal populations and its efficacy in preventing neurodegeneration have led to the proposal to evaluate its use in the treatment of neurological diseases such as Alzheimer's disease [70,71], diabetic neuropathy [72–74] and skin dermatitis. [75–77] Preclinical and clinical studies carried out in animal models and in patients diagnosed with these diseases have shown promising results. Difficulties in central infusion of NGF caused by stimulation of other sensitive neural populations have spurred the initiative to develop more effective delivery strategies.

When sensory nerves are stimulated by certain activations, they release biologically active neuropeptides to transmit indicators and signals. Substance P and CGRP are the typical neuropeptides acting immediately on the vascular cells and smooth muscle cells, with vascular effects. SP boosts vascular penetrability with consequent plasma flareup and oedema

[78]. The discharge of SP enhances intercellular adhesion molecules and vascular cell adhesion molecules on vascular epithelial cells and stimulates them to release from mast cells facilitating hypervascularization and penetration of inflammatory cells.

CGRP as an effective microvascular vasodilator contributes to most of the neurogenic vasodilation and is engaged in enrolment of inflammatory cells. [79,80] Both, SP and CGRP perform their activities through G-protein coupled receptor, in addition to many other neuropeptide receptors. [47,67] Lately, it was demonstrated in mouse models that NK1 receptor antagonists, which is one the most important CGRP receptors- inhibits itch in dermatitis and showed therapeutic efficacy in chronic pruritus in humans. [81–83] The CGRP receptor antagonist and the anti-CGRP antibodies have been shown clinically promising for migraine treatment, in which CGRP play a crucial role in the pathogenesis. [84–88]

1.3 Skin neurogenic inflammation

There is an old term known as ‘neurodermitis’, implying eczema or allergic dermatitis, that describes a correlation between nerves and skin. It illustrates through clinical examination that the advancement and the evolution of allergic dermatitis is susceptible to sensitive stress and environmental stimulus. It has been a long-term clinical study that skin disorders caused by chronic inflammation, such as Dermatitis, psoriasis, rosacea, and itching are aggravated by stress and nervous-related stimuli. [89] Neurogenic inflammation as described above, is a process in which sensory nerves lead to inflammation.

Both the immune system and somatosensory nervous system are important for the prospective harmful infection and tissue damage in each individual

host. Immune system guards the host by battling against infective mediators and rebuilds damaged tissues. In addition to that, the somatosensory nervous system improves its ability of avoiding the noxious stimuli by eliminating the danger. There are many nociceptors in the skin covering and protecting the host from the external environment. [90–93] These receptors react to any harmful stimuli instantly and transduce them to the electrical signals to generate reactions. Nociceptor neurons can transfer the potentials antidromically, from the central points to the outside, in addition to the orthodromic feedback from the periphery to central nervous system (CNS). [94,95] This process is known as axon reflex. [96,97] Therefore, the neuronal facilitators are distributed from the terminals of depolarized axon to the aroused area, activating a rapid reaction prior to the immune system's activation.

In the last five years, numerous studies have shed light on the role of the nervous system in the pathogenesis of Dermatitis. [98–103] The nervous system has a great impact on the progression of the disease through a modified pattern of cutaneous innervation in addition to an irregular expression of neuropeptides in lesioned skin. Many actions are mediated by neuropeptides contributing to the progression of Dermatitis, modifying the course of the disease. [98,100,101] SP and CGRP are the most effective factors that initiate the degranulation of mast cells and stimulate chemotaxis of neutrophils and lymphocytes. [42,104–106] Furthermore, neuropeptides regulate the cytokines release, control the activity of immune cells, and reduce the itch threshold. Besides, numerous studies have shown that the concentration of CGRP neuropeptides in the human blood plasma is considerably increased in the papillary dermis of Dermatitis patients when compared to the non-lesional samples. [107–109] The

enhancement of CGRP nerves in the epidermis of Dermatitis lesions may stimulate keratinocytes to release cytokines affecting various cell types, developing inflammation and as a result, producing inflammatory diseases such as dermatitis. [110–113] Several studies indicate a correlation between an increased maternal CGRP level and risk of developing Dermatitis in young age. [114–117]

In addition, there is evidence suggesting that neurotrophins, such as NGF, may also be involved in the pathogenesis of Dermatitis and may regulate the progression of the disease. [111,118–120] The NGF and its receptors has an important role in the involvement of the peripheral nervous system specially in cutaneous nerves. This impact includes neuronal growth, differentiation, and regeneration of injured or diseased nerves. [121] It is suggested that NGF defines the innervation density of human skin and contributes to neuro-hyperplasia in Dermatitis. [119,122,123] Also, another study shows that the increased expression of neurotrophin receptor and neurotrophins functional activity reduces the itch thresholds in a mouse model suffering from Dermatitis. [124] Moreover, high concentration of nerve growth factor in the plasma is a risk factor in the Dermatitis. Recent studies have also shown that psychological stress induces degranulation of dermal mast cells and enhances the amount of SP and CGRP- positive nerve fibers in mice. [53,59,89,122]

1.3.1 Mechanisms of neurogenic inflammation in human skin

(i) Nervous system in the skin

One of the most important tasks of the skin is to sense and react to signals from the external environment in addition to defend our bodies. Profuse

nerve fibers, such as autonomic and sensory nerves, are spread all over the skin layers. They are connected with various cell types in the different layer of the skin by releasing different kinds of neuropeptides. Nearly all of cutaneous cells express operational receptors by receiving signals from the nervous system. In response, dermal cells generate neuropeptides in order to accelerate nerve fibers reactions. [125,126] These sets of action and reactions produce a positive bidirectional response loop capable of enhancing the inflammatory response. The finding that different types of chronic inflammatory skin disorders, eg, dermatitis and psoriasis, have the characteristics of enhanced neurotrophin expression and peptidergic nerve fibers help this pathophysiologic fact. [100,101]

In epidermis, neuropeptides distributed from the nerve fibers activate and stimulate keratinocytes to deliver proinflammatory cytokines such as IL-1α, IL-4, IL-5, IL-6, IL-8, IL-33 and more. [127] In epidermis, specifically on Langerhans cells, SP has the ability to increase migration and antigen presentation, resulting to stimulating allergic sensitization. [128,129] Additionally, in dermis, sensory nerve fibers are fused with noradrenergic and acetylcholinergic nerve fibers having further neuropeptides, for instance neuropeptide Y or vasoactive intestinal peptide. Sensory nerve fibers are generally in close interaction with mast cells, blood vessels or hair glands in dermis. Dermal mast cells have remarkably close connection with the nervous system in the case of neurogenic inflammation. CGRP and SP stimulates the vascular endothelial growth factor release from mast cells helping the proliferation and vascularization of endothelial cell resulting to acceleration of the inflammatory process. Fibroblasts in dermis also express CGRP receptors and produce SP, the release of both peptides increases after exposure to SP or to interferon (IFN)-γ. Therefore,

neuropeptides have a great impact on producing and enhancing the inflammation in skin by overexpressing CGRP, SP and NGF. Later these neuropeptides contribute to the fibrosis in chronic skin inflammation resulting to inflammatory skin disorders such as Dermatitis. In accordance with these findings, CGRP is one of the critical players in chronic relapsing inflammation in Dermatitis. Therefore, physiological interference of CGRP-mediated neurogenic inflammation can be a key factor in finding an alternative therapeutic target in the treatment of Dermatitis.

1.4 Vertebral column (Spine)

The spine structures the central alignment of the skeleton. Together, the sternum and the twelve pairs of ribs, shape the skeleton of the trunk. The spine is a very strong yet flexible midline structure. It attaches with the base of the skull through its upper end and supports the skull. From its inferior part, it articulates with the corresponding hip bone on each side. To form the pelvic girdle, two iliac bones articulate anteriorly at the pubic symphysis. In turn, each iliac bone accommodates the head of the subsequent femur to form the hip joint. The spine protects the spinal cord, contained in the vertebral canal. [130–133] The posterior part of the spine gives attachment to powerful muscles providing skeleton support and maintenance of the upright posture (Figure 6). [134,135]

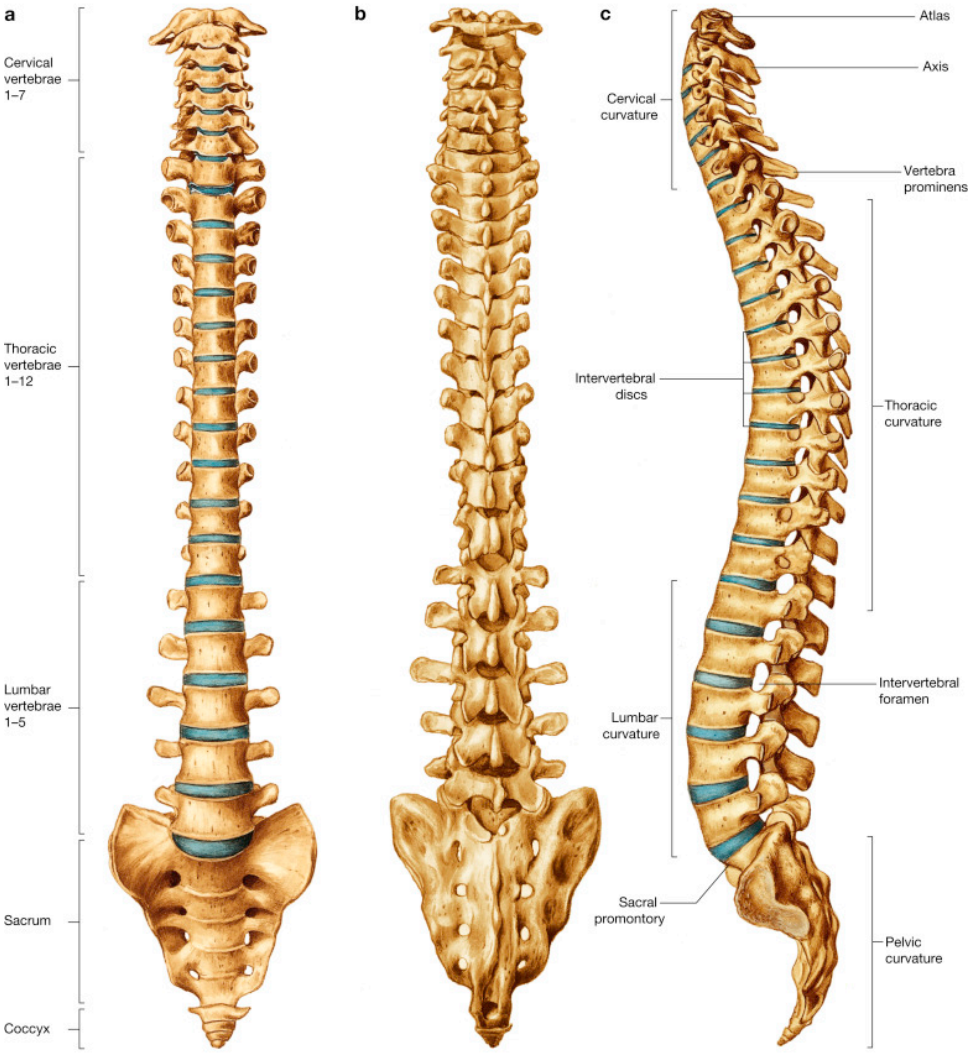


Figure 6- The articulated vertebral column view from anterior (A), posterior (B), and lateral (C). Reprinted by permission from [136]

Anatomically, the spine is divided into five regions. From top to bottom: the cervical, thoracic, lumbar, sacral, and coccygeal regions.

1.4.1 Cervical Spine

The cervical vertebrae are smaller than the rest of of the spinal segments. They are shaped like a cylinder and help to move the head and neck. Diametrically speaking, the cervical vertebrae are larger in the transverse side than in the anteroposterior side. The size of cervical vertebrae increases gradually-from C3 to C7. [137,138]

The first two segments C1 (Atlas) and C2 (Axis) have a unique shape being 'atypical' while the rest of the cervical segments, C3-C7, are considered 'typical cervical vertebrae'. The cervical transverse processes modify their shape as they ascend towards the brain to ensure the passage of the vertebral arteries.[139] (Figure 7)

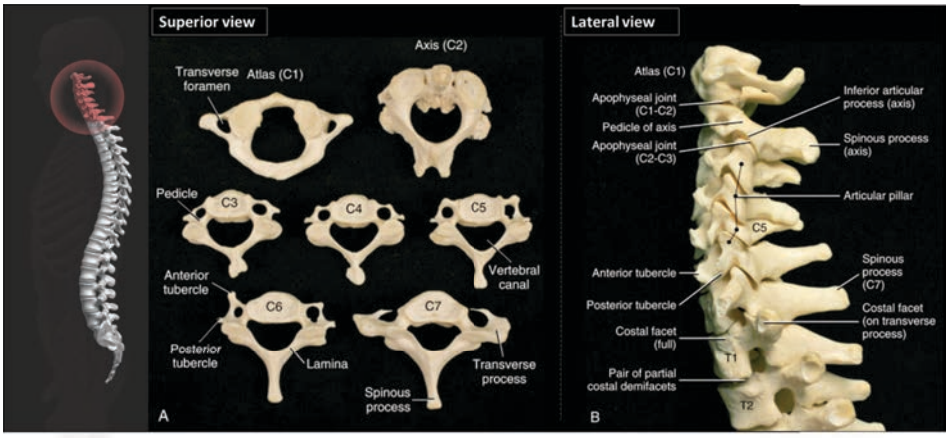


Figure 7- Cervical vertebra. Superior (A) and lateral (B) view of the seven cervical vertebrae. Reprinted by permission from [136]

The rectangular-shaped structures of C3-C7 are posteriorly-laterally surrounded by *uncinate processes.* The articulation of vertebrae with C3-C7 forms the *uncovertebral joints* making this region of the cervical spine a sensitive and complex zone.

Most cervical *spinous processes* are bifid providing attachment for muscles from both sides of the body. The apophyseal (facet) joints through

C3-C7 are positioned about 45 degrees between the horizontal and frontal planes. (Figure 7B) This characteristic plays and important role in the cervical biomechanics. [136]

1.4.2 Atlas (C1)

In Greek folk tradition and mythology, Atlas is a Titan responsible for holding the weight of the heavens on his shoulders. Similarly, the first cervical vertebra is also named *Atlas,* indicating its role in supporting the weight of the head. The atlas is formed by two connected lateral masses (Figure 8). Its two large bowl-shaped superior parts adhere to these adjacent masses creating the *atlanto-occipital joint* . [136]

1.4.3 Axis (C2)

C2 is also named axis because of its odontoid process that acts as vertical axis allowing the rotation of the head on the neck. (Figure 8). The superior part of the axis (C2) is flat, matching the leveled inferior parts of the atlas. This characteristic structure is designed to allow the atlas (in addition to head) to freely rotate horizontally around the axis. [136]

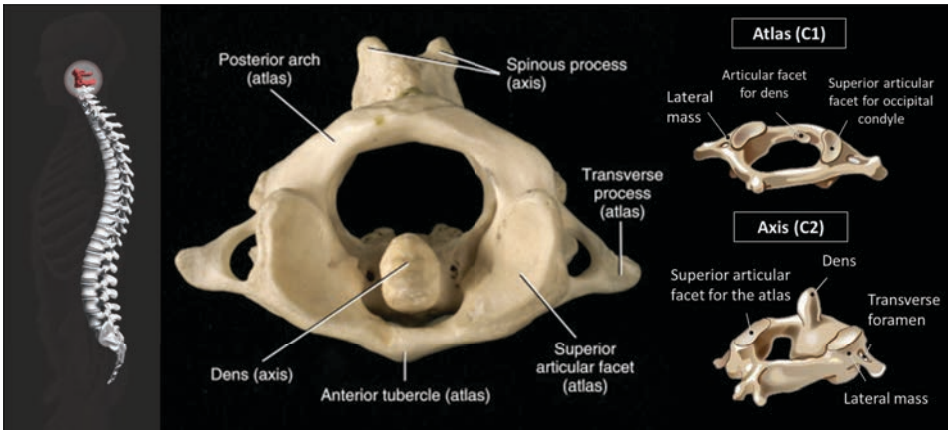


Figure 8- Atlas and Axis- Top view of the atlas (C1) laying on top of the axis (C2), shaping the atlanto-axial joint. Reprinted by permission from [136]

1.4.4 C3- C7

C2 - C3 is one the most important joints of the cervical spine. This joint allows the movement of the chin toward the chest (flexion) and the backward movement of the head (extension). Generally, patients injured at C3 level may have limited movement in both flexion and extension. [140] In addition, the C3 is consistent with the lower part of the jaw and the hyoid bone, which gives attachment to the muscles of the floor of the mouth and to the tongue, the larynx, the epiglottis, and the pharynx. This is a crucial spine area, which communicates the neck and the head with the jaw and many parts of the body. The spinal nerves roots exiting between C3-C4-C5 contain nerves fibers that make up the phrenic nerves, which innervate the diaphragm and ensure breathing. C4 is located at the level of the thyroid cartilage.

C5 plays an important role because it can influence the severity of the injury to the neck and spine. If the injury occurs at or above C5, the injured person may not be able to breathe as the phrenic nerves, that control breathing, are located between C3- C5. Injury to the C5 vertebra also disrupts the vocal cords, biceps, and deltoid muscles in the upper arms.

1.4.5 Thoracic

There are 12 thoracic vertebrae. [141] They are distinguished by their sharp, large posterior, inferiorly pointed, and their transverse processes, which is laterally projected. The transverse processes of most thoracic vertebrae have *costal features* for articulation with the subsequent aspect of the ribs (Figure 9). [142] The frontal section of most ribs connects either directly or indirectly to the sternum. Consequently, thoracic vertebrae, the ribs, and sternum describe the capacity of the thoracic cavity. Notable is that the apophyseal joints that are parts of the thoracic vertebrae are aligned almost in the anterior plane.

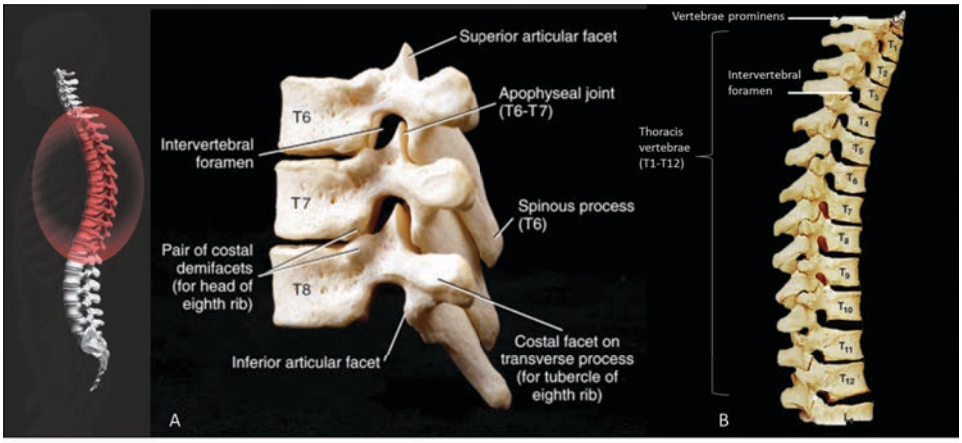


Figure 9- Thoracic vertebra- Lateral view of the sixth through eighth thoracic vertebrae (A) and the whole 12 thoracic vertebra (B). Reprinted with permission from [136]

1.4.6 Lumbar Vertebrae

The lumbar vertebrae are shaped to support the weight of the body. They have wide and massive bodies and rectangular spinous processes. The lateral joints of the upper lumbar area point close to the sagittal plane. However, in the lower regions its transition is towards the frontal facet (L4 and L5). [136] (Figure 10)

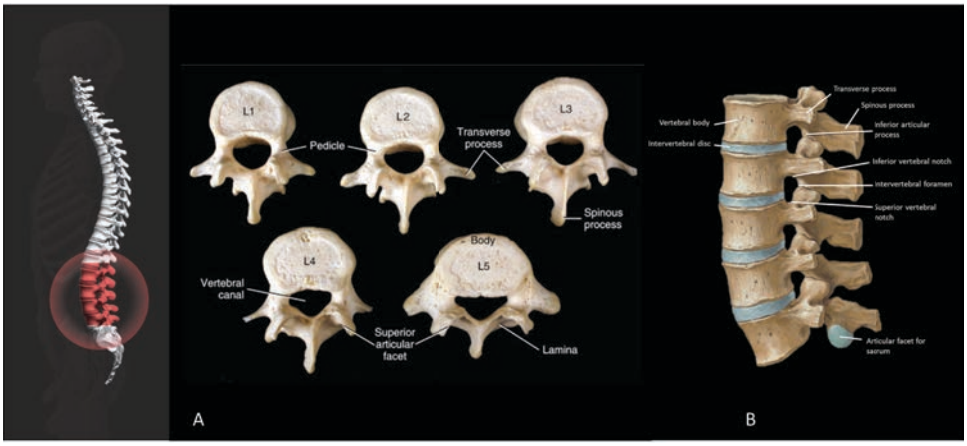


Figure 10- Lumbar vertebrae- Superior (A) and lateral (B) view [136]

1.4.7 Vertebral arteries

The critical difference between the cervical and other spinal areas is the existence of the vertebral arteries which arise from the subclavian artery (Figure 11) and go up the cervical transverse processes. When the artery reaches the atlas, it goes horizontally (Figure 11) and then joins the foramen magnum to merge with its neighbor to form the basilar artery (Figure 11). The vertebral arteries provide nearly 30% of the brain blood. The remaining 70% of the flow is provided by and the carotid structure. [143]

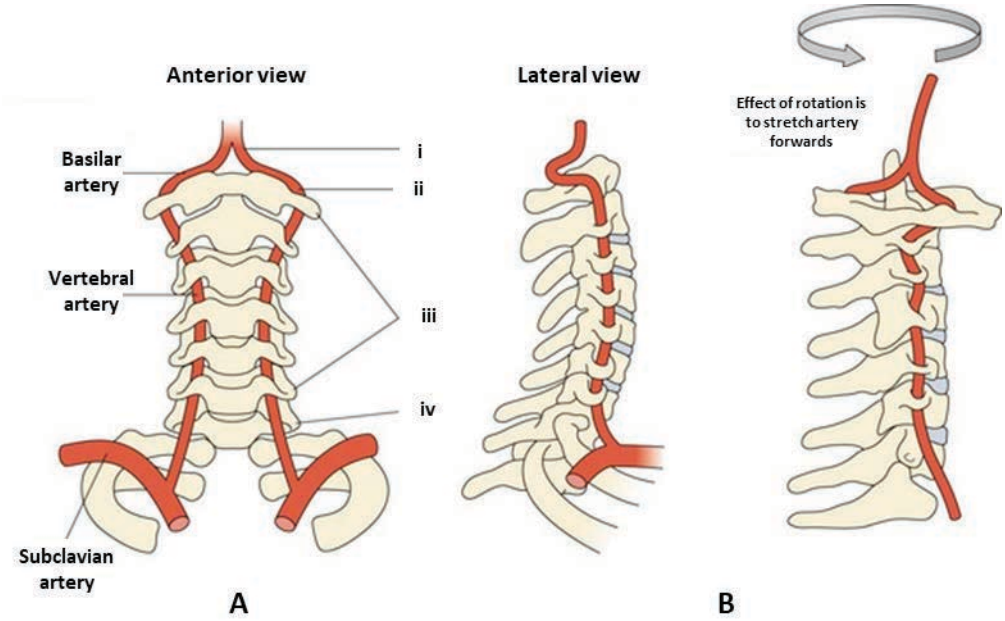


Figure 11- Structure of the vertebral artery- (A) Anterior and lateral view, (i) Branch from subclavian artery to C6, (ii) Vertical track through foramen transversaria, (iii) Horizontal section from C1, (iv) Entry to foramen magnum to join neighbour, (B) Effect of rotation is to stretch artery forwards. Reprinted by permission from [144]

1.4.8 Sacral

The sacrum is a triangular- shaped bone that articulates with the last lumbar segment (L5), forming the *lumbosacral junction.* The dorsal surface of the sacrum is u-shaped and rough, reflecting many muscular and ligamentous connections. The *sacral canal* covers and protects the cauda equina (peripheral nerves that extend from the bottom end of the spinal cord). On the pelvic (frontal) facet of the sacrum *ventral sacral foramina* (see Figure 12), a four-paired vertebrae, spread the ventral rami of spinal nerves. This represents of the sacral plexus [136].

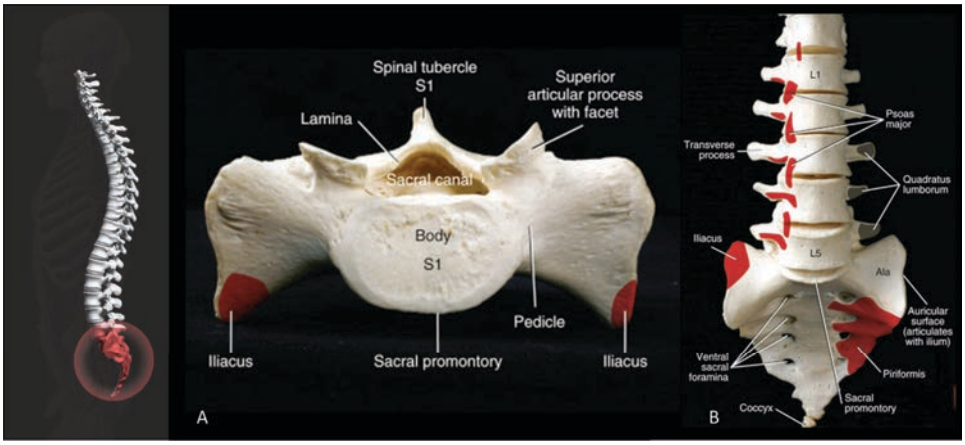


Figure 12- Structure of the sacrum-. Superior view of the sacrum (A) and anterior view of the lumbosacral region (B). (Attachments of the iliacus muscles are shown in red). Reprinted by permission from [136]

1.4.9 Coccygeal regions

Coccyx or Coccygeal, which sometimes described as the tailbone, is a small triangular bone structured by four fused vertebrae (Figure 12). The bottom of the coccyx communicates with the inferior sacrum, shaping the *sacrococcygeal* joint [136].

1.5 Spinal Biomechanical Alterations (SBA)

Altered spinal biomechanics lead to premature vertebral, discs and ligamentous degenerative changes and result in musculoskeletal disorders (MSD), such as osteoarthritis (OA) and intervertebral disc pathology such as prolapse or herniation.

Spinal MSD are the most widespread cause of work-related health problems in the world, investigated by the European Agency for Safety and Health at Work. Nowadays, technology is being more involved in our lives. A vast majority of the people use laptops, personal computers and

cell phones at school, work, home, and almost everywhere to keeps connected. Driving cars has become a habitual activity and sitting behind a desk or standing for a long time became a work condition more than before. Certainly, the technology is attractive and can hold you up for hours, however, this fact does not come without consequences. [145–148] Kids, teens, and youth are consequently complaining of musculoskeletal discomfort including neck, back and shoulder pain. Our lifestyle, the way we sleep, walk, sit, drive etc., in addition to the accidents, have contributed to an increased rate of spinal musculoskeletal disease. Spinal musculoskeletal disorders are either occupational or accidental. Once described as an occupational disease, a full analysis is necessary, as the repair system. However, although there are many available methods for studying the causes of occupational, injuries these problems have not been analyzed in depth, and therefore, there is a lack of examination methods [149,150] This explains the need for a better understanding of the causes of spinal musculoskeletal disorders. in order to prevent them. It also implies the need to further consider the role of spinal biomechanical alterations (SBA) as a precursor to MSD and the importance of identifying and correcting them at an early stage. Some of the most common spinal biomechanical alterations are summarized below.

1.5.1 Atlantoaxial rotatory

One of the important roles of the cervical spine is to support and control movement of the head and neck. Once the kinematics of the neck are altered or disturbed, the irregular motion may result to clinical symptoms. [151] Axial rotation of the cervical spine occurs mostly at the atlantoaxial

complex. In healthy individuals, the C1–C2 joint is in charge of handling almost 60% of the total rotation of the neck. [152]

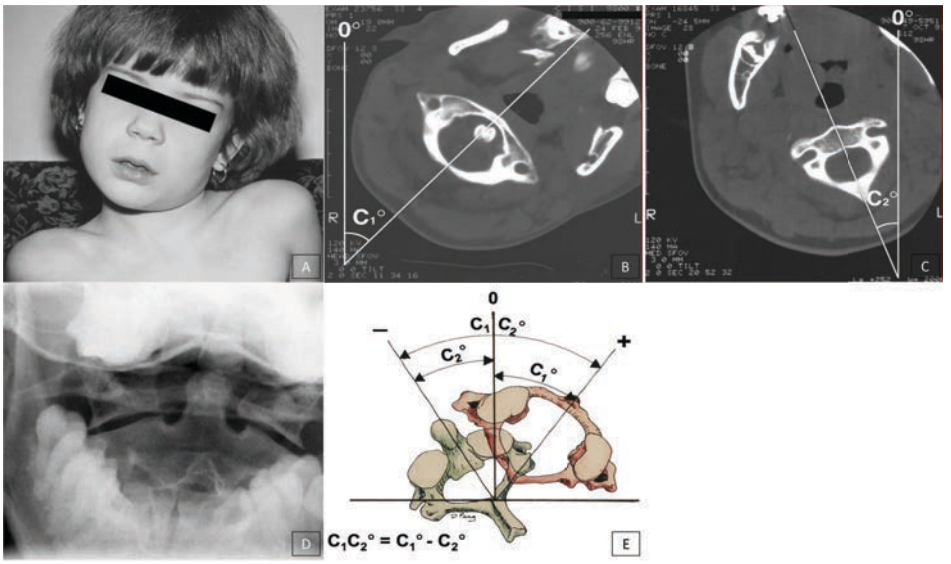


Figure 13- Atlantoaxial rotatory- Severe appearance of the Atlantoaxial rotatory (A), Measurement of the C1 angle (B) and C2 (C) on axial computed tomography, poorly centered X-ray showing odontoid lateral mass asymmetry (D), schematics of the C1 and C2 superimposed on the measurement grid to showing how the C1–C2 angle is obtained by algebraically subtracting the C2 angle from the C1 angle. Reprinted by permission from [153]

The atlantoaxial formation is the main rotational event of the cervical spine, but these anatomic structures also influence this complex to a disorder categorized as a persistent, rotational deformity, frequently painful, called atlantoaxial rotatory fixation (AARF) [153]. Its noticeable "fixed" states to voluntary/ involuntary correction. Patients suffering from AARF generally present with the head in a position so-called "cock robin" (Figure 13 - A), described as the chin turns in the direction of one side and the neck is horizontally moved to the opposite side, similar to a robin listening and waiting for worms [153]. There are several affecting factors such as trauma, upper respiratory infections, and surgery of the neck and head. In addition, about 24% of AARF cases can occur without an obvious

affecting cause. Down syndrome, rheumatoid arthritis, and a variety of inherited cervical abnormalities have also been related [154–156].

1.5.2 The posterior arch abnormalities

The posterior arch abnormalities such as congenitally absent cervical pedicle and cervical spondylolysis, are generally unusual. Incidentally, these deformities are mainly can be found on cervical radiographs. It is critical to distinguish these typical radiological features since radiographic analysis may tend to confuse them with other serious pathologies, such as tumor-induced bony erosions. Additionally, it is important to differentiate these anomalies from related pathologies to avoid using of improper therapy [157] (Figure 14).

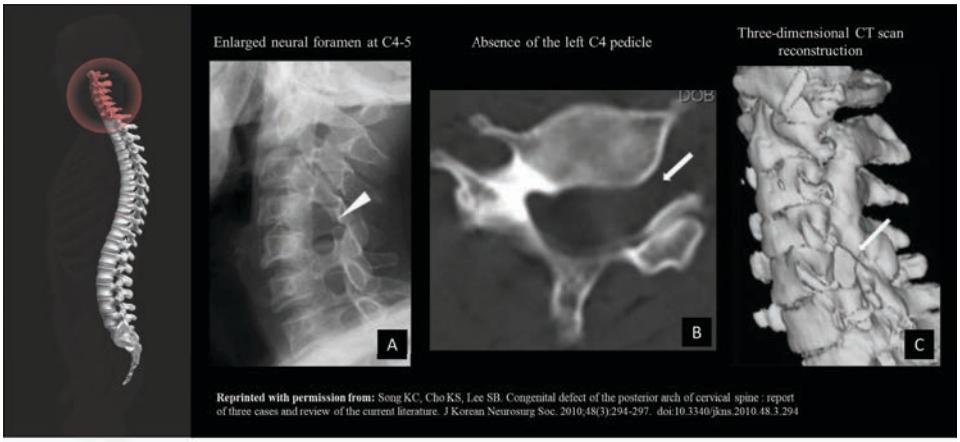


Figure 14- Posterior arch abnormality- Case of a 50-year-old woman. Left anterior oblique view displays an enlarged neural foramen at C4-5 (A). Cervical spine CT reveals the absence of the left C4 pedicle (B). Three-dimensional CT scan shows the absence of C4 left pedicle at C4-5 (C). Reprinted and modified with permission from [157].

Patients with these abnormalities have tendency to show up with cervical pain after trauma. Primary assessments with typical radiography normally result to misguided intervention; it may mimic independent facet fracture,

jumped locked facet or nerve root tumour. [158] Three-dimensional computer tomographic (CT) studies have helped the knowledge of the morphology of absent cervical spine pedicle. CT scan should be done to precisely calculate the radiological analysis. A majority of reports have advised a moderate nonsurgical management for a successful conclusion. Neural solidity or instability is rare with these abnormalities and only on few occasions we can find the surgical intervention appropriate. [159]

1.5.3 Alterations in cervical sagittal alignment

In recent decades, more attention has been paid–to the loss of normal cervical sagittal alignment as a sign of spinal biomechanical alterations (SBA) and, therefore, an important causal factor of cervical pathology. Recent studies have indicated that the loss of normal cervical spine lordosis is correlated with neck pain, cervical spondylosis and many other disorders related to neurogenic inflammation. [160–165]

The significance of abnormal cervical lordosis is controversial. Maintaining the integrity of cervical lordosis is important due to its great impact on many biological and biomechanical processes. This part of the spine influences breathing, chewing, vocalization, movement of eyes, and absorbs the shock when walking and running. According to recent reports, cervical spine lordosis has major clinical effects. [166–168] Four types of cervical sagittal alignment have been described clinically: lordotic, straight, double curvature, and kyphotic. (Figure 15)

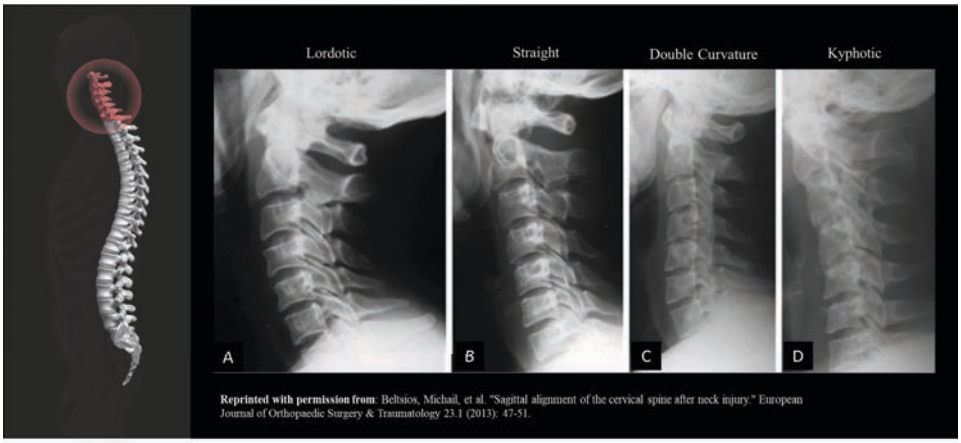


Figure 15- Different types of sagittal alignment of the cervical spine. Lordotic (A), Straight (B), Double curvature (C) and Kyphotic (D) [169]

The balance of cervical lordotic curvature was found to correlate with better surgical outcomes in patients with neurological deficits. Improving cervical lordosis after surgery is also believed to be an important issue, as it can affect nerve tissue injury.

In the last decades, the routine of daily life, especially in younger population, has become increasingly desk-bounded, with spending long hours sitting behind desks, especially students and office workers, using computers for many hours a day. This contributes to loss of cervical lordosis and a higher incidence of spinal biomechanical disorders due to alterations of normal spinal biomechanics (SBA). [170,171]. A study on Chinese teenagers suffering from neck pain found 37 (61.67%) cases of irregular cervical curvature in the teenagers aged 6 to 15 years, 430 (71.67%) cases in the teenagers and young people aged 16 to 25 years, and 1105 (76.42%) incidents of abnormal cervical curvature in people aged 26 to 35 years, respectively. [172]. Also, Gao et al studied 4681 students in a random-based selection doing cervical spine analysis and observed 1362 abnormal curvature cases (29.1%).[173] The measurement can be done by

various means, such as cervical curvature index (CCI), Borden measurement, Cobb angle measurement, and tangent angle measurement of posterior edge of vertebral body. Although numerous investigations have reported a correlation between sagittal alignment and intervertebral discs, degenerative changes of the cervical spine, its consequences and in particular, its relationship with nervous system needs to be studied further. [174]

1.5.4 Spondylolisthesis: Anterolisthesis and Retrolisthesis

The slippage of vertebra to forward or backwards is called Spondylolisthesis. [175,176] Patients who are diagnosed with spondylolisthesis may have symptoms such as neck pain, back pain, tightness in hamstrings, numbness sensations in the legs, in addition to some chronic diseases such as migraine and chronic skin inflammations. Forward slippage of the vertebra is known as anterolisthesis (See Figure 16). And backward slippage of vertebra is known as retrolisthesis (See Figure 17). [177–179]

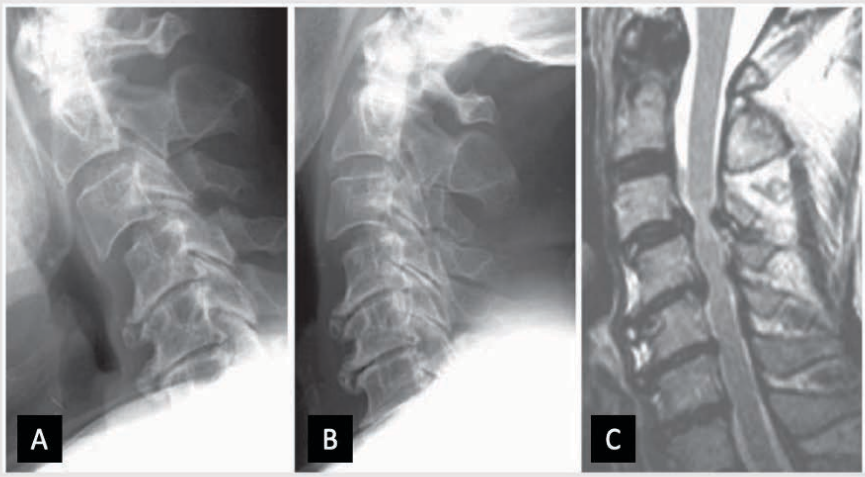


Figure 16- Spondylolisthesis: Anterolisthesis- Lateral radiographs of the cervical spine of a 68- year-old patient with the neck in flexion (A) and in neutral position (B). Sagittal T2-weighted magnetic resonance imaging (MRI) scan indicates anterolisthesis (C). [180]

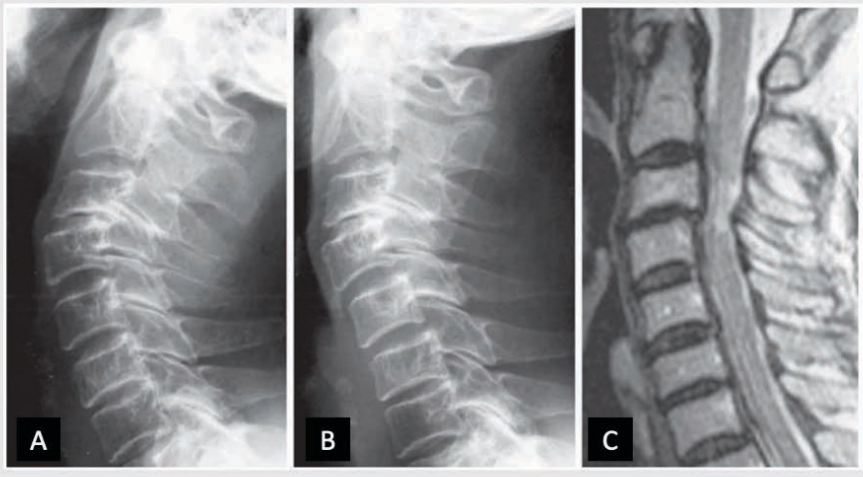


Figure 17- Spondylolisthesis: Retrolisthesis- Lateral view of the cervical spine with the neck in extension (A) and in neutral position (B). Sagittal T2-weighted MRI scan shows posterior degenerative spondylolisthesis, referred to as retrolisthesis, in a 76-year-old patient (C). [180]

1.5.5 Cervical and lumbar stenosis

Stenosis refers to a narrowing of the spinal canal that compresses the spinal cord. This disorder occurs most commonly due to aging and undetected chronic SBA. The intervertebral discs, may become dry and herniated (also called bulged, slipped, or ruptured). A herniated disc refers to rupture of the disc nucleus that is forced out of the annulus and slips into the spinal canal through a tear or burst. Herniated discs are usually an early stage of degeneration. The space of spinal canal is inadequate, and the herniated disc fragment may compress the spinal nerve. This may result in feeling pain, discomfort, and more complex reactions such as neurogenic inflammation.[181] This situation can arise in any part of the spine; more commonly in the in the neck (cervical spine) and lower back (lumbar spine) (Figure 18).

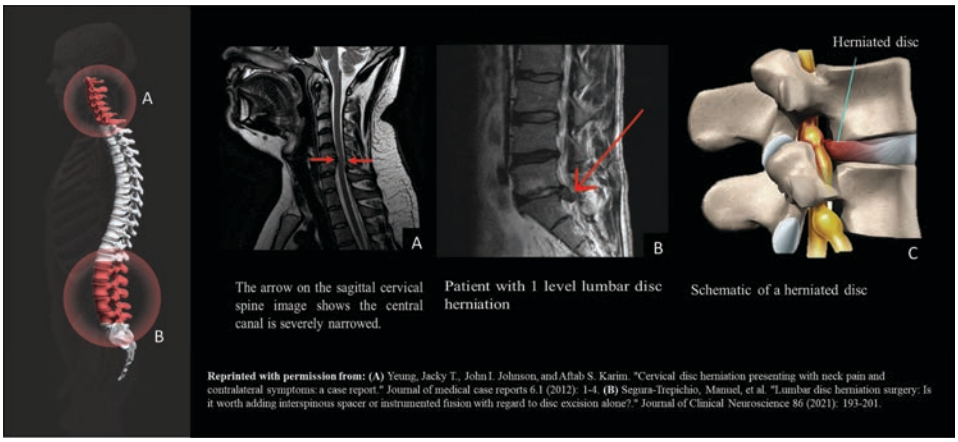


Figure 18- Cervical stenosis. Herniation of cervical (A) and Lumbar (B) disc [182–184].

In summary, the shock absorption ability of the intervertebral discs may be lost due to altered spinal biomechanics. For the same reason the vertebrae and ligaments can also degenerate prematurely, and cause the spine to become less flexible and stiff. Therefore, alterations in spinal biomechanics produce bone and soft tissue degeneration often

accompanied by osteophytes that cause narrowing of the spinal canal or cervical stenosis. [185] The growth of bone spurs (osteophytes) can compress the nerve roots. Moderate stenosis can be treated conservatively for prolonged periods of time if the symptoms are limited to neck pain. Severe stenosis needs recommendation of a neurosurgeon. [186]

Poor posture, trauma, overuse or sports injuries result in chronic SBA, contributing to premature spinal degeneration such as OA. Also, illnesses such as inflammatory arthritis can result in worsening of the vertebral joints, especially in the cervical spine, causing disc impingement or degenerative disc herniation. Unexpected serious neck trauma may also cause disc herniation, stroke, destruction of blood vessel, injuries on vertebral bone or tendon, and, in severe cases, everlasting paralysis. [187]

There are many studies suggesting that degenerative changes in structure and function of cervical discs have a direct connection with neurogenic inflammation and thus, results to pain. [188–193] Pain is usually associated with neck stiffness, headache, unilateral or bilateral shoulder pain, arm pain, pain in the upper chest, ophthalmic dysfunction, etc.

On the other hand, the degree of association of cervical disc degeneration and clinical neck pain remains still unknown. [194]

Inflammatory cytokines level generally increases due to intervertebral disc degeneration. For instance, level of inflammatory cytokines such as TNF-α, IL-1 α/β, IL-2, IL-4, IL-6, IL-8, and IFN-γ are affected by the degeneration of discs, sequentially, indicating that expression of NGF's mRNA increases. Another study revealed that, in the presence of IL-1β, human nucleus pulposus cells show a significant increase in NGF DNA expression. [195] On the other hand, treatment with TNF-α was related to upregulation of SP and CGRP in these cells. [196] It was shown that levels of

NGF, SP, and CGRP are enhanced due to the degeneration of intervertebral discs. [197] (Figure 19)

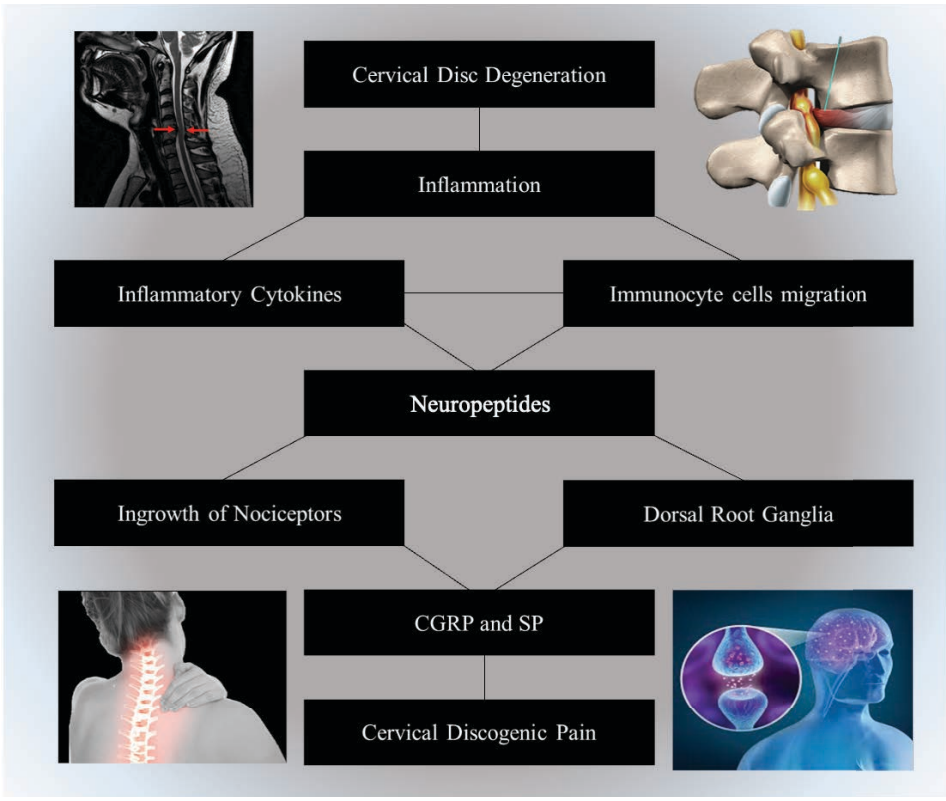


Figure 19- A diagram of the relationship between cervical disc degeneration, inflammation and discogenic pain. Reprinted and modified with permission from [198].

In addition to cervical stenosis, lumbar stenosis is the most commonly seen form of degenerative type spinal stenosis. Degenerative lumbar stenosis is correlated with aging, and it develops in combination with age-associated degeneration of the lumbar discs and vertebral joints. The degenerative process in lumbar vertebrae, same as in cervical vertebrae, results to a loss of disc height and infoldings of the ligamentum flavum. Facet osteoarthritis (OA) frequently takes the lead to osteophyte formation and stiffening of the joint capsule (See Figure 20) Advanced facet joints OA, tends to cause a much more severe condition [199].

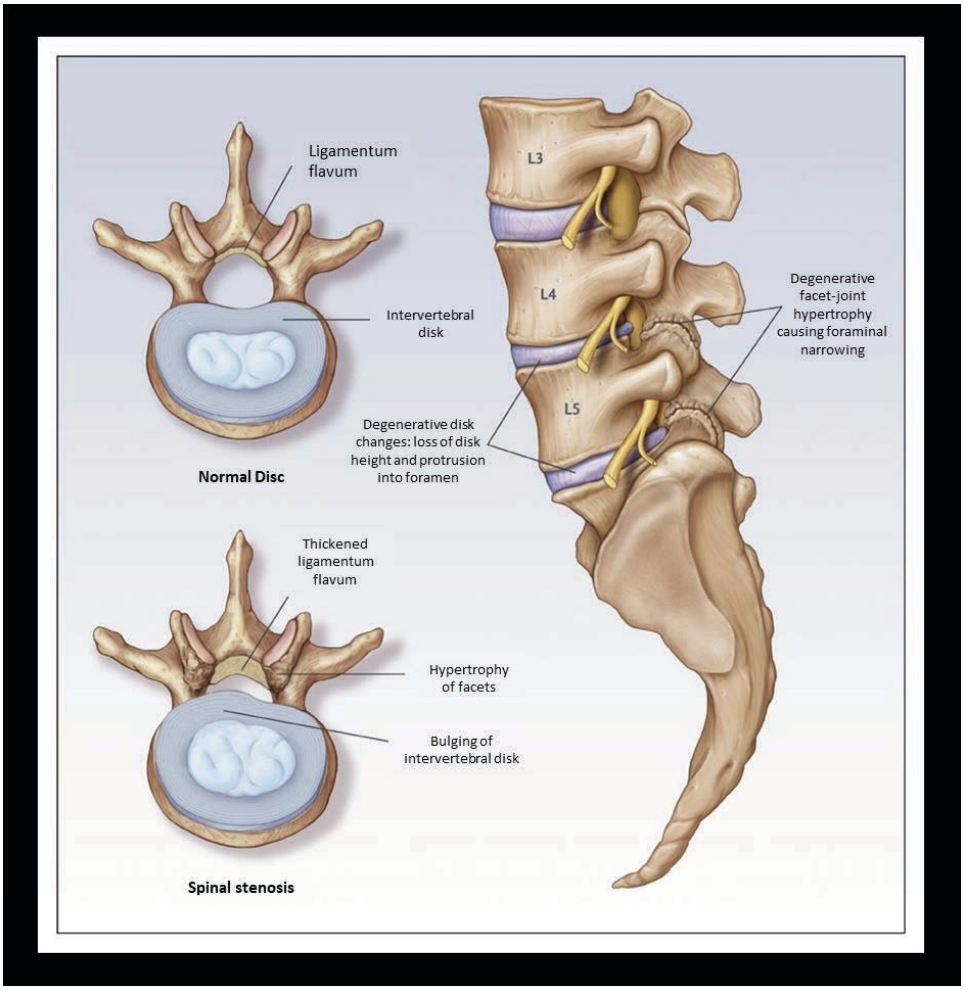


Figure 20- Pathoanatomical Features of Degenerative Lumbar Spinal Stenosis. Reprinted with permission from [200].

1.5.5 Sagittal balance of the spine (SBS)

The sagittal balance of the spine refers to physiological spinal alignment in the sagittal plane. This balance is maintained by the muscular forces. During walk 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 spino-cranial position. Apart from the cervical lordosis, the thoracic and lumbar spine are kyphosis and lordosis, respectively [201]. The most efficient parameter to analyze the global balance is the odontoid hip axis (OD-HA) angle. Many studies reported the average values of these parameters as an important analysis of the spinal alignment [202–205] (Figure 21).

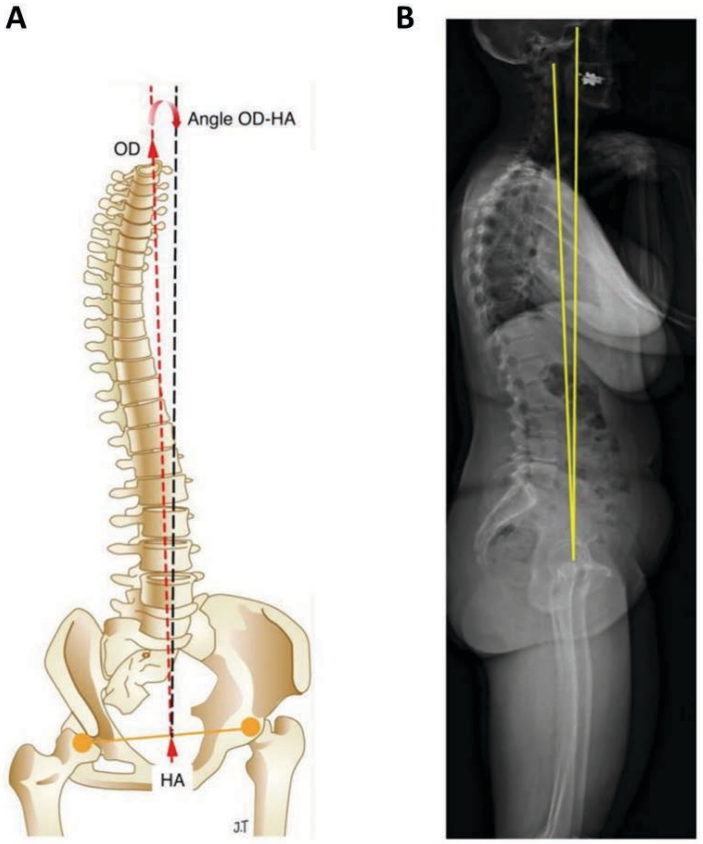


Figure 21- Odontoid hip axis measurement (OD-HA)- (A) 3D drawing of the OD-HA angle from dens of C2 to hip axis and vertical line through hip axis. (B) OD-HA measured on a 2D X-ray, lateral view. Reprinted with permission from [206]

1.5.6 Spondylolysis

Lumbar spondylolysis is a disorder supposed to emerging in childhood or adolescence by excessive stress on the pars interarticularis from bipedal movements during certain strenuous sport activities. [207,208] The etiology of lumbar spondylolysis differs between reports. Spondylolysis occurs in children as soon as they begin to walk, however, it is rare before the age of 5. At the age of 7 or 8 years the lesion is more common. This disorder can lead to painful episodes; however, low back pain has not been shown to correlate with spondylolysis. [208]

Although there are many studies on spondylolysis in the symptomatic population, fewer studies attempted to determine the significance of spondylosis in adults. Recently, Sonne-Holm et al. by using lateral plain film radiographs indicated that lumbar spondylolysis could develop in adulthood [209] (Figure 22).

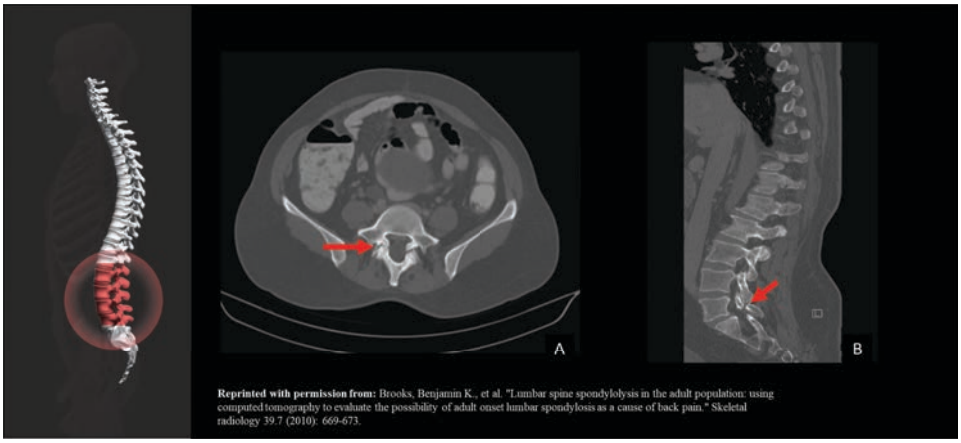


Figure 22- Lumbar spondylolysis. ***(A)*** *Bilateral spondylolysis in L5, (the arrow delineating the pars defect),* ***(B)*** *Sagittal reconstruction, L5 pars defect (the arrow delineating the defect). Reprinted with permission from* [210].

In addition, in some studies of lumbar spondylolysis there are certain methodological limitations. For instance, in some cases, a single lateral

radiograph, which is less precise than computed tomography (CT) for unilateral defects, has been used. [211–213] Another study examined spondylolysis with CT in adults, however, they did not establish the correlation between age and prevalence. [211] Therefore, there is a significant requirement for studying spinal disorders with a well-planned methodology and by using new technology. [214,215]

1.6 Spinal cord

The spinal cord is a section of the central nervous system (CNS). It is located in the interior part of the spinal vertebral canal. Throughout the development of CNS, there is a difference between growth of the spinal cord and spinal growth Generally, growth of the spinal cord ends at the age of 4, however, the spine stops growing at age 14-18. That is why, in adults, the spinal cord dominates the superior two thirds of the vertebral canal. [216] The spinal cord is also defined as an extension of the brainstem. It broadens from the base of the skull (the foramen magnum) to the L1/L2 vertebra, where it ends as the medullary cone. Throughout, its length the spinal cord illustrates two well defined extensions to aid innervation of the upper and lower limbs; one at the upper limbs (cervical level), and the other at the lower limbs (lumbosacral level). [216] Like the spinal column, the spinal cord is divided into different divisions: cervical, thoracic, lumbar, sacral, and coccygeal. Every single section of the spinal cord supports several pairs of spinal nerves, which leave the vertebral canal across the intervertebral foramina. There are a total of 31 pairs of spinal cord segments: 8 pairs of cervical, 12 thoracic, 5 lumbar, 5 sacral, and 1 coccygeal pair of spinal nerves. [216] (Figure 23)

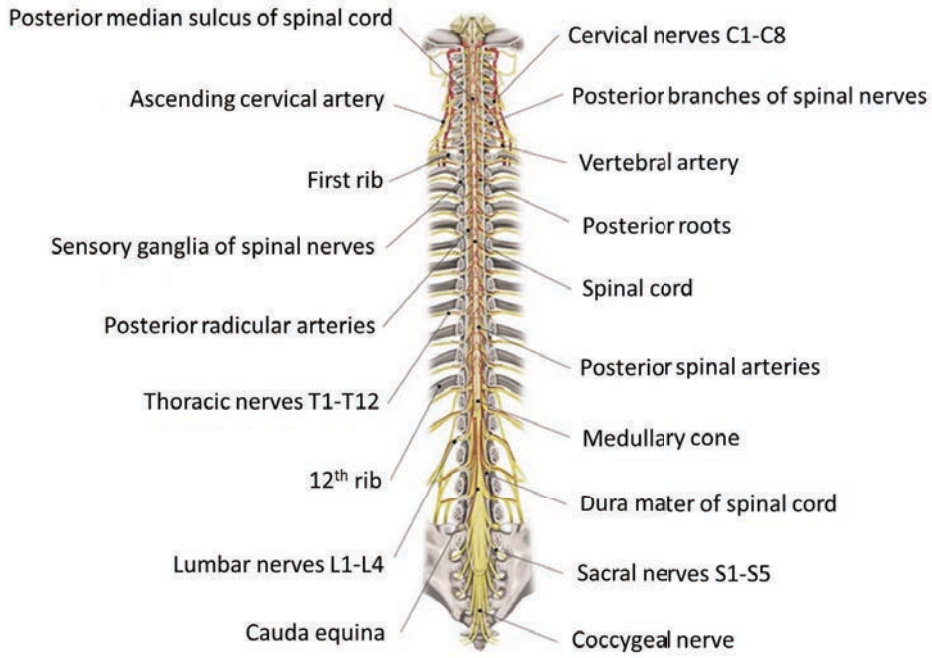


Figure 23- Spinal cord- Reprinted with permission from [216].

1.7 Spinal nerves

Spinal nerves are classified as cervical (C1-C8), thoracic (T1-T12), lumbar (L1-L5), sacral (S1-S5), and coccygeal (Co1), varying from which section of the spinal cord they develop. Division of the spinal cord relates to the intrauterine period in which the spinal cord dominates the whole vertebral canal. [216,217] For this reason, in adulthood, the spine is basically more extended and longer than the cord. Consequently, each spinal cord division is positioned more elevated than its subsequent vertebra. These variations become more noticeable distally in the direction of the lumbar and sacral segments of the spinal cord. [217] For instance, spinal cord section L5 is at the level of the L1 vertebra. (Figure 24)

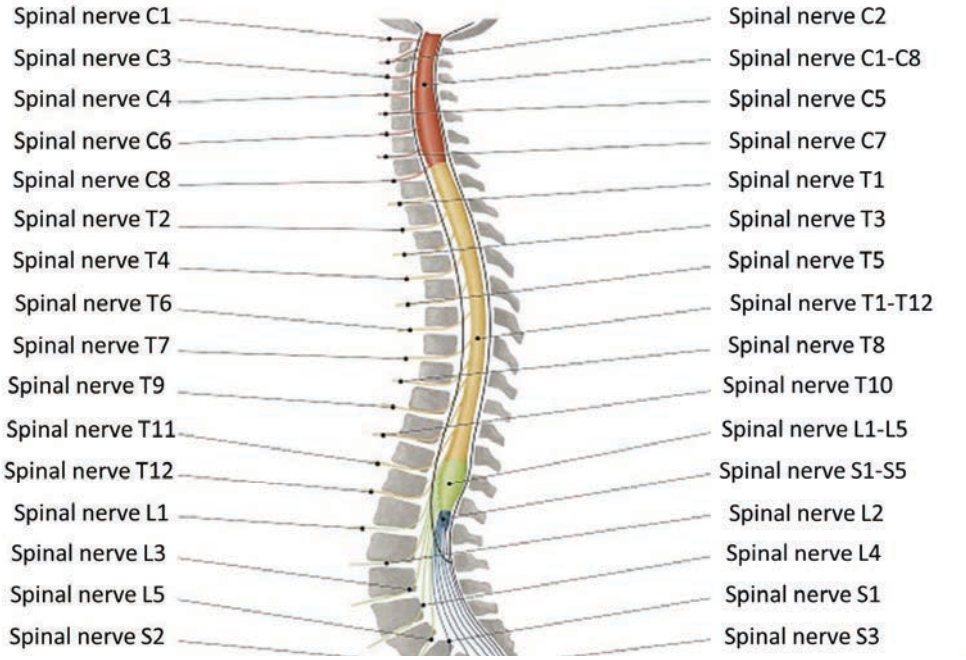
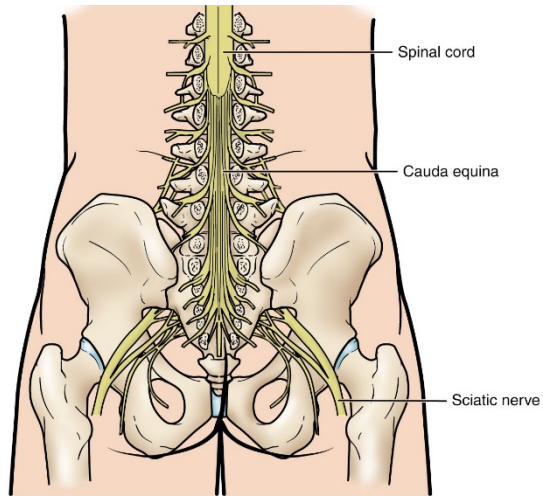


Figure 24- Spinal nerves diagram. Reprinted with permission from [217]

On the other hand, the spinal nerves exit the spinal column at their corresponding numbered vertebrae. Cervical spinal nerves exit through the intervertebral foramina just above their corresponding vertebrae. Lumbar and sacral spinal nerves are the longest nerves as they are the farthest from their intervertebral foramina. As these nerves falling towards their subsequent intervertebral foramina, lumbosacral spinal nerves shape a bundle known as the cauda equina (Horse's tail) [218] (Figure25).



Every single spinal nerve has an anterior and a posterior root. Frontal roots carry motor information. They originate from the anterior part of the gray matter and leave the spinal cord via the anterolateral sulcus. The posterior roots carry sensory information and have sensory ganglion connected to each one of them. They come from the posterior part of gray matter and leave via the posterolateral sulcus of the spinal cord. [216,217]

The anterior and posterior roots combine just prior to the intervertebral foramen and create the trunk of the spinal nerve. The trunk is short in length, and shortly after leaving the spine, it divides into four sections: anterior branch, posterior branch, communicating branch, and meningeal branch. Each one of these branches according to individual lifestyle, are in danger of tensions, and pressure resulting from different injuries and disorders. Injury to the spinal cord immediately generates inflammatory reactions that can worsen the initial injury and may lead to secondary injury. [219,220] Until now, researchers and clinicians have concentrated on regulating severe inflammation to keep sensorimotor role functional. Chronic inflammation negatively impacts the general health of people with a spinal cord injury when it expresses itself as neurogenic inflammation. [220]

1.9 Spinal cord, Nerves, and Skin

In order to get a better understanding of the connection between spinal cord, nerves, and skin, we need to comprehend three phenomenal systems. Autonomic nervous system (ANS), Trigeminal nerves, and Dermatome.

1.9.1 Autonomic nervous System

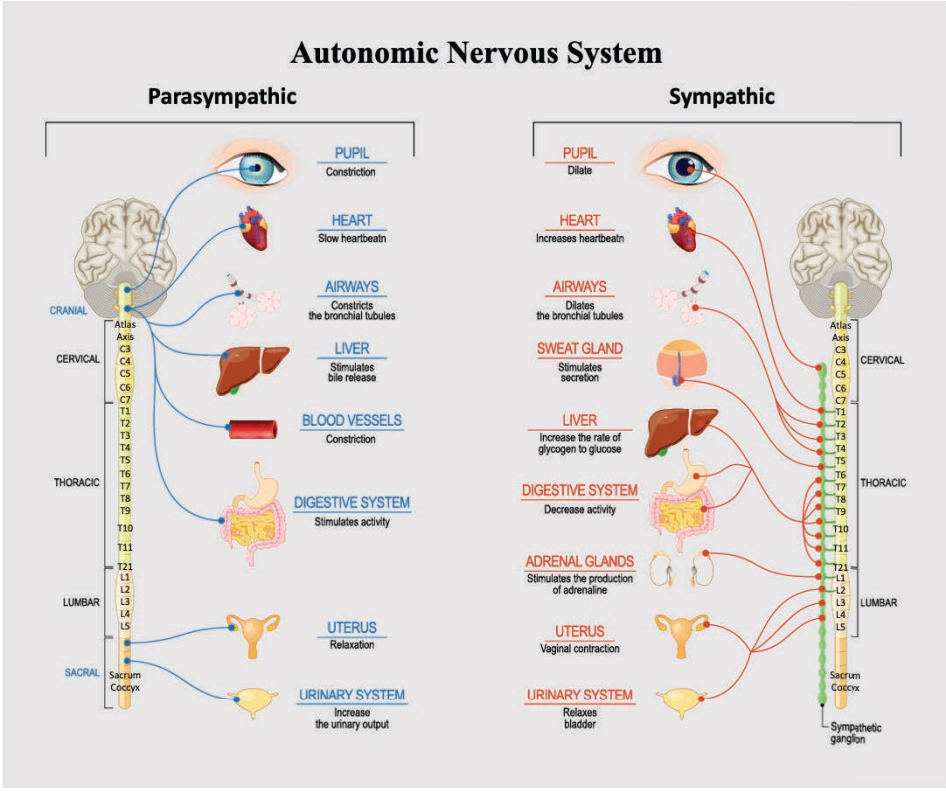


Figure 26- Autonomic Nervous System (ANS); Reprinted with permission from[221]

The autonomic nervous system is a part of the peripheral nervous system that is responsible to normalise unintentional physiologic progressions such as heart rate, respiration, digestion, and many other involuntary processes of human body. [222] This complex system has extensive innervation to almost all organ system in the body. [223] The autonomic

nervous system has a complicated network of associations to excellently adjust the systemic reaction to nearly any situation. Traditionally, this part of nervous system was considered two distinct systems- sympathetic and parasympathetic-, however, recently a third component of this system has been introduced as enteric nervous system. Many studies have been using the ANS map to get a better understanding on the connection of nervous system and different organs (Figure 26). [221,223,224]

In peripheral tissues, there is a deep innervation network between sensory and autonomic fibres. Neural transduction permits fast local and systemic neurogenic modulation of immunity. [225] Therefore, understanding the coordinated connection of ANS and peripheral neurons- as a contributor role player of immune dysfunction in autoimmune and allergic diseases- advance therapeutic approaches and can help us in understanding the neurogenic inflammation. [41,226]

1.9.2 Trigeminal Nerves

The trigeminal nerves consist of the 12 cranial nerves that transmit sensory signals and information to the different parts of the face including skin, sinuses, and mucous membranes. [227] This system also has a crucial role in the movement of the jaw muscles. [228] This group of the nerves rooted from the upper part of the spinal cord consist of mesencephalic nucleus, sensory nucleus, and spinal nucleus. [227–229] A significant body of research has indicated an association between trigeminal nucleus and C1, C2, and C3 of the cervical spine and this fact may relate the cervical spine biomechanical alterations and neurogenic inflammation of the face. [230–239]

The trigeminal nerves consist of three different divisions rooting from Gasserion ganglion: Ophthalmic, Maxillary, and Mandibular division. (Figure 27)

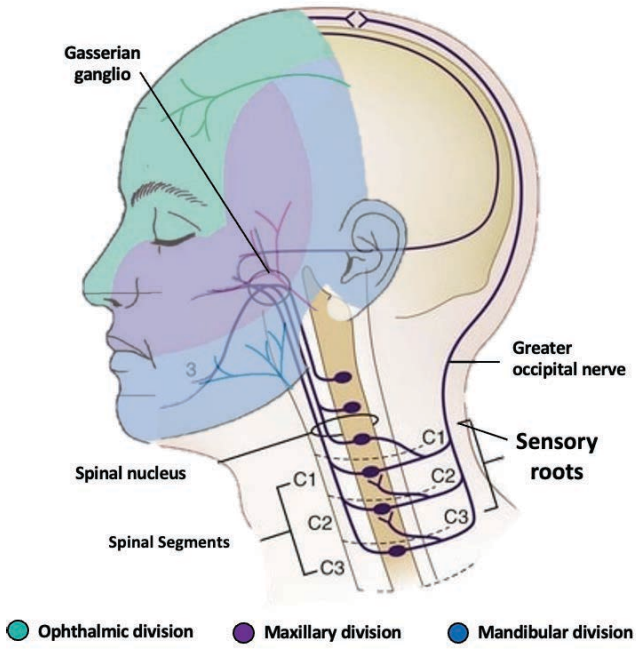


Figure 27- The trigeminal nerves- (In green) Ophthalmic division, (In purple) Maxillary division, and (In blue) Mandibular nerve. Reprinted with permission from. [240]

(i) Ophthalmic division

The ophthalmic division communicates sensory information from the forehead, scalp, upper parts of the sinuses, bridge of the nose and the cornea of the eye. (See Figure 27-Green area)

(ii) Maxillary division

the maxillary division conveys sensory information from the middle part of the sinuses, nasal cavity of the nose, upper lip, cheeks, and roof of the mouth. (See Figure 27- Purple area)

(iii) Mandibular

The mandibular division associates sensory information from the lower part of the mouth, outer part of the ear, front and middle part of the tongue, lower lip, and chin. This division of trigeminal nerves is also associated with teeth of the lower jaw. Mandibular division is in charge of movement stimulation of the muscles in the jaw, in addition to some of the muscles within the inner ear. (See Figure 27- Blue area)

1.9.3 Dermatome

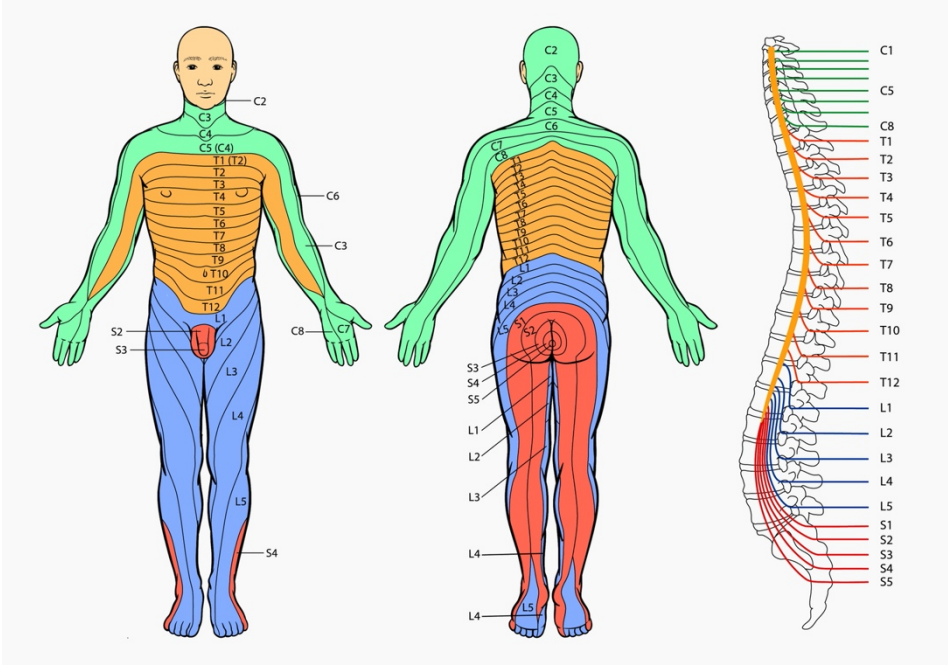


Figure 28- Dermatome chart by Netter. Reprinted with permission from[241]

Typically, a "dermatome" is described as the area of skin provided by cutaneous divisions of a single spinal nerve. [242] Early investigations to establish the range of each dermatome was carried out in Europe in 19th century. In 1886, Sir Wilmot Herringham established the first findings of the segmental fibers of the limbs. [243] His outcomes were grounded on his divisions of neonatal and adult cadavers and 7 years later, Sir Henry Head, established the first dermatome map through studying visceral pain and traumatic lesions of the spinal cord. [244] Many other researchers such as, Sherrington et al., [245] Foerster et al., [246] Keegan and Garrett, [247] Denny-Brown et al. [248] and Kirk et al. 249 were studied the construction and definition of dermatome during late 19th and early 20th century. By beginning of the 21st century and emersion of technology, researchers

reached to a better level of understanding on spinal cord and nervous system. Consequently, in 2008, Lee et al. [250] established a new dermatome map according to new clinical studies and peripheral nerve stimulation.
A dermatome can simply explain the innervation of the skin in entire human body that affect by neurons rooted in different division of spinal cord. In our study, the dermatome chart suggested by Netter is used to evaluate neuroanatomic distribution of the inflammations in patient's skin. (Figure 28).

1.9 Chiropractic Adjustment or Spinal Manipulative Therapy (SMT)

Chiropractic adjustment, consists of a specific spinal manual maneuver, applied to one or more vertebral segments, to correct misalignment with maximum precision, without straining the joints, to restore proper spinal biomechanics.

In the scientific literature this type of manual correction is generally known as chiropractic Spinal Manipulation Therapy (SMT). [141,251]. The chiropractors are primary health care professionals, academically trained and highly specialized in diagnosis and correction of neuromuscular disorders with primary focus on spinal care. Aside from various manual techniques, selected according to specific clinical needs, chiropractors may use a small percussion instrument called 'Activator'. [252] Activator technique (AT) is employed to insure specific, non-force, vertebral joints correction.
Generally, chiropractors start by a thorough physical exam which includes erect body posture balance and gait, neurological reflexes, motion

palpation of the spine, breathing patterns, full spine radiographic analysis etc. Aside from back pain relief, the goal of chiropractors is to restore proper spinal biomechanics by identifying and correcting all causal factors of musculoskeletal imbalance. [253,254] Like others health care professionals specialized in restoring neuromuscular function chiropractors counsel patients with respect to spinal hygiene: postural habits, ergonomics, daily exercises, and specific physical activities, etc. However, chiropractors encourage all patients to continue spinal care throughout the entire life through periodic check-ups of the spine, similar to a dental check-up.

Generally, when treating low back pain (LBP), chiropractors usually recommend 1 to 3 visits per week for a duration of 2 to 4 weeks depending on various factors including severity of pain, age, level of spinal degeneration and osteoarthritis (OA), etc. Some researchers suggest that having 2-3 chiropractic treatments per week for a few weeks may be advantageous for decreasing back pain. Haas et al. reported that 4 weeks of treatment, 3 to 4 chiropractic sessions per week, provided significant back pain relief. [255] In another study, Iben et al. [256] analysed patients who visited a chiropractor for 6 weeks, 1 to 3 sessions per week. Despite the fact that all groups with chiropractic treatment showed improvements, the group who had received 2 treatments per week, showed better results. [256] Once the patient is pain free, chiropractors recommend a maintenance care program that includes daily exercises, periodic spinal checks, and vertebral adjustments, if needed. [257]

Chiropractors demonstrated that their responsibility in management of patients goes beyond pain relief. They advocate for preventative spinal care and for educating patients to take responsibility for their spinal and overall health rather than waiting for symptoms to appear. A chiropractor

may use various diagnostic techniques to establish which the spinal segments require treatment. These techniques include, but are not limited to, static and motion palpation techniques to determining if spinal segments are hypo mobile (restricted in their movement) or fixated. [254] Depending on the results of the examination, a chiropractor may use additional diagnostic tests, such as X-ray to locate 'subluxations' (the altered position of the vertebra), s EMG (surface electromyography), neuro-calometer (a device that detects the temperature of the skin in the paraspinal region to identify spinal areas with a significant temperature variance that may require manipulation). Many chiropractors utilize a holistic, biomechanical concept of treating the bipedal musculoskeletal in its entirety. [258,259]

In an attempt to restore and maintain body balance chiropractors look for all factors that may induce spinal biomechanical alterations. These may include all lower extremities weight bearing joints (feet knees, hips) and the stomatognathic system: dental occlusion, temporomandibular joints. [259] In chiropractic, analysis of full spine x-ray is a crucial analytical tool for evaluating structural disfunctions.

CHAPTER 2: HYPOTHESIS and OBJECTIVES

2.1 Hypothesis of the study

Our hypothesis is that biomechanical alteration of the spine is one of the causes of neurogenic inflammation in the skin. Mechanical stressors, muscle tensions, pressures, vertebral misalignments cause neurons to release specific neuropeptides and produce neurogenic inflammation. The definition of the null hypothesis (H0) and the alternative hypothesis is described below:

- The null hypothesis (H0) is that there is no relationship between biomechanical alterations of the spine and inflammatory process of the skin, which results in dermatological disorders such as dermatitis.

- The alternative hypothesis (H1) is that there is a relationship between biomechanical alterations of the spine and inflammatory process of the skin, which results in dermatological alterations such as dermatitis.

2. Objectives of the study

The main objective of this work is to carry out a prospective study to determine the relationship between alterations in the spine and dermatitis by focusing on the level of CGRP in patients' plasma. Furthermore, in this study we set out to investigate whether chiropractic can be an effective treatment for dermatitis.

In summary, the specific objectives of this study are as follows:

1. To determine if the quantification of the spinal biomechanical alterations (SBA) correlates with the quantification of the dermatitis lesions.

2. To determine if there is a correlation between CGRP level and the SBA quantification.

3. To determine if there is a correlation between CGRP level and the quantification of dermatitis lesions.

4. To determine whether chiropractic SMT affects the level of CGRP.

5. To determine if chiropractic SMT can help improve the outcome of dermatitis lesions.

CHAPTER 3: Materials and Methods

3.1 Patients

This project is designed as a prospective study involving a group of dermatologists, radiologists, laboratory analysis and chiropractors.
Ethics Committee for Drug Research (CEIm) - Group Quirónsalud, Barcelona - approved the study protocol (Protocol code: **INCV-001**). Patients were evaluated with a complete dermatological examination, blood test, full spine x-ray, and chiropractic evaluation. All patients have signed an agreement to participate in the study, available in the supplementary documents section. Data from patients suffering with dermatitis were collected at the Umbert Institute of Dermatology of the Corachan Clinic, Barcelona, Spain.
The inclusion criteria for this study were patients aged between 7 and 70 years of both sexes with symptoms of dermatitis. In the beginning of the study, 94 patients were included, however, 21 patients were excluded because they were unable to finish the study. The remaining 73 patients were evaluated as the final sample. According to the levels of immunoglobulin E (IgE), which are the antibodies against common environmental allergens, none of the participated patients had high level of IgE, which means none of the patients considered as Atopic Dermatitis patients. In addition, psoriatic patients were excluded from the study.

3.1.1 Inclusion and exclusion criteria

Inclusion criteria of the study meet the following requirements:

(1) Dermatological problems (dermatitis),

(2) Age: 7 to 70 years,

(3) To accept informed consent.

(4) There is no financial compensation for participating patients.

The exclusion criteria are the following:

(1) Diagnosis of dermatitis along with other dermatological conditions.

(2) Diagnosis of dermatitis along with other intercurrent systemic diseases.

(3) Ages younger than 20 and older than 70 years.

(4) Patients who did not sign informed consent.

(5) Patients who have high IgE level (consider as Atopic)

(6) Patients with Psoriasis

3.2 Study Design

73 patients suffering from dermatitis participated in this study. 51 of these patients were randomly assigned to the treatment group (TG) and 22 patients were also randomly assigned to the control group (CG).

All patients in both, treatment and control groups, were prescribed a topical compound cream, containing emollient corticosteroid-indomethacin, and antioxidants. However, only patients in the treatment group (TG) underwent chiropractic treatment (SMT) while patients in the control group (CG) only received the above-mentioned topical treatment.

A summary of divisions in patients group provided in Table 2.

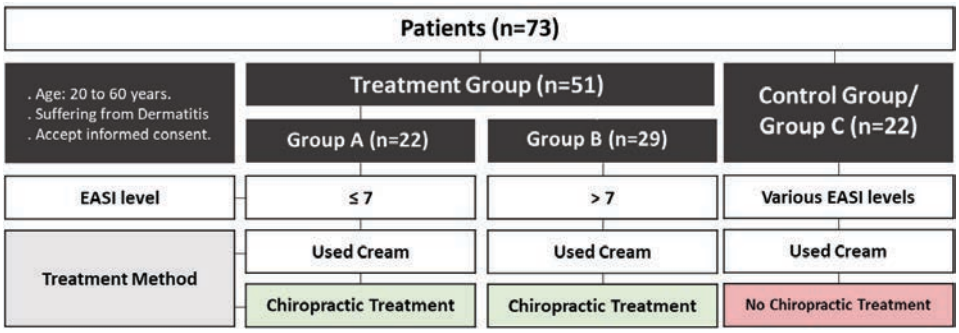


Table 2- Definition of the treatment and the control group

In order to accomplish our objectives, the following data was analyzed in patients of the treatment group: *(1)* Dermatological examination quantified using the EASI score method, *(2)* Radiographic description and quantification of the severity level of spinal biomechanical alterations (SBA), hereinafter referred to as (spinal) severity score. *(3)* Biological data including blood tests and measurement of plasma calcitonin gene-related peptide (CGRP) level in all the patients and *(4)* chiropractic spinal examination and treatment (SMT) and on a 3-month weekly plan. All data was compared and analyzed before and after the treatment in the 73 study patients.

3.3 Interventions

In order to manage the time and all clinical considerations, patients attended dermatology visits on a monthly basis. In addition, treatments' group (TG) patients underwent 12 sessions of chiropractic treatment, twice a week for 3 weeks and once a week for 4 weeks and twice a month for 1 month. The duration of the chiropractic treatment was approximately 3 months.

3.4 Determination of Sample Size

In calculation of sample size, studies by Tvedskov et al.[260], Aikawa et al.[261], and Altman et al.[262] indicated that if we consider the risk of type 1 error equal to 5% and the risk of type 2 error equal to 10% (90% power), with a standard variation lower than 50%, the necessary number of patients would be 15 (see figure 15.2 in Altman, *Practical Statistics for Medical Research,* London, Chapman and Hall, 1991, p.455–60). However, referring to the chapter 2, the objectives of this study consist of changes in the level of 3 different factors (CGRP, EASI, and the spine severity score), not only between two different groups but before and after the chiropractic treatment. In this case, considering $\alpha = 0.05$ and power = 0.80, we additionally conducted a sample size calculation using G*Power® software [263,264] to determine a sufficient sample size. Power analysis revealed that 45 samples for treatment group and 20 samples for the control group. Yet, considering 10% of the loss to follow-up, the estimated number of patients to be recruited was 50 for treatment group and 22 patients for control group were needed to detect a difference of CGRP, EASI, and spine score levels between the two groups. Nevertheless, the sample size calculation could not be accurate since it was the first study investigating the correlation of CGRP, EASI and spine severity score, therefore, a wider cohort study is needed.

3.5 Statistics

To compare non-parametric variables U-Mann Whitney test was performed for groups comparison. In addition, non-parametric linear

Gaussian test was performed to find correlations between the level of variables. All statistics analysis was performed using GraphPad Prism® version 9.0.0 for Mac, GraphPad Software, San Diego, California, USA.

3.6 Clinical Evaluations

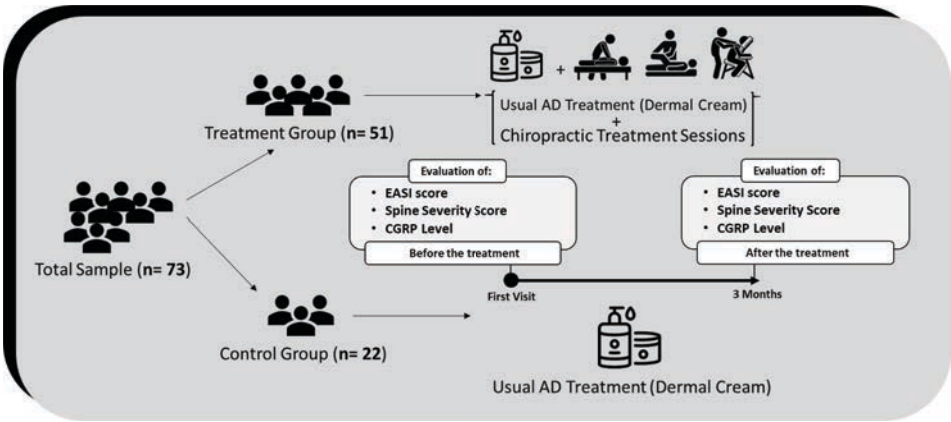


Figure 29- Study Design

Study of the following areas of which photographs are taken if they in case of being affected: scalp, forehead, eyes, ears, face, chin, neck, trunk, arms, and hands, legs, genital area, and feet. These areas are reviewed and quantitatively assessed the degree of disease's severity and involvement. In addition, the signs described by the medical team used the system "The Eczema Area and Severity Index (EASI)" for their quantification [265–267].

The level of neuropeptides in the plasma of 73 patients suffering from dermatitis has been tracked for 3 months. We reviewed the patient's blood test results and the X-ray analysis of their spine's situation in different checkpoints of 2 weeks, 1 month, and 3 months after their first visit. The study design is shown in Figure 29.

3.6.1 Eczema Area and Severity Index (EASI)

Eczema Area and Severity Index is an investigator-assessed tool determining the severity of dermatitis clinical signs. The EASI is a validated scoring system that rates the severity levels of physical signs of Dermatitis. The severity levels in the EASI calculation are indicated as: 0=clear; 0.1-1=almost clear; 1.1-7=mild; 7.1-21=moderate; 21.1-50=severe; 50.1-72=very severe. The EASI has also been verified to be adequate in terms of ease of use, as evaluations by expert researchers take about six minutes. [265]

EASI mainly focuses on four regions of human body.

- **Head and neck**
  - It includes the face by 33% (17% each side of the face), 33% for the neck (front and back of the neck), and 33% for the scalp of the head and neck region.

- **Trunk**
  - It is occupied by front of the trunk with 55% and 45% of the back trunk. (It also includes genital area.)

- **Upper limbs**
  - Upper limbs area is occupied by each arm with 50% (Front or back of one arm calculates as 25%)

- **Lower limbs**
  - It includes each leg with 45% (Front or back of one leg is 22.5%) and buttocks with 10%.

The severity of dermatitis in 51 patients of this study have been evaluated by reviewing their skin condition during the study. Pictures have been taken at each visit (before, during, and after chiropractic treatment) and EASI level have been calculated at different stages of this study.
Dermatitis severity score was calculated for all patients in four regions of the body. The average intensity of each sign in each body region is assessed as: clear (none) (score= 0), mild (score= 1), moderate (score= 2) and severe (score= 3). As a definition, the severity score is the total of the intensity scores for four signs. Those four signs are:

(i) Erythema

Erythema in dermatology is described as reddened skin as a result of increased blood supply [268,269]. Calculation of EASI score in reddened skin portrayed in Figure 30.

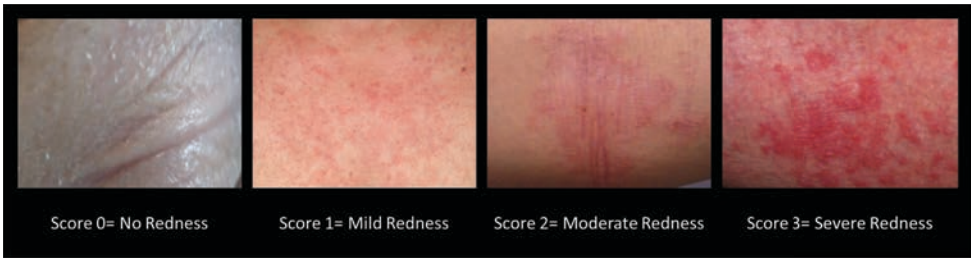


Figure 30- Definition of EASI scores in erythema sign[270]

(ii) Oedema/ Papulation

Papulation is an abnormal thickness of the skin. It may be due to fibrosis and feels dried and thickened. [271,272] (Figure 31)

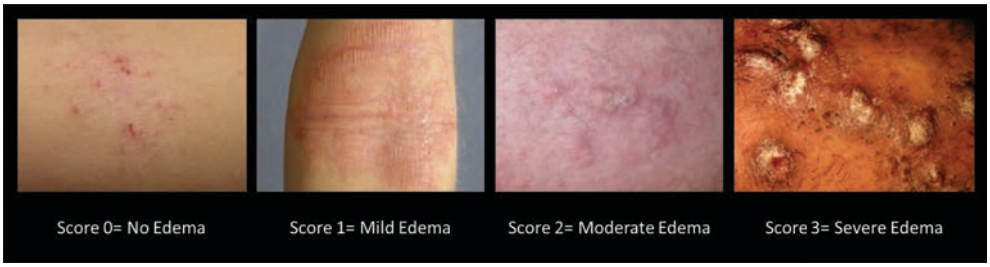


Figure 31 - Definition of EASI scores in oedema sign[270]

(iii) Excoriation

Excoriation, also called a scratch mark, results from loss of epidermis and a part of the dermis caused by scratching [273–275]. Excoriation potentially has a major effect on a patient's life. They usually try to cover or hide the wounded areas. Feelings of shame and embarrassment may cause them to avoid social places and activities altogether [275]. As people with the disorder become isolated, they may even fail to seek medical attention. The appearance of excoriation and the definition of EASI scores in that symptom is presented in Figure 32.

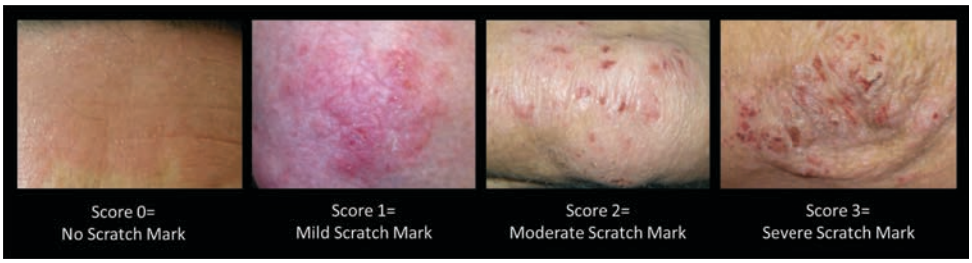


Figure 32- Definition of EASI scores in excoriation sign[270]

(iv) Lichenification

Lichenification is the development of skin thickening, changing to a leathery touch with increased skin markings resulted from chronic scratching [276,277]. The definition of EASI score in lichenification sign is provided in Figure 33.

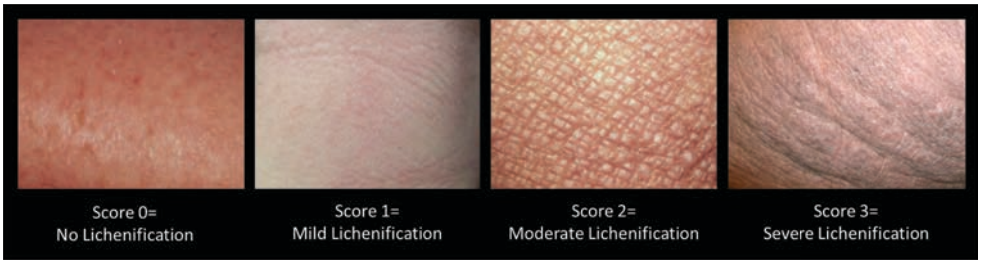


Figure 33- Definition of EASI scores in lichenification sign[270]

The EASI score as the scale of evaluating the severity of dermatitis results from summing up the score of each of the aforementioned signs.

3.7 Full Spine X Ray (Scoliogram)

To calculate the severity score for spinal biomechanical alterations (SBA) full spine x-rays (scoliogram) were taken for each patient. (Figure 34)

X-ray analysis was performed by an MD radiologist and quantified according to literature-based criteria [278–285] in different parts of the spine- cervical spine [285], thoracic [279], lumbar 282, and sacrum [284]. In order to allow statistical analysis a

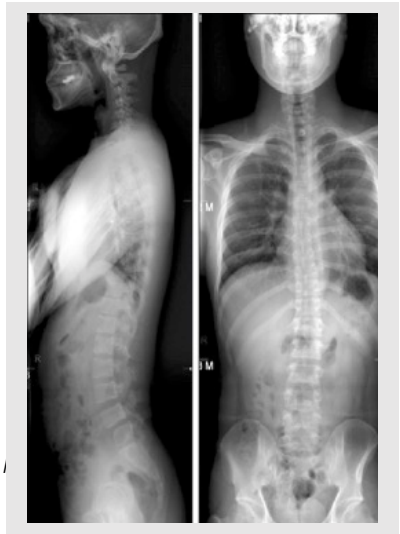


Figure 34- Full Spine X-Ray (Scoliogram)

numerical description or score was assigned to each radiological finding as described below.

3.7.1 Radiographic (X-Ray) analysis and Segmental description

A. Cervical Spine - Coronal Anteroposterior (AP) and open mouth views

(i) Atlas- Axis relationship

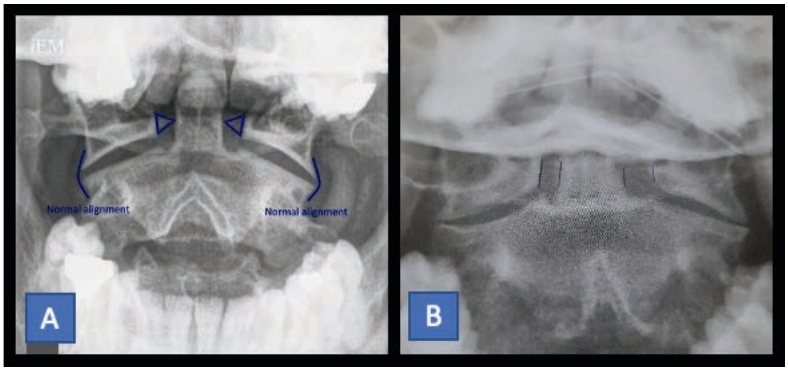


Figure 36- Atlas- Axis positions, (A) neutral position, (B) Asymmetric atlanto-odontoid distance – greater left

The severity score (of biomechanical alterations) of the cervical spine, starts by examining the position of the first two cervical vertebrae: C1 – C2 (Figure 36), also known as Atlas-Axis atlantoaxial or atlanto-odontoid joint. [283,285]

Two situations that are expected to be found here:

1. **Neutral** atlanto-odontoid relationship, meaning that the atlantoaxial distance in the coronal plan is symmetrically conserved right and left. (Figure 36-A)

2. **Asymmetric** atlanto-odontoid distance, meaning that the atlantoaxial distance presents discrete asymmetry in the coronal plan, where greater distance right or left is observed. (Figure 36-B)

In case of having a neutral situation (conserved) the score was calculated as 0, while an asymmetric relationship,-was scored as 1.

Neutral (conserved): 0,

Asymmetry Right =Right > Left: Score 1

Asymmetry Left = Left > Right: Score 1

In addition to the bilateral preservation of atlantoaxial joint distance, radiological signs of eventual incipient degenerative mechanical changes of the articular surfaces or facet joints of C1-C2 have been reviewed.

(ii) Vertebra C1 (Atlas) - AP view

In the case of C1 preservation of its zygopophyseal or facet joints has been examined.

(Zygoapophyseal or facet joints 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.)

For preserved zygopophyseal joints of C1, the score would be calculated as 0; in case of finding degenerative mechanical change, the score is calculated as 1.

Furthermore, according to various degrees of degenerative mechanical changes of the zygopophyseal joints of C1, the severity score is said to be: 2 (incipient), 3 (moderate), and 4 (severe).

To resume, radiographic findings of zygoapophyseal joints of C1 have been described as follows:

Conserved (normal joints) = 0

Mechanical Changes = 1

Degenerative Changes =2 (incipient), 3 (moderate), and 4(severe).

(iii) Vertebra C2 (Axis) - AP view

Similarly, in case of preserved zygopophyseal joints of C2, the score would be calculated as 0; in case of finding degenerative mechanical change, the score is calculated as 1.

Furthermore, to describe various degree of degenerative mechanical changes of the zygopophyseal joints of C2, the severity score is said to be 2 (incipient), 3 (moderate), and 4 (severe).

Conserved (normal joints) = 0

Mechanical Changes = 1

Degenerative Changes =2 (incipient), 3 (moderate), and 4(severe).

(iv) Cervical Vertebrae C3 – C4 – C5- C6 - C7 - AP view

For the cervical vertebral segments: C3 - C4 - C5 – C6 – C7 the zygoapophyseal joints and uncoapophyseal joints, also called 'Lushka joints', were examined and described as follows:

Conserved (normal joints) = 0

Mechanical Changes = 1

Degenerative Changes =2 (incipient), 3 (moderate), and 4(severe).

Furthermore, presence of a posterior arch closure defect with failure of union in the spinous process, also known as spina bifida occulta (SBO), in any of the above-mentioned cervical vertebrae was described as follows:

1. *Conserved (Posterior Arch) = 0,*
2. *Closure defect (SBO) = 1*

When the eventual presence of megapophysis of the transverse process (TP) of the vertebrae C7 was observed it was described as ‘discreet bilateral megapophysis of the TP of C7’ and it was considered within normal.

Spinal transitional anomalies of the cervicothoracic junction were described as follows:

- Cervicothoracic junction with bilateral TP megapophysis of C7
- Cervicothoracic junction with bilateral TP megapophysis of C7 with articulated ossicles (cervical pseudo-ribs)
- Cervicothoracic junction with bilateral TP megapophysis of C7 and presence of true cervical ribs (frequently associated with Thoracic outlet, Scalene syndrome)

The following numerical description or score was assigned to the above-described radiographic anomalies:

- Bilateral TP megapophysis of C7 = 0
- Bilateral TP megapophysis of C7 with articulated ossicles (cervical pseudo-ribs) = 1
- Bilateral TP megapophysis with true cervical ribs = 2

B. Cervical Spine X -ray Analysis and Segmental Description - Lateral (LAT) view

Observation of cervical spine initiates by the X-Ray analysis of cervical spine indicating the anterior and posterior vertebral line, and intervertebral cartilage spaces. (Figure 37)

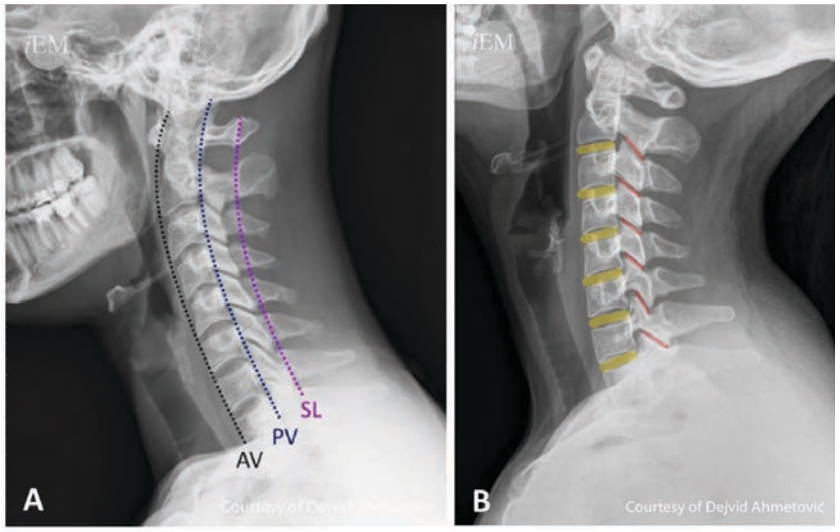


Figure 37- Cervical Spine X-ray. (A) Anterior vertebral (AV), posterior vertebral (PV) and spinolaminar lines (SL). (B) intervertebral cartilage spaces[173]

(v) Description of radiographic finding of the C1 - C2 (atlantoaxial) joint – lateral view

- Preserved atlantoaxial joint.

- Degenerative mechanical changes of the atlantoaxial joint surfaces with preserved joint space.

- Degenerative mechanical changes of the atlantoaxial joint surfaces with a slight decrease in the joint space.

The above-described radiographic findings were assigned the following numerical description:

Conserved = 0 (N atlantoaxial distance 2-3 mm)

Degenerative = 1 (N atlantoaxial distance 2-3 mm)

Degenerative = 2 (N atlantoaxial distance <2 mm)

Static instability = 3 (N atlantoaxial distance> 3 mm)

(vi) Description of cervical physiological lordosis - LAT view

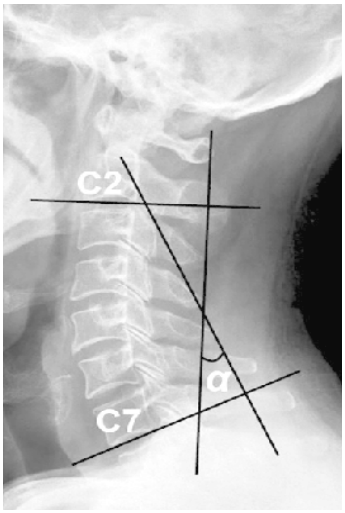


Figure 38- C2-C7 cervical lordosis angle

Value of the cervical lordosis angle, between C2- C7, also known as 'angle of Cobb' [286] is measured in degrees "xº"

C2-C7 cervical lordosis angle (Cobb): -xº (Normal between -25º and -40º (<-25º = rectification /> -40º = hyperlordosis) (See Figure 38).

A negative value "-xº " (minus) is assigned to lordosis, whereas a positive value "+xº " (plus) is considered kyphosis.

- Conserved cervical physiological lordosis, measured between C2-C7 refers to normal physiological lordosis of the cervical spine, ranging from -25º to - 40º.

- Rectification of the physiological lordosis (hypolordosis) of the cervical spine, present if the cervical lordosis angle, measured between C2-C7, is less than - 25º >

- Rectification of the physiological lordosis of the cervical spine, measured between C2-C7 with kyphotic inversion of is assigned a positive value of + x º.

The score of cervical spine lordosis is described below:

Conserved lordosis = 0

Rectification = 1 (value between 0º and -25º)

Rectification with kyphotic inversion = 2 (value +xº)

(vii) C2- C 7 – Description of intersomatic spaces

- Intersomatic spaces of the proximal segments C2-C4 conserved diminished in their global height.
- Intersomatic spaces of the distal segments C4-C7 conserved diminished in their global height,

with signs of degenerative disc disease and marginal osteophytosis.

Conserved = 0

Decreased = 1

Diminished with signs of degenerative disc disease = 2

Diminished with signs of degenerative disc disease and anterior / posterior marginal OA = 3

(viii) C2- C 7 – Description of interfacetal joints -LAT View

- Preserved interfacetal joints of the cervical spine.
- Incipient generalized degenerative mechanical changes of the interfacetal joints of the cervical spine (adjacent subchondral sclerosis).
- Generalized degenerative mechanical changes of the interfacetal joints of the cervical spine.

Conserved = 0

Mechanical changes = 1

Incipient degenerative changes = 2

Degenerative changes = 3

(ix) C1 - C7- Description of cervical segmental instability in sagittal plan– LAT view

- No signs of segmental instability are observed in relation to the sagittal alignment of the posterior vertebral walls.

- Signs of segmental instability in relation to the sagittal alignment of the posterior vertebral walls with discrete anterolisthesis stepped retrolisthesis and discrete anterolisthesis with stepped retrolisthesis

Score assigned:

Preserved = 0 (sagittal alignment of the posterior vertebral walls)

Instability = 1 (<or = 2 mm) (anterolisthesis vs retrolisthesis)

Instability = 2 (> 2 mm) (anterolisthesis vs retrolisthesis)

In case of spondylolisthesis description followed the Meyerding classification or grading (G) scale:

G1: Low-grade spondylolisthesis with slip between 0 - 25%= 1

G2: Low-grade spondylolisthesis with slip between 26% - 50%= 2

G3: High-grade spondylolisthesis with slip between 51% and 75%= 3

G4: High-grade spondylolisthesis with slip between 76% and 100%= 4

Eventual radiographic anomalies or variants of normal, observed on the lateral view of the cervical spine such as:

- bilateral calcification of the stylohyoid ligament.
- posterior arch of C1 showing an arcuate hole formed by the calcification of the oblique ligaments of the atlanto-occipital junction.
- occipital spur (calcified enthesopathy in insertion area).
- heterotopic ossification of the posterior nuchal ligament (circumscribed myositis ossificans).
- posterior arch defect of the Atlas (C1) due to congenital aplasia of the posterior tubercle (Corrarino Type A).
- segmentation defect of two or more cervical vertebrae, whereby a congenital complete fusion of vertebral bodies and posterior arches (Klippel-Feil deformity),

were considered, for the purpose of this study, as normal (variants).

C. Full Spine X ray of the Spine (Scoliogram) AP and LAT views

AP and LAT views Scoliogram were taken barefoot and without elevation on a Focus-Plate - distance of 180 cm- in standing position.

(i) AP view 1 – Radiographic description of upper dorsal spine – Clavicular symmetry

- There is no difference in clavicular height - conserved symmetry
- Unequal clavicular height: right ‘x’ mm lower than left or the other way around.

Score of clavicular symmetry was assigned as follows:

Conserved = 0

Asymmetry = 1

(ii) AP view 2 – Description of radiological findings Pelvis Symmetry:

- Coronal Pelvic Balance (Pelvic Scale) with neutral value 0º.
- There is no difference in the height of the iliac crests.
- There is no difference in femoral head height.
- Coronal Pelvic Balance (Pelvic Scale) with right-left descending inclination of `x` º.
- Iliac crest height difference: lower right left measured in millimeters (mm).
- Femoral head height difference: lower right left 'x' mm.

Score of pelvic symmetry or dysmetria was assigned as follows:

Conserved = 0

Dysmetria = 1 (1 mm)

Dysmetria = 2 (1.5 -3 mm).

Dysmetria = 3 (> 3 mm).

(iii) AP view 3 – Description of Coronal Vertebral Balance (CVB)

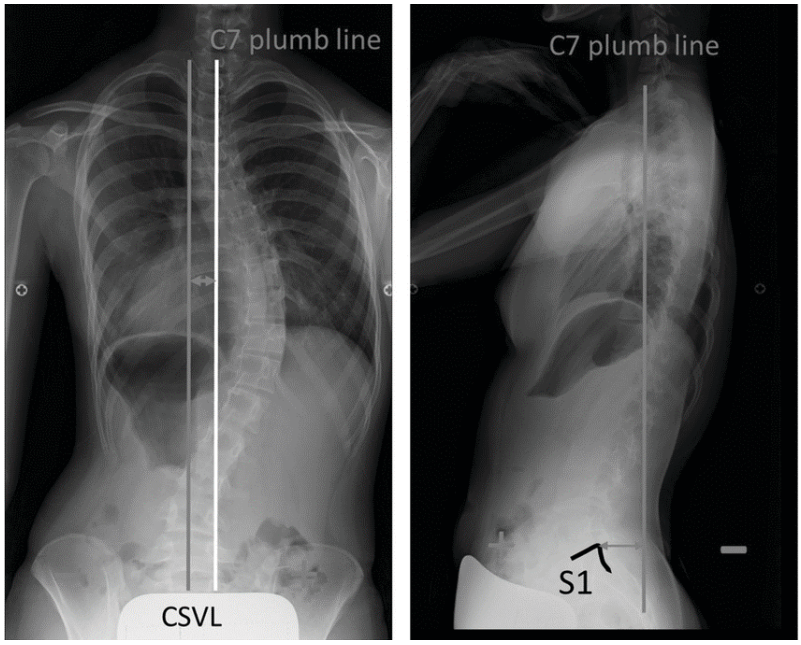


Figure 39 - Coronal Vertebral Balance X-Ray analysis [206]

Neutral global vertebral coronal balance: Plumb Line C7 (PLC7) located in the same vertical plane as the Central Sacrum Vertical Line (CSVL) and is considered normal aligned spine. (See Figure 39)

Normal (N) = 0 with a standard deviation of +/- 20 mm. Value > 30 mm = Coronal Imbalance: loss of biomechanical alignment). (Figure 39)

- Negative vertebral coronal balance (PLC7 located to the left of CSVL) of 'x' mm (A) (N = 0 with a deviation of +/- 20 mm. Value> 30 mm = Coronal Unbalance: loss of biomechanical alignment or balance).

- Positive vertebral coronal balance (PLC7 located to the right of CSVL) of + mm (A) (N = 0 with deviation of +/- 20 mm. Value> 30 mm = Coronal Unbalance: loss of biomechanical balance).

Coronal Vertebral Balance (CVB)

N = 0 (overlapping PLC7 and CSVL)

PLC7 located to the left of CSVL:

- *Negative CVB (Normal = 0 with deviation of -20 mm. Within normal range) = 1*
- *Negative CVB (between -20 and -30-mm. Value higher than the N range) = 2*
- *Negative CVB (Value> -30 mm. Coronal biomechanical loss and imbalance:)= 3*

PLC7 located to the right of CSVL:

- *Positive CVB (N = 0 with deviation of -20 mm. Within normal range. = 1*
- *Positive CVB (between +20 and + 30 mm. Value higher than the N range) = 2*
- *Positive CVB (Value> +30 mm. Coronal biomechanical loss and imbalance). = 3*

(iv) AP view – 4 Description of Scoliotic Curves

- Scoliotic attitude with right (dextroconvex) or left (levoconvex) lateral inclination of the spine in the coronal plane,
- Scoliotic attitude (main curve value <11º):
- Mild degree of scoliosis (main curve value <20º):
- Moderate degree of scoliosis (main curve value between 20º and 40º):
- Moderate to severe scoliosis (main curve value between 40º and 50º):
- Severe degree of scoliosis (main curve value> 50º):

The score assigned to scoliotic curves is as follows:

- *Normal spinal alignment (no curve) = 0*

- *Scoliotic attitude (main curve value <11º) = 1*
- *Scoliosis in mild degree (main curve value <20º) = 2*
- *Moderate degree scoliosis (main curve value between 20º and 40º) = 3*
- *Moderate / severe scoliosis (main curve value between 40º and 50º) = 4*
- *Scoliosis in severe degree (main curve value> 50º) = 5*

(v) AP view 5 – Description of Lumbar Spine and Sacral Segments

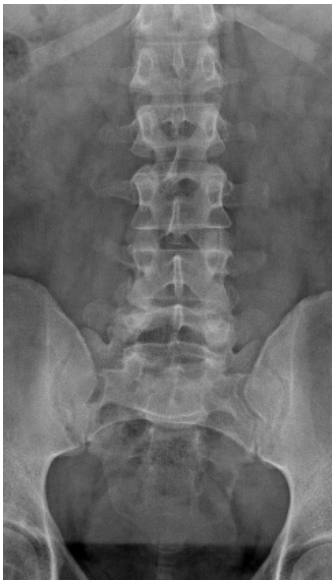


Figure 40- Lumbar Spine and Sacral Segment X-Ray

- Vertebral bodies and posterior elements of the spine preserved.
- Incipient generalized mechanical changes.
- Generalized mechanical changes in the spine.
- Incipient generalized interfacetal subchondral sclerosis in the lumbar spine, predominantly L3-S1 with slight loss of joint space.
- S1 posterior arch closure defect with absence of union in the spinous process (spina bifida occulta) (See Figure 40).

The score assigned is as follows:

- *Vertebral bodies and posterior elements of the spine preserved = 0*
- *Mechanical changes = 1*

- *Degenerative changes (incipient degree) = 2*
- *Degenerative changes (moderate degree) = 3*
- *Degenerative changes (severe degree) = 4*

(vi) AP view 6 – Description of Sacroiliac and symphysis pubis joints

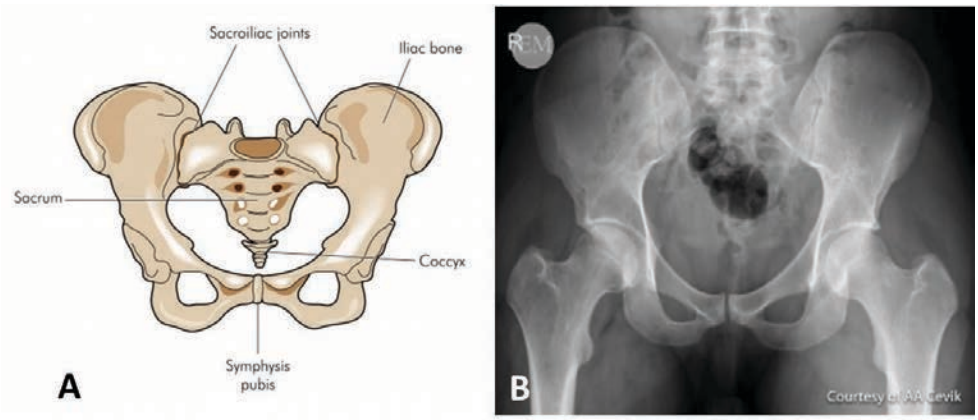


Figure 41- An illustration (A) and an X-Ray photo of the sacroiliac and symphysis pubis[287]

Incipient mechanical changes of the bilateral sacroiliac joint and pubic symphysis (See Figure 41).

- Mechanical changes of the bilateral sacroiliac joint and pubic symphysis. Numerical Score assigned is as follows:

- *Bilateral sacroiliac joint and preserved pubic symphysis = 0*
- *Incipient mechanical changes = 1*
- *Mechanical changes = 2*
- *Degenerative changes = 3*

(vii) AP 7 view – Description of the Femoroacetabular joints

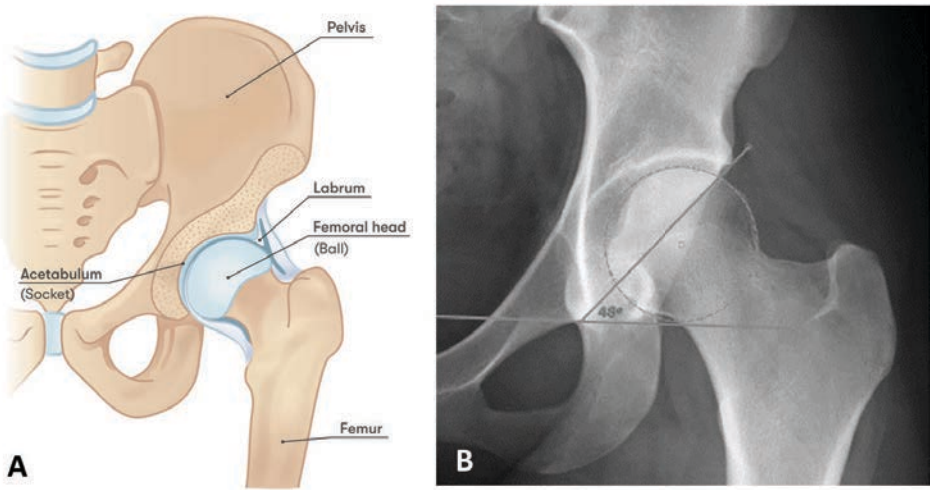


Figure 42- An illustration (A) and an X-Ray photo of the Femoroacetabular joints [287]

Preserved bilateral femoroacetabular joint spaces and surfaces (See Figure 42).

- Diminished femoroacetabular joint spaces without degenerative mechanical changes of the articular surfaces.

- Diminished femoroacetabular joint spaces with incipient, moderate, or severe mechanical degeneration (Coxarthrosis).

The numerical description score assigned is as follow:

- *Preserved femoroacetabular joint = 0*
- *Femoroacetabular joint incipient mechanical changes = 1*
- *Femoroacetabular joint mechanical changes = 2*
- *Femoroacetabular joint incipient degenerative changes (coxarthrosis) = 3*
- *Femoroacetabular joint moderate degenerative changes (coxarthrosis) = 4*

- *Femoroacetabular joint severe degenerative changes (coxarthrosis) = 5*

(viii) AP view 7 – Description of eventual presence of hip joint deformity

- "CAM-type" hump deformity (pistol grip deformity) on the lateral margin of the cervicocephalic junction of the bilateral right left femur. Clinically assessed as femoroacetabular impingement (Figure 43). [287]

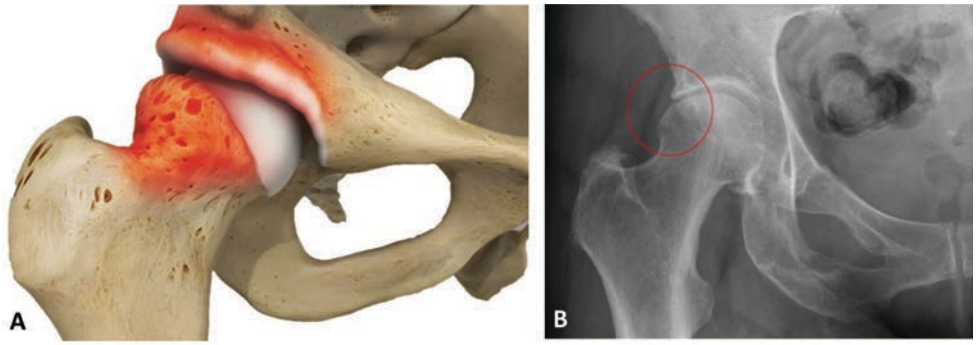


Figure 43- An illustration (A) and an X-Ray photo (B) of femoroacetabular impingement[287]

The numerical description was assigned as follows:

Conserved femoral head sphericity = 0

FAI = 1

(ix) Full Spine (Scoliogram) - LAT View 1 – X ray Analysis Description

a. Parameters of the sagittal vertical axis (SVA) relative to the C7PL line

To quantify the x ray findings on the full spine LAT view and to statistically describe the severity of eventual biomechanical alterations for each patient, a numerical score was assigned to the following points:

- Angle of thoracic kyphosis T4-T12: + º (N between + 20º and + 40º,> + 50º = hyperkyphosis).

- T10-L2 transitional kyphosis angle: + º (N "+" <+ 20º /> + 20º = hyperkyphosis).

- Lumbar lordosis angle L1-S1 (LL): -º (N between -40º and -70º).

- L4-S1 lumbar distal segment lordosis angle: `x`º

- Pelvic Incidence Angle (PI: Pelvic Incidence): º (PI = SS + PT).

- Angle of the Sacral Slope (SS: Sacral Slope): º.

- Pelvic Tilt Angle (PT: Pelvic Tilt): º

(Moderate pelvic retroversion: 20º-30º).

(Severe pelvic retroversion:> 30º).

- Ranges by age of the normal values of the spinopelvic sagittal balance (pelvic parameters):

- Between 21-40 years: PI = 52º +/- 10º (42º-62º); SS = 39º +/- 9º (30º-48º) and PT = 13º +/- 7º (6º-20º).

- Between 41-60 years: PI = 53º +/- 8º (45º-61º); SS = 40º +/- 7º (33º-47º) and PT = 14º +/- 6º (8º-20º).

- Age> 61 years: PI = 51º +/- 9º (42º-60º); SS = 36º +/- 9º (27º-45º) and PT = 16º +/- 9º (7º-25º).

- Positive global vertebral sagittal balance- PLC7 (Plumb line at C7)-located in front of the postero-superior corner of S1) of + mm (A) (N = 0 +/- 30 mm. Value> 50 mm = Sagittal imbalance: loss of biomechanical balance).

- Negative global vertebral sagittal balance (PLC7 located behind the postero-superior corner of S1) of - mm (A) (N = 0 +/- 30 mm. Value> 50 mm = Sagittal imbalance: loss of biomechanical balance).

- Neutral global vertebral sagittal balance (PLC7 located in the same vertical plane as the poster corner -superior of S1) considering it as a normal spinal alignment (N = 0 with a deviation of +/- 20 mm. Value> 50 mm = Sagittal imbalance: biomechanical loss of balance).

(ix) LAT view 1 - Description of Vertebral Sagittal Balance (VSB)

- Compensated global neutral vertebral sagittal balance.
- Positive vertebral sagittal balance: Sagittal Vertical Axis (SVA) anterior of + mm, with a value within the range of normality (N = 0 +/- 30 mm).
- Positive vertebral sagittal balance (SVA anterior of + mm) with a value within the normal range and close to the upper limit (N = 0 +/- 30 mm).
- Positive vertebral sagittal balance (SVA anterior of + mm) with a value in the upper limit of the range of normality (N = 0 +/- 30 mm).
- Positive vertebral sagittal balance (SVA anterior of + mm) with a value higher than the normal range (N = 0 +/- 30 mm //> +/- 50 mm = Sagittal Unbalance).
- Positive sagittal imbalance (SVA anterior of + mm) in a moderate degree (value between +50 mm and +95 mm).
- Positive sagittal imbalance (SVA anterior of + mm) in severe degree (value> +95 mm).
- Negative vertebral sagittal balance (SVA posterior of - mm) with a value within the normal range (N = 0 +/- 30 mm).
- Negative vertebral sagittal balance (SVA posterior of - mm) with a value within the normal range and close to the upper limit (N = 0 +/- 30 mm).
- Negative vertebral sagittal balance (SVA posterior of - mm) with a value in the upper limit of the range of normality (N = 0 +/- 30 mm).

- Negative vertebral sagittal balance (SVA posterior of - mm) with a value higher than the normal range (N = 0 +/- 30 mm //> +/- 50 mm = Sagittal Imbalance).

- Moderately negative sagittal imbalance (SVA posterior of - mm) (value between -50 mm and -95 mm).

- Severe negative sagittal imbalance (SVA posterior of - mm) (value> -95 mm).

Vertebral Sagittal Balance (VSB) - N = 0 (PLC7 located in the same vertical plane as S1 postero-superior corner) (SVA Sagittal Vertical Axis)

PLC7 located in front of the poster-superior corner S1:

Positive VSB (N = 0 with deviation of +30 mm. Within the range of normality) = 1

Positive VSB (between +30 mm and +50 mm. Value above the N range) = 2

VSB Moderate positive imbalance (Value between +50 mm and +95 mm = biomechanical loss and imbalance) = 3

VSB Positive imbalance (Value> +95 mm = biomechanical loss and unbalance) = 4

PLC7 located behind poster-superior corner S1:

Numerical scores for the description of VSB were assigned as follows:

Negative VSB (N = 0 with deviation of -30 mm. Within the range of normality) = 1

Negative VSB (between -30 mm and -50 mm. Value above the N range) = 2

VSB Moderate negative imbalance (Value between -50 mm and -95 mm = loss and biomechanical imbalance) = 3

VSB Negative unbalance (Value> -95 mm = biomechanical loss and unbalance) = 4

(x) LAT view 2- Description of Thoracic Physiological Kyphosis

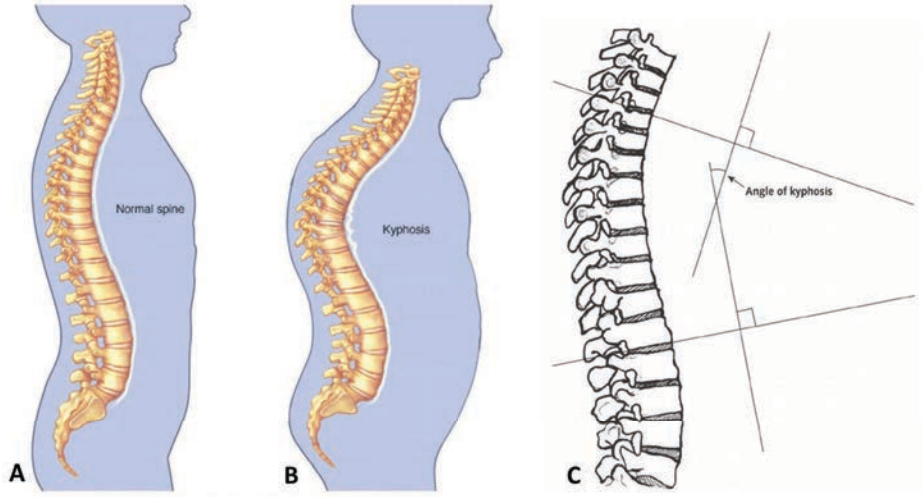


Figure 44- Thoracic Physiological Kyphosis. (A) Normal lateral formation of spine, (B) Thoracic physiological kyphosis, and (C) description of angle of kyphosis. Reprinted with permission from [288]

- Physiological kyphosis (Figure 44) of the thoracic spine T4-T12 preserved (value + º: N between + 20º and + 40º> + 50º = hyperkyphosis).

- Thoracic Spine Sagittal Modifier: Based on the Cobb angle or grade of thoracic kyphosis (T4-T12) according to Lenke's classification:

- Modifier "N" (neutral): Angle of thoracic kyphosis between + 10º and + 40 °.

- Thoracic hypokyphosis (T4-T12 = + º) with "flat back" deformity (+ º: N value between + 20º and + 40º / <+ 10º = flat back).

- Thoracic Spine Sagittal Modifier: Based on the Cobb grades of thoracic kyphosis (T4-T12) according to Lenke's classification:

- Modifier "N" (neutral): Angle of thoracic kyphosis between + 10º and + 40 °.

- Modifier "-" (negative): Angle of thoracic kyphosis <+ 10 °.

- Tendency to T4-T12 thoracic hyperkyphosis (value + º: N between + 20º and + 40º,> + 50º = hyperkyphosis).

- Sagittal Thoracic Spine Modifier: Based on the Cobb grades of thoracic kyphosis (T4-T12) according to Lenke's classification:

- Modifier "+" (positive): Angle of thoracic kyphosis> + 40 °.

- Hyperkyphosis of the thoracic spine T4-T12 (value + º> + 50º = hyperkyphosis-kyphoscoliosis).

- Thoracic Spine Sagittal Modifier: Based on the Cobb grades of thoracic kyphosis (T4-T12) according to Lenke's classification:

- Modifier "+" (positive): Angle of thoracic kyphosis> + 40 °.

Numerical scores for the description of thoracic kyphosis were assigned as follows:

Preserved T4-T12 thoracic kyphosis (N between + 20º and + 40º) = 0

Tendency to thoracic hyperkyphosis T4-T12 (between + 40º and + 50º) = 1

Hyperkyphosis of the thoracic spine T4-T12 (> + 50º) = 2

T4-T12 thoracic hypokphosis ("flat back" deformity) (<+ 10º = flat back) = 3

(xi) LAT view 3 – Description of transitional Thoracolumbar physiological kyphosis

- Transitional physiological kyphosis T10-L2 preserved (value + º: N "+" <20º /> + 20º = hyperkyphosis).

- Hyperkyphosis of the thoraco-lumbar transition T10-L2 (value + º:> + 20º = hyperkyphosis).

- Rectification of the transitional thoraco-lumbar kyphosis T10-L2 with a neutral value (0º).

- Lordotic inversion of transitional kyphosis T10-L2 (-º value: N "+" <20º /> + 20º = hyperkyphosis).

Numerical scores for the description of the transitional thoracolumbar kyphosis were assigned as follows:

Transitional physiological kyphosis T10-L2 preserved (N "+" <20º) = 0

Lordotic inversion of T10-L2 transitional kyphosis ("-" value) = 1

T10-L2 thoraco-lumbar transitional kyphosis rectification with neutral value (0º) = 2

Hyperkyphosis of the thoraco-lumbar transition T10-L2 (> + 20º) = 3

(xii) LAT view 4 – Description of the physiological lordosis of the lumbar spine

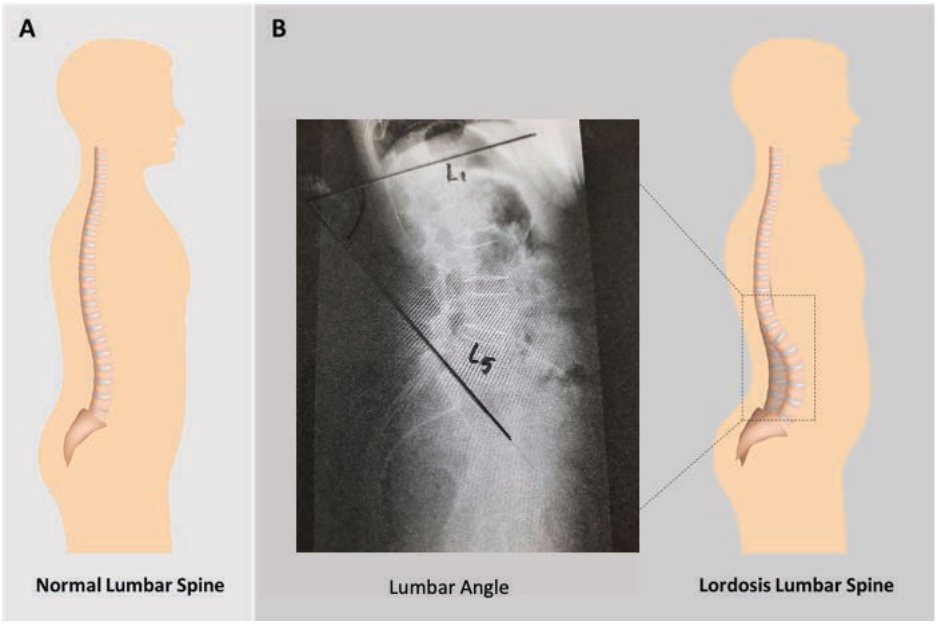


Figure 45- Lumbar Spine- Lateral view. (A) Normal Lumbar Spine, and (B) Lordosis Lumbar Spine

- Physiological lordosis of the lumbar spine L1-S1 (Figure 45) (LL = -º) preserved with synchronous value with respect to the PI (PI =º) (N = PI - LL <10º).

- Physiological lordosis of the lumbar spine L1-S1 (LL = -º) preserved with asynchronous value with respect to the PI (PI =º) (N = PI - LL <10º; LL = PI +º; PI = LL +º).

- Hypolordosis of the lumbar spine L1-S1 (LL = -º) with a synchronous value with respect to the PI (PI =º) (N = PI - LL <10º).

- Hypolordosis of the lumbar spine L1-S1 (LL = -º) with asynchronous value with respect to the PI (PI = º) (N = PI - LL <10º; LL = PI + º; PI = LL + º).

- Hyperlordosis of the lumbar spine L1-S1 (LL = -º) with a synchronous value with respect to the PI (PI =º) (N = PI - LL <10º).

- Hyperlordosis of the lumbar spine L1-S1 (LL = -º) with asynchronous value with respect to the PI (PI = º) (N = PI - LL <10º; LL = PI + º; PI = LL + º).

Numerical description of the lumbar lordosis, based on the Cobb angle measurement was assigned the following score:

Lumbar lordosis angle L1-S1 (LL) preserved (N between -40º and -70º) = 0

Hyperlordosis L1-S1 (LL> -70º) = 1

L1-S1 hypolordosis (LL <-40º) = 2

(xiii) LAT view 5 – Description of lumbar lordosis distribution angle (LDI)

- Lordosis Distribution Index (LDI) (L4-S1 = -º): L4-S1 / L1-S1 X 100 =% (Aligned and compensated distribution L4-S1: 50% -80%).

The following score was assigned to numerically describe the LDI:

- Severe L4-S1 hypolordotic maldistribution: <40% = 3

- Moderate L4-S1 hypolordotic maldistribution: 40% -49% = 2

- L4-S1 hyperlordotic poor distribution:> 80%= 1

- Distribution aligned and compensated L4-S1: 50% -80% = 0

(xiv) LAT view 6 – Description of thoracic spine intersomatic spaces

- Intersomatic spaces of the thoracic spine preserved diminished in their overall height.
- Intersomatic spaces of the thoracic spine T4-T9 conserved diminished in their overall height.

in the anterior margin.

- Intersomatic spaces of the thoracic spine T9 -T12 conserved diminished in their overall height.

The score assigned to numerically describe the thoracic spine intersomatic spaces is as follows:

Intersomatic spaces of the thoracic spine preserved in their overall height = 0

Intersomatic spaces of the thoracic spine decreased in overall height = 1

(xv) LAT view 7 – description oflumbar spine intersomatic spaces

- Intersomatic spaces of the lumbar spine L1-L3 (proximal segment) conserved diminished in their overall height.
- Intersomatic spaces of the lumbar spine L3-S1 (distal segment) conserved diminished in their overall height.

The score assigned to numerically describe the lumbar spine intersomatic spaces is as follows:

Intersomatic spaces of the lumbar spine preserved in their overall height = 0

Intersomatic spaces of the lumbar spine decreased in their overall height = 1

Diminished with signs of degenerative disc disease = 2

Diminished with signs of degenerative disc disease + anterior / posterior marginal osteophytosis = 3

(xvi) LAT view 8 – General Description of all spinal vertebral bodies and posterior arches

- Vertebral bodies and posterior arches of the spine preserved.
- Preserved vertebral bodies, posterior arches and intersomatic spaces of the spine.

Numerical description assigned is as follows:

Preserved vertebral bodies and posterior arches of the spine = 0

Preserved vertebral bodies, posterior arches and intersomatic spaces of the spine = 0

(xvii) LAT view 9 - Description of Thoracic Vertebral segments

- Incipient signs of intervertebral osteochondrosis in the thoracic spine.
- Signs of intervertebral osteochondrosis in the thoracic spine.

The score assigned to describe the general status of the thoracic segments is as follows:

Vertebral bodies and posterior elements of the thoracic spine preserved = 0

Mechanical changes = 1

Degenerative changes = 2 (incipient degree)

Degenerative changes = 3 (moderate grade)

Degenerative changes = 4 (severe grade)

(xviii) LAT view -10 Description of the lumbar vertebral segments

- Incipient generalized mechanical changes of the lumbar spine.
- Incipient generalized interfacetal subchondral sclerosis in the lumbar spine, predominantly L3-S1 with slight loss of joint space.

- Incipient generalized interfacetal mechanical changes in the lumbar spine, predominantly L3-S1 with subchondral sclerosis and slight loss of joint space.
- Incipient generalized interfacetal degenerative changes in the lumbar spine, predominantly L3-S1.
- Generalized interfacetal degenerative changes in the lumbar spine, predominantly L3-S1.
- Marked generalized interfacetal degenerative changes in the lumbar spine, predominantly L3-S1 (subchondral sclerosis, bone hypertrophy and loss of joint space).
- Signs of generalized degenerative disc disease in the lumbar spine.
- Signs of degenerative disc disease

The score assigned to describe the general status of the lumbar segments is as follows:

Preserved vertebral bodies and posterior elements of the lumbar spine = 0

Mechanical changes = 1

Degenerative changes = 2 (incipient degree)

Degenerative changes = 3 (moderate grade)

Degenerative changes = 4 (severe grade)

Degenerative changes with signs of degenerative disc disease = 5

Degenerative changes with signs of degenerative disc disease + anterior / posterior marginal osteophytosis = 6

(xix) LAT view 11 –Description of sagittal alignment of the posterior vertebral walls – Lumbar spine

The following parameters have been considered:

- Sagittal alignment of the posterior vertebral walls preserved.

- Discrete staggered asymmetric degenerative retrolisthesis
- Staggered asymmetric degenerative retrolisthesis
- Discrete asymmetric staggered retrolisthesis L1-L4 probably related to compensation mechanism.
- L1-L4 staggered asymmetric retrolisthesis probably related to compensation mechanism.
- Degenerative anterolisthesis - isthmic (congenital) - dysplastic (congenital).

(G1: Low-grade spondylolisthesis with displacement <or = 25% according to the Meyerding classification[289]).

(G2: Low-grade spondylolisthesis with displacement between 26% and 50% according to the Meyerding classification).

(G3: High-grade spondylolisthesis with displacement between 51% and 75% according to the Meyerding classification).

(G4: High-grade spondylolisthesis with displacement between 76% and 100% according to the Meyerding classification).

Sagittal alignment of posterior vertebral walls preserved = 0

Retrolisthesis = 1

Antherolisthesis:

G1: Low-grade spondylolisthesis with displacement <o = 25% according to the Meyerding classification = 1

G2: Low-grade spondylolisthesis with displacement between 26% and 50% according to the Meyerding classification = 2

G3: High-grade spondylolisthesis with displacement between 51% and 75% according to the Meyerding classification = 3

G4: High-grade spondylolisthesis with displacement between 76% and 100% according to the Meyerding classification = 4

3.7.2 Total Spinal Severity Score

Calculation of spinal biomechanical alterations severity score for each patient was done by summing up all the above-mentioned scores.

3.8 Treatment Methods

3.8.1 Usual Treatment

Once Dermatitis is diagnosed in patients, they generally receive a topical compound cream to use 2-3 times a day for duration of 15 days. The compound cream is under European patent number 2311454 and contains the following: 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%. This treatment cures the disease temporarily and relapses after 45 days.

3.8.2 Chiropractic treatments (SMT)

It is explained in section 3.10.

3.9 Determination of neuropeptide levels (Biomarkers)

Neuropeptide analysis in blood is routinely determined in patients with dermatitis as a disease-based index according to the literature. These determinations carried out by Synlab® laboratory located in Barcelona,

Spain. All tests were based on the ELISA technique, however, CGRP measured by the EAI kit (K-015–09, Phoenix Pharmaceuticals).

3.10 Chiropractic Treatment (SMT)

The objective of chiropractors is to detect and treat with specific manual techniques, called "adjustments", also known as Spinal Manipulation Therapy (SMT), any alteration in the normal dynamic, anatomical or physiological joint relationships of contiguous structures, both in the spine and in the extremities, in order to restore proper biomechanics, structural and physiological balance.

There are more than 90 chiropractic SMT techniques. These are chosen according to the therapeutic objective and the psychophysical characteristics of the patient and the therapist.

3.10.1 Methodology of the Chiropractic Treatment (SMT)

Postural evaluation and palpation of intervertebral movement of the spine and full spine X- ray analysis was made for each of the 73 patients of this study. However, as it is explained in section 2.2, patients were divided in two groups: treatment group (TG) and control group (CG) 51 patients were assigned randomly to the TG while the rest of 22 patients were assigned to the CG.

All patients assigned to the TG received chiropractic SMT using two types of techniques:

1. *High-velocity, low-amplitude (HVLA) - Diversified Technique*
2. *Activator Technique.*

A. High-velocity, low-amplitude (HVLA) technique

HVLA is one of the most frequently used chiropractic techniques for correcting spinal biomechanical. Most chiropractic clinical research, particularly for low back, mid-back, and neck pain has focused on the effectiveness analysis of spinal treatment. A clinical study concluded that SMT can be beneficial for many health-related conditions such as migraine, neck-related headaches, and whiplash-associated disorders. (Figure 46)

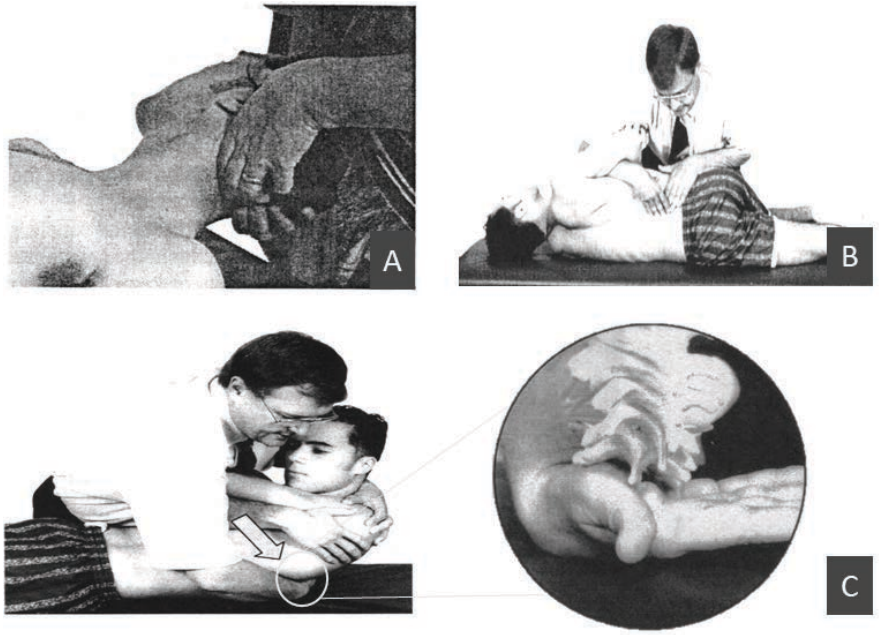


Figure 46- High-velocity, low-amplitude (HVLA) technique. (A) HLVA for Cervical spine problems, (B) HLVA for Lumbar spine problems, (C) HLVA for Thoracic spine problems [290].

There are different types of HVLA manipulation methodologies. A few of the more frequent HVLA manipulation techniques are described below:

- **Diversified technique (DT)**: This method is traditionally related with manual adjustments of chiropractic. For this technique, chiropractors employ a short and rapid force over selected joints (one at a time) in order to restore normal joint motion. The patient's body is placed in different particular ways to enhance the adjustment of the spine [291].

- **Gonstead adjustment technique:** Comparable to the diversified technique, the Gonstead adjustment is an HVLA correction method. However, DT- HVLA and Gonstead technique differ in the evaluation of locating the restricted (or subluxated) joint and in the spine positioning. Specific chairs and tables may be utilized to place the patient for treatment, for instance the cervical chair or the chest-knee table (Figure 47). This method is also known as the "Palmer-Gonstead" method. [292]

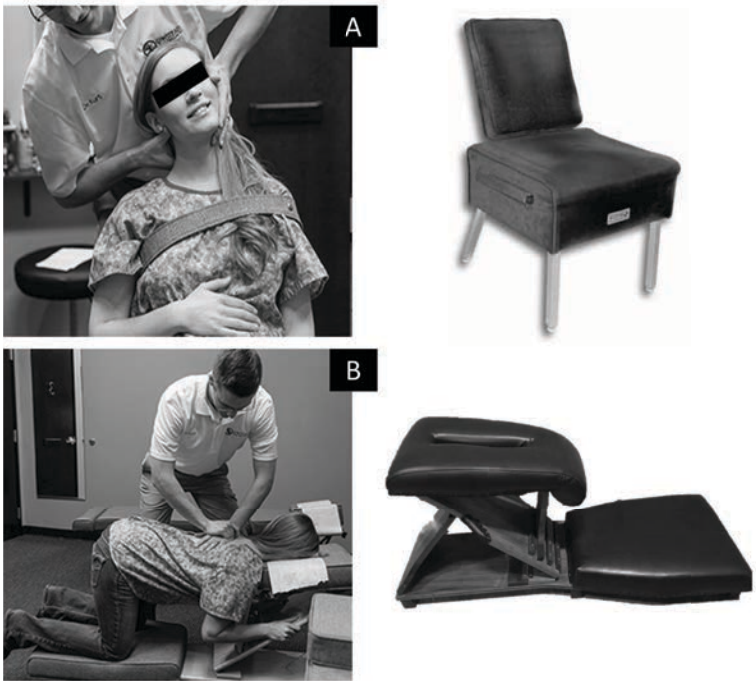


Figure 47- Gonstead adjustment tools, (A) Cervical chair, (B) Chest-knee table. Reprinted with modification from [292]

- **Thompson Terminal Point (or Drop) technique (TTP):** This method includes particular treatment tables that have separated parts dropping a brief gap through an HVLA force, with the idea that the dropping of the table can be helpful for the movement of the joint. This modification method is occasionally used instead of the traditional HVLA adjustment. In this method, the "cracking sound" may or may not happen and consequently this type of adjustment may also be measured a form of deployment, or a moderate adjustment methodology. [293]

- **Toggle Drop Technique (TDT):** Using both hands one on top of the other, the chiropractor takes advantage of gravity to induce joint correction. The table has different divisions (drop pieces) to raise

and fall in accordance with the placement of the spinal correction. [294]

- **Activator method**: The Activator is a hand-handled, soft-loaded method that delivers a fast HVLA mild-force impulse on different area of the spine. [294]

3.10.2 Chiropractic Evaluation (SMT evaluation)

All 51 patients assigned to the TG underwent 12 sessions of chiropractic treatment, twice a week for 3 weeks and once a week for 4 weeks and twice a month for 1 month. The duration of the chiropractic treatment was approximately 3 months.

After the first 3 weeks of treatment re-evaluation was done by the Doctor of Chiropractic (DC) to establish the outcome of the therapy and decide whether to:

- *Resume chiropractic treatment,*
- *Withdraw the patient from chiropractic therapy if neurogenic inflammation symptoms did not begin to subside.*

CHAPTER 4:
RESULTS

A. Correlation between the severity of dermatitis and the spinal condition

4.1 Evaluation of the severity level of Dermatitis in Treatment Group

As already explained in section 4, the severity level of dermatitis has been calculated by EASI score. Because none of the patients, participating in this study, were found to be free of spinal biomechanical alterations (SBA) and of degenerative changes, evidenced radiographically we divided the 51 treatment group (TG) patients in two subgroups classifying them according to the severity of the dermatitis, based on the EASI score (i.e., skin condition). group A, consisting of 22 patients with mild dermatitis (EASI≤7) and group B consisting of 29 patients suffering from severe dermatitis (EASI>7).

This additional classification helped us figure out if there ~~is~~ were any significant difference between the patients with mild dermatitis and patients with severe dermatitis in terms of the spinal severity score or the neuropeptide levels

A scatter plot of EASI score of patients in groups A and B is provided in Figure 1. In addition, as expected, the Mann-Whitney non-parametric test between two groups demonstrated that there is a significant difference ($P<0.0001$) (Table 3). The Figure 48 demonstrate us the severity level of dermatitis (EASI score) in group A (defined as patients with mild Dermatitis) is significantly lower than the group B (defined as patients with severe Dermatitis).

Table Analyzed	Treatment Group
	EASI Low vs High
Column B	EASI High
vs.	vs.
Column A	EASI Low
Mann Whitney test	
P value	<0.0001
Exact or approximate P value?	Exact
P value summary	****
Significantly different (P < 0.05)?	Yes
One- or two-tailed P value?	Two-tailed
Sum of ranks in column A,B	253 , 1073
Mann-Whitney U	0
Difference between medians	
Median of column A	3.950, n=22
Median of column B	18.90, n=29
Difference: Actual	14.95
Difference: Hodges-Lehmann	14.80

Table 3- Analytical data of Mann-Whitney test of the EASI levels between two subgroups of TG-A and TG-B.

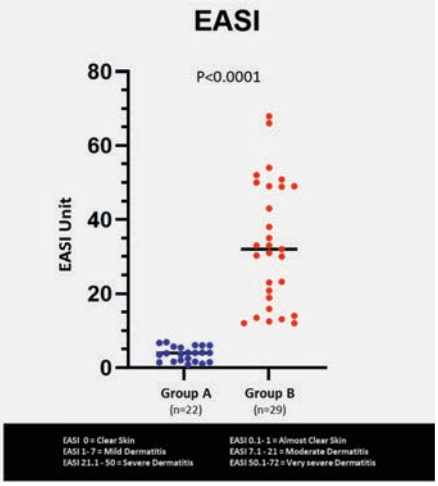


Figure 48- Scatter plot of the patients EASI level in each group of TG-A and TG-B.

4.2 Evaluation of the spine severity score

One of the objectives of this study was to evaluate if there is a correlation between the severity level of dermatitis (EASI score) and of the spinal biomechanical alterations (SBA). This last one refers to vertebral misalignments and their subsequent degenerative changes, such as osteoarthritis (OA), and disk degeneration. To find the answer, in addition to calculating the EASI scores we needed to have numerical data on the spine situation of each patient. For this, we analyzed the Xray images of each patient and numerically described the radiographical findings. We then calculated a score that shows the SBA severity score of each patient. (Calculation of Spinal Severity Score is explained in the section 3 of Methods.)

We added up all the scores calculated of the different parts of the spine in each patient and obtained the total spine severity for each patient.

Figure 49 illustrates the total spinal score in patients of subgroups TG-A and TG-B. As indicated in Table 4, there is a significant difference (P<0.0001) between the spinal severity score in patients of TG- A and patients of TG-B. (Figure 49)

Table Analyzed	Treatment Group
	Spine Severity Scores
Column B	Group B
vs.	vs.
Column A	Group A
Mann Whitney test	
P value	<0.0001
Exact or approximate P value?	Exact
P value summary	****
Significantly different (P < 0.05)?	Yes
One- or two-tailed P value?	Two-tailed
Sum of ranks in column A,B	231.5 , 1044
Mann-Whitney U	0.5000
Difference between medians	
Median of column A	18.00, n=22
Median of column B	37.00, n=29
Difference: Actual	19.00
Difference: Hodges-Lehmann	20.00

Table 4- Analytical data of Mann-Whitney test of the Spine Severity Score between two groups of TG-A and TG-B.

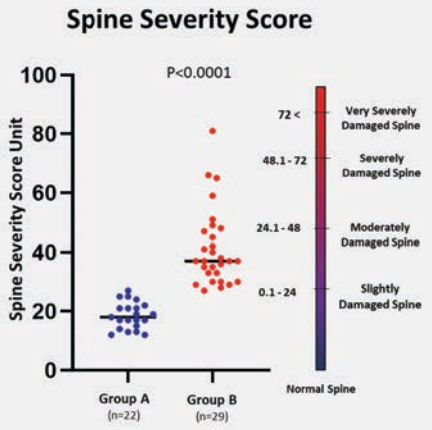


Figure 49- Scatter plot of the patient's spine severity score level in each group.

In addition, Figure 49, indicates a higher spinal severity score in patients with higher EASI (Group B) than in patients with lower EASI score. Given all this, the question arises as to whether there may be any correlation between the EASI level and the spinal severity score in patients suffering from Dermatitis.

To find the answer we made a Gaussian correlation test between EASI scores and spinal severity scores in patients of the treatment group that suffer of severe Dermatitis (Group B). The data presented in Figure 50

clearly shows a good correlation (r=0.76, P<0.0001) between EASI score and spinal severity score. In other words, by increasing the spinal severity score, the EASI level has been increased.

Gaussian	Treatment Group B
Best-fit values	EASI vs Spine Cor.
Amplitude	Unstable
Mean	1929
SD	354.2
95% CI (profile likelihood)	
Amplitude	(Very wide)
Mean	
SD	
Goodness of Fit	
Degrees of Freedom	26
R squared	0.7627
Sum of Squares	1364
Sy.x	7.244
Constraints	
SD	SD > 0
Number of points	
# of X values	29
# Y values analyzed	29

Table 5- Analytical data of Gaussian correlation test of the EASI levels vs. Spine Severity Score in patients with severe Dermatitis.

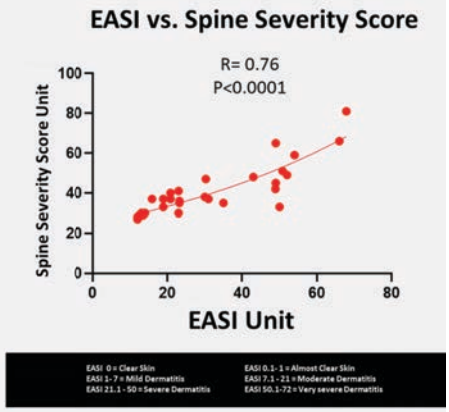


Figure 50- Scatter plot of the correlation between the EASI levels and Spine Severity Score in patients with severe Dermatitis.

In order to describe the SBA, we evaluated the severity score for each area of the spine. The spinal severity score has been calculated starting from the upper section (C1- Atlas) to the lower spinal section (Sacral section) separately. This calculation was intended to help us to find out what specific area of the spine could be associated with Dermatitis.

4.2.1 Cervical Spine

A) Analytical Data

i) Cervical Spine Total Severity Score Analysis

(*As mentioned before Severity Score refers to the Spinal Biomechanical Alteration [SBA] score)*

Evaluation of the total severity score of the cervical spine, in the sagittal plane, has been done by calculating the score of each segment of the cervical spine individually. To calculate the cervical spine SBA severity score, in the coronal plane, (Anterior Posterior or AP view) we divided it in three parts: C1 - C2 (Atlas -Axis) were described as AP1, C3-C5 as AP2 and C5- C7, as AP3.

Finally, we added the spinal severity score of all the individual spinal cervical segments and obtained the cervical spine total severity score (CSTS).

The comparison of CSTS between the groups A and B demonstrated a significant difference ($P<0.0001$) between the level of CSTS in the group A (patients with mild Dermatitis) and the group B (patients with severe Dermatitis) (Figure 51). In addition, *Gaussian* nonlinear regression test on these sets of data showed a good correlation ($r=0.81$) (Figure 52).

Table Analyzed	Treatment Group
	Cervical Spine Total Sever Sc.
Column B	Group B
vs.	vs.
Column A	Group A
Mann Whitney test	
P value	<0.0001
Exact or approximate P value?	Exact
P value summary	****
Significantly different (P < 0.05)?	Yes
One- or two-tailed P value?	Two-tailed
Sum of ranks in column A,B	354 , 972
Mann-Whitney U	101
Difference between medians	
Median of column A	3.000, n=22
Median of column B	6.000, n=29
Difference: Actual	3.000
Difference: Hodges-Lehmann	3.000

Table 6- Analytical data of Mann-Whitney test of the cervical spine total severity score between two patient groups of A and B.

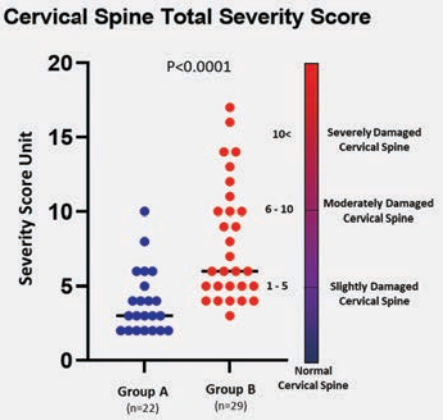


Figure 51- Scatter plot of the mean level of the cervical spine total severity score Severity score in each group of the study.

Gaussian	Treatment Group B
Best-fit values	Cervical Spine Sev. Cor.
Amplitude	18.76
Mean	107.6
SD	63.95
95% CI (profile likelihood)	
Amplitude	13.03
Mean	61.64
SD	38.62
Goodness of Fit	
Degrees of Freedom	26
R squared	0.8168
Sum of Squares	69.36
Sy.x	1.633
Constraints	
SD	SD > 0
Number of points	
# of X values	29
# Y values analyzed	29

Table 7- Analytical data of Gaussian correlation test of the EASI levels vs. cervical spine total severity score in patients with severe Dermatitis.

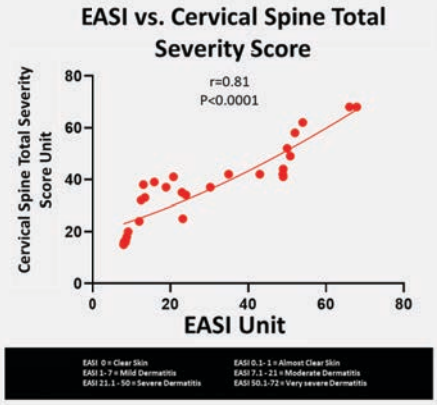


Figure 52- Scatter plot of the correlation between the EASI levels and cervical spine total severity score in patients with severe Dermatitis.

ii) C1 (Atlas)- C2 (Axis) Severity Score

This score describes the SBA of the Atlas and Axis (AT-AX)

Table Analyzed	Treatment Group
	AT-AX Total Sc.
Column B	Group B
vs.	vs.
Column A	Group A
Mann Whitney test	
P value	<0.0001
Exact or approximate P value?	Exact
P value summary	****
Significantly different (P < 0.05)?	Yes
One- or two-tailed P value?	Two-tailed
Sum of ranks in column A,B	335.5 , 990.5
Mann-Whitney U	82.50
Difference between medians	
Median of column A	0.5000, n=22
Median of column B	1.000, n=29
Difference: Actual	0.5000
Difference: Hodges-Lehmann	1.000

Table 8- Analytical data of Mann-Whitney test of the AT-AX Total score between two patient groups of A and B.

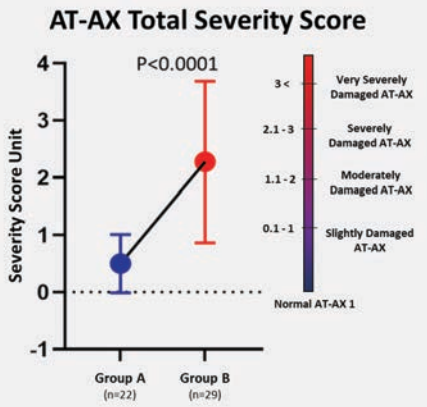
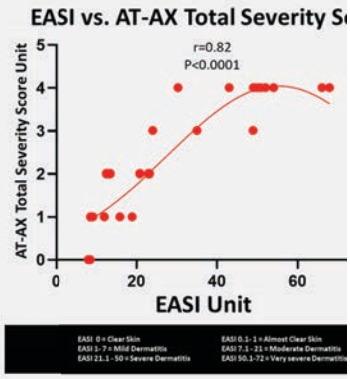


Figure 53- Scatter plot of the mean level of AT-AX Total score in each group of the study.

The results show that the SBA of AT-AX in patients with high EASI score level is almost 4 times higher than in patients with mild EASI score level (Figure 53). Moreover, the correlation between EASI level and the spinal severity score of the C1 – C2 (AT-AX) in patients with severe Dermatitis is presented in Figure 54. As shown, there is an important correlation (r=0.82) between the EASI level and the level of AT-AX SBA severity in patients affected by dermatitis.

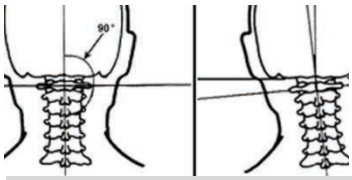
Gaussian	Treatment Group B
Best-fit values	AT-AX Total Cor.
Amplitude	4.038
Mean	55.25
SD	27.25
95% CI (profile likelihood)	
Amplitude	3.603 to 4.588
Mean	48.01 to 71.29
SD	21.99 to 37.52
Goodness of Fit	
Degrees of Freedom	26
R squared	0.8237
Sum of Squares	10.54
Sy.x	0.6368
Constraints	
SD	SD > 0
Number of points	
# of X values	29
# Y values analyzed	29

Table 9- Analytical data of Gaussian correlation test of the EASI levels vs. At-AX Total score in patients with severe Dermatitis.



gure 54- Scatter plot of the corr :tween the EASI levels and At-AX toto patients with severe Dermatitis.

To analyze and to calculate the AT-AX severity score, two different examinations (AT-AX 1 and AT-AX 2) have been used. Through the first examination (AT-AX 1), we checked the anatomical integrity of atlanto-odontoid joint (AT-AX). (See Figure 5 :ricity of AT-AX has been checked in the coronal plane of the spine.



gure 55 - Determination of norma bluxated spine in Atlas- Axis

Table Analyzed	Treatment Group
	AT-AX 1
Column B	Group B
vs.	vs.
Column A	Group A
Mann Whitney test	
P value	<0.0001
Exact or approximate P value?	Exact
P value summary	****
Significantly different (P < 0.05)?	Yes
One- or two-tailed P value?	Two-tailed
Sum of ranks in column A,B	349.5 , 976.5
Mann-Whitney U	96.50
Difference between medians	
Median of column A	0.000, n=22
Median of column B	1.000, n=29
Difference: Actual	1.000
Difference: Hodges-Lehmann	1.000

Table 10- Analytical data of Mann-Whitney test of the AT-AX-1 score between two patient groups of A and B.

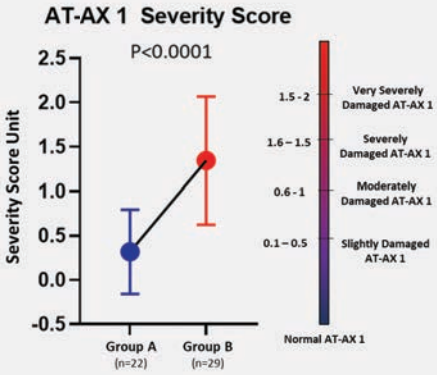


Figure 56- Scatter plot of the mean level of AT-AX-1 scores in each group of the study.

Gaussian	Treatment Group B
Best-fit values	AT-AX1 Cor.
Amplitude	2.091
Mean	56.71
SD	27.05
95% CI (profile likelihood)	
Amplitude	1.757 to 2.913
Mean	47.04 to 93.34
SD	20.13 to 47.30
Goodness of Fit	
Degrees of Freedom	26
R squared	0.6964
Sum of Squares	5.904
Sy.x	0.4765
Constraints	
SD	SD > 0
Number of points	
# of X values	29
# Y values analyzed	29

Table 11- Analytical data of Gaussian correlation test of the EASI levels vs. At-AX-1 score in patients with severe Dermatitis.

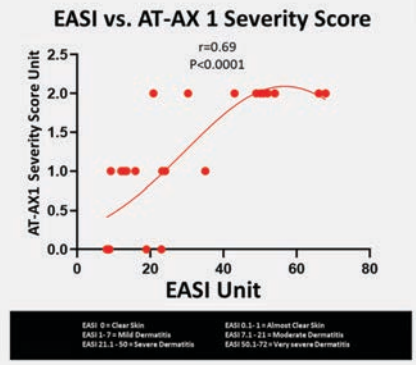


Figure 57- Scatter plot of the correlation between the EASI levels and At-AX-1 score in patients with severe Dermatitis.

The results provided in Figure 56 show a significant difference (P<0.0001) between the level of AT-AX 1 severity scores between patients of the group A and B. Moreover, there is a slight correlation (r= 0.69) between EASI level and the severity of spine situation in the AT-AX1, which is presented in Figure 57.

In addition, the incipient degenerative mechanical changes of the articular surfaces of the AT-AX joint have been described by means of the AT-AX 2 severity score.

Table Analyzed	Treatment Group
	At-AX 2
Column B	Group B
vs.	vs.
Column A	Group A
Mann Whitney test	
P value	<0.0001
Exact or approximate P value?	Exact
P value summary	****
Significantly different (P < 0.05)?	Yes
One- or two-tailed P value?	Two-tailed
Sum of ranks in column A,B	365 , 961
Mann-Whitney U	112
Difference between medians	
Median of column A	0.000, n=22
Median of column B	1.000, n=29
Difference: Actual	1.000
Difference: Hodges-Lehmann	1.000

Table 12- Analytical data of Mann-Whitney test of the AT-AX-2 score between two patient groups of A and B.

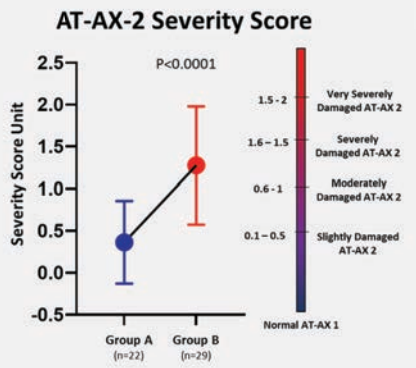


Figure 58- Scatter plot of the mean level of AT-AX-2 scores in each group of the study.

As shown in Figure 58, there is a significant difference between the severity level of AT-AX2 in patients with mild Dermatitis and patients with severe Dermatitis. Moreover, the correlation between the ~~level of~~ EASI level versus the severity level of AT-AX2 in patients with severe dermatitis has been examined. As it is shown in Figure 59, there is a moderate correlation between these two.

Gaussian	Treatment Group B
Best-fit values	At-AX 2
Amplitude	2.071
Mean	58.26
SD	28.52
95% CI (profile likelihood)	
Amplitude	1.704 to 4.128
Mean	46.93 to 127.7
SD	20.52 to 61.24
Goodness of Fit	
Degrees of Freedom	26
R squared	0.6509
Sum of Squares	6.790
Sy.x	0.5110
Constraints	
SD	SD > 0
Number of points	
# of X values	29
# Y values analyzed	29

Table 13- Analytical data of Gaussian correlation test of the EASI levels vs. At-AX-2 score in patients with severe Dermatitis.

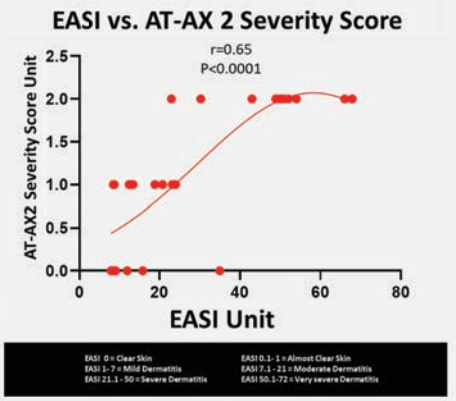


Figure 59- Scatter plot of the correlation between the EASI levels and At-AX-2 score in patients with severe Dermatitis.

iii) C3 (3rd Cervical Segment) Severity Score Analysis

The C3 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.

In order to see if there was any correlation between the condition of C3 and the EASI level, the C3 severity score was measured for all patients. There was a significant difference ($p<0.0001$) between the level of C3 severity score in the two groups ~~of~~ A and B (Figure 60). However, the correlation between the EASI level in group B and the C3 severity score was not very good ($r=0.57$). (Figure 61)

Table Analyzed	Treatment Group
	C3 Severity Sc.
Column B	Group B
vs.	vs.
Column A	Group A
Mann Whitney test	
P value	0.0001
Exact or approximate P value?	Exact
P value summary	***
Significantly different (P < 0.05)?	Yes
One- or two-tailed P value?	Two-tailed
Sum of ranks in column A,B	390 , 936
Mann-Whitney U	137
Difference between medians	
Median of column A	0.000, n=22
Median of column B	1.000, n=29
Difference: Actual	1.000
Difference: Hodges-Lehmann	1.000

Table 14- Analytical data of Mann-Whitney test of the C3 severity score between two patient groups of A and B.

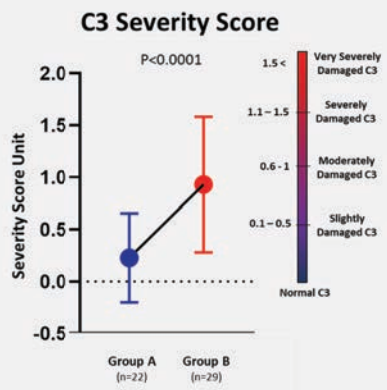


Figure 60- Scatter plot of the mean level of C3 Severity score in each group of the study.

Gaussian	Treatment Group B
Best-fit values	C3 Severity Cor.
Amplitude	Unstable
Mean	1512
SD	208.5
95% CI (profile likelihood)	
Amplitude	(Very wide)
Mean	****
SD	****
Goodness of Fit	
Degrees of Freedom	26
R squared	0.5728
Sum of Squares	4.507
Sy.x	0.4164
Constraints	
SD	SD > 0
Number of points	
# of X values	29
# Y values analyzed	29

Table 15- Analytical data of Gaussian correlation test of the EASI levels vs. C3 severity score in patients with severe Dermatitis.

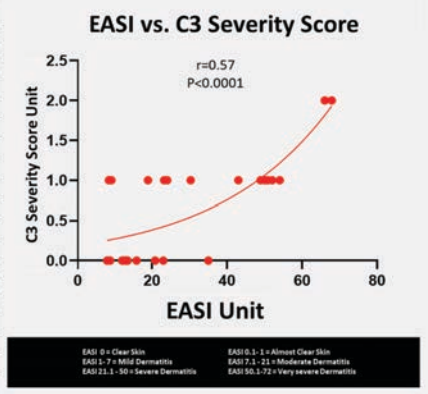


Figure 61- Scatter plot of the correlation between the EASI levels and C3 severity score in patients with severe Dermatitis.

iv) C4 (4th Cervical Segment) Severity Score Analysis

The severity score of C4 in cervical spine for all patients has been evaluated. Our data shows that there is a highly significant difference ($p<0.0001$) between the C4 severity score in the two groups of A and B (Figure 62). However, as in the case of C3, there was not a good correlation between C4 severity score and the level of EASI ($r=0.51$). (Figure 63)

Table Analyzed	Treatment Group
	C4 Severity Sc.
Column B	Group B
vs.	vs.
Column A	Group A
Mann Whitney test	
P value	<0.0001
Exact or approximate P value?	Exact
P value summary	****
Significantly different (P < 0.05)?	Yes
One- or two-tailed P value?	Two-tailed
Sum of ranks in column A,B	375.5 , 950.5
Mann-Whitney U	122.5
Difference between medians	
Median of column A	0.000, n=22
Median of column B	1.000, n=29
Difference: Actual	1.000
Difference: Hodges-Lehmann	1.000

Table 16- Analytical data of Mann-Whitney test of the C4 severity score between two patient groups of A and B.

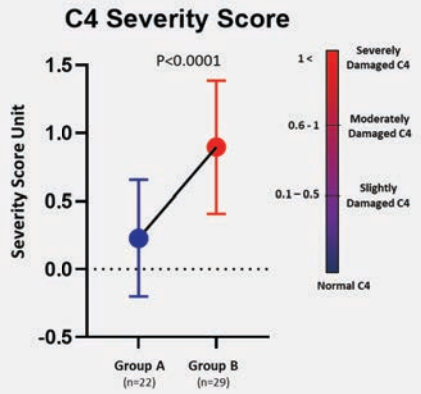


Figure 62- Scatter plot of the mean level of C4 Severity score in each group of the study.

Gaussian	Treatment Group B
Best-fit values	C4 Severity Cor.
Amplitude	1.630
Mean	78.73
SD	32.07
95% CI (profile likelihood)	
Amplitude	0.9987
Mean	53.20
SD	11.83
Goodness of Fit	
Degrees of Freedom	26
R squared	0.5153
Sum of Squares	5.348
Sy.x	0.4535
Constraints	
SD	SD > 0
Number of points	
# of X values	29
# Y values analyzed	29

Table 17- Analytical data of Gaussian correlation test of the EASI levels vs. C4 severity score in patients with severe Dermatitis.

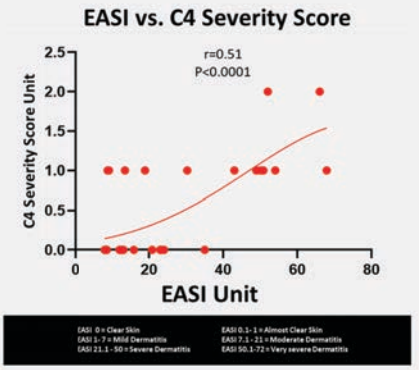


Figure 63- Scatter plot of the correlation between the EASI levels and C4 severity score in patients with severe Dermatitis.

v) C5 (5th Cervical Segment) Severity Score Analysis

In addition to the other parts of the cervical vertebrae, the severity score of C5 in cervical spine (in the Figure at the left in red) for all patients has been measured. Similar to C1, C2, C3 and C4, there was a significant difference ($p<0.0017$) between C5 severity score in the two groups of A and B (Figure 64).-Nevertheless, there was a good correlation between C5 severity score and the EASI level in group B ($r=0.73$). (Figure 65)

Table Analyzed	Treatment Group
	C5 Severity Sc.
Column B	Group B
vs.	vs.
Column A	Group A
Mann Whitney test	
P value	0.0017
Exact or approximate P value?	Exact
P value summary	**
Significantly different (P < 0.05)?	Yes
One- or two-tailed P value?	Two-tailed
Sum of ranks in column A,B	421 , 905
Mann-Whitney U	168
Difference between medians	
Median of column A	0.000, n=22
Median of column B	1.000, n=29
Difference: Actual	1.000
Difference: Hodges-Lehmann	1.000

Table 18- Analytical data of Mann-Whitney test of the C5 severity score between two patient groups of A and B.

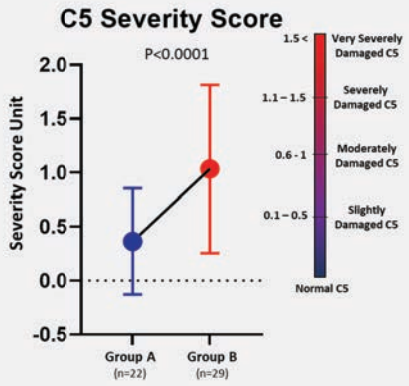


Figure 64- Scatter plot of the mean level of C5 Severity score in each group of the study.

Gaussian	Treatment Group B
Best-fit values	C5 Severity Cor.
Amplitude	1.630
Mean	78.73
SD	32.07
95% CI (profile likelihood)	
Amplitude	0.9987
Mean	53.20
SD	11.83
Goodness of Fit	
Degrees of Freedom	26
R squared	0.5153
Sum of Squares	5.348
Sy.x	0.4535
Constraints	
SD	SD > 0
Number of points	
# of X values	29
# Y values analyzed	29

Table 19- Analytical data of Gaussian correlation test of the EASI levels vs. C5 severity score in patients with severe Dermatitis.

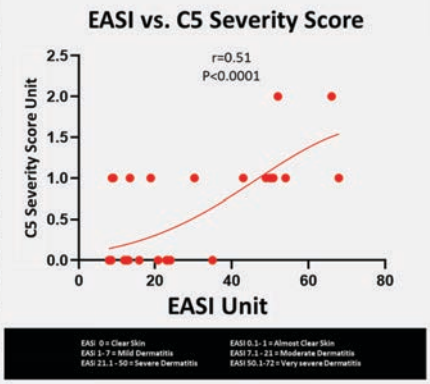


Figure 65- Scatter plot of the correlation between the EASI levels and C5 severity score in patients with severe Dermatitis.

vi) C6 (6th Cervical Segment) Severity Score Analysis

The two-tailed non-parametric t-test (Mann Whitney test) on the data obtained from the C6 showed a significant difference (P<0.0001) between the two groups A and B. Nevertheless, the correlation between the C6 severity score and the EASI level in the group of patients with high level was moderate (r=0.62). The results of the analysis of C6 are presented in Figure 66 and Figure 67.

Table Analyzed	Treatment Group
	C6 Severity Sc.
Column B	Group B
vs.	vs.
Column A	Group A
Mann Whitney test	
P value	<0.0001
Exact or approximate P value?	Exact
P value summary	****
Significantly different (P < 0.05)?	Yes
One- or two-tailed P value?	Two-tailed
Sum of ranks in column A,B	372 , 954
Mann-Whitney U	119
Difference between medians	
Median of column A	0.5000, n=22
Median of column B	3.000, n=29
Difference: Actual	2.500
Difference: Hodges-Lehmann	2.000

Table 20- Analytical data of Mann-Whitney test of the C6 severity score between two patient groups of A and B.

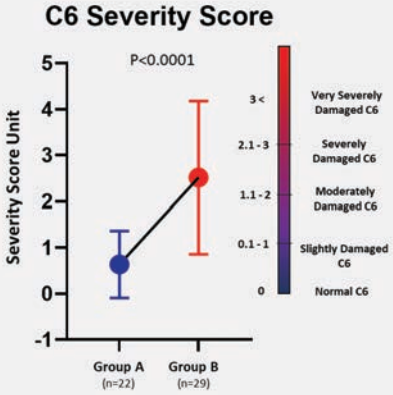


Figure 66- Scatter plot of the mean level of C6 Severity score in each group of the study.

Gaussian	Treatment Group B
Best-fit values	C6 Severity Cor.
Amplitude	4.433
Mean	64.96
SD	35.47
95% CI (profile likelihood)	
Amplitude	3.548
Mean	47.02
SD	23.49
Goodness of Fit	
Degrees of Freedom	26
R squared	0.6221
Sum of Squares	29.19
Sy.x	1.060
Constraints	
SD	SD > 0
Number of points	
# of X values	29
# Y values analyzed	29

Table 21- Analytical data of Gaussian correlation test of the EASI levels vs. C6 severity score in patients with severe Dermatitis.

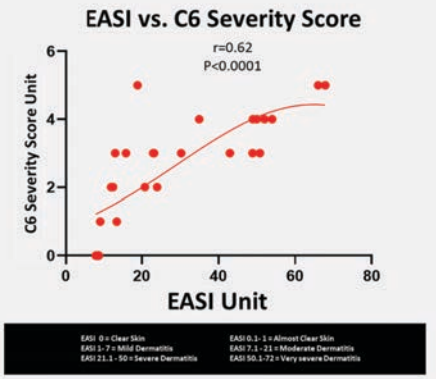


Figure 67- Scatter plot of the correlation between the EASI levels and C6 severity score in patients with severe Dermatitis.

vii) C7 (7th Cervical Segment) Severity Score Analysis

Analysis of the data collected from C7- the last segment of the cervical spine- showed a significant difference between the level of C7 severity score between two groups of the patients (P<0.0001) (Figure 68). However, as in the case of C6, there was no correlation between the level of C6 severity score and EASI level in the patients with high EASI (r=0.48). (Figure 69)

Table Analyzed	Treatment Group
	C7 Severity Sc.
Column B	Group B
vs.	vs.
Column A	Group A
Mann Whitney test	
P value	0.0039
Exact or approximate P value?	Exact
P value summary	**
Significantly different (P < 0.05)?	Yes
One- or two-tailed P value?	Two-tailed
Sum of ranks in column A,B	432 , 894
Mann-Whitney U	179
Difference between medians	
Median of column A	0.000, n=22
Median of column B	1.000, n=29
Difference: Actual	1.000
Difference: Hodges-Lehmann	1.000

Table 22- Analytical data of Mann-Whitney test of the C7 severity score between two patient groups of A and B.

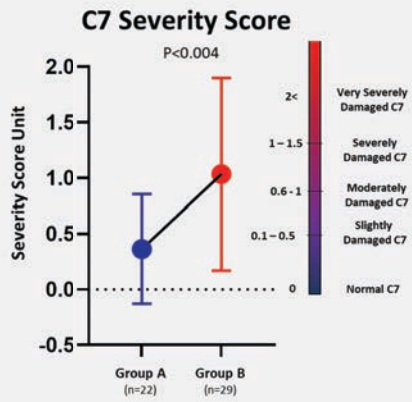


Figure 68- Scatter plot of the mean level of C7 Severity score in each group of the study.

Gaussian	Treatment Group B
Best-fit values	C7 Severity Cor.
Amplitude	17.32
Mean	206.2
SD	71.22
95% CI (profile likelihood)	
Amplitude	****
Mean	****
SD	****
Goodness of Fit	
Degrees of Freedom	26
R squared	0.4888
Sum of Squares	13.22
Sy.x	0.7131
Constraints	
SD	SD > 0
Number of points	
# of X values	29
# Y values analyzed	29

Table 23- Analytical data of Gaussian correlation test of the EASI levels vs. C6 severity score in patients with severe Dermatitis.

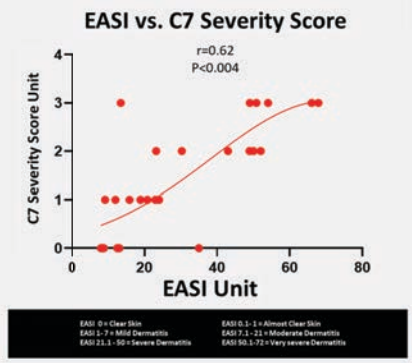
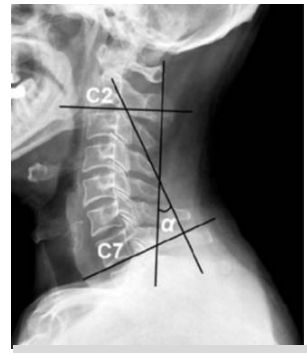


Figure 69- Scatter plot of the correlation between the EASI levels and C6 severity score in patients with severe Dermatitis.

viii) Rectification of the cervical lordosis Angle - C2-C7

The neutral lateral cervical spine radiographs were evaluated The C2–C7 angles were measured twice by the same radiologist independently, using the same methods. 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) (Figure 70). The value of C2–C7 angles indicated a lordosis at the measured segments. The rectification angle in the 51 patients varied from 0 to 38. There was a significant between the C2-C7 rectification angle in patients with low EASI level (Group A) and patients with high EASI level (Group B) (Figure 71). On the other hand, the correlation between the level of C2-C7 rectification angle and the EASI level was moderate (r=0.66). (Figure 72).



e 70- Rectification of cal lordosis angle C2-C7

Table Analyzed	Treatment Group
	C2-C7 Rect. Degree
Column B	Group B
vs.	vs.
Column A	Group A
Mann Whitney test	
P value	<0.0001
Exact or approximate P value?	Exact
P value summary	****
Significantly different (P < 0.05)?	Yes
One- or two-tailed P value?	Two-tailed
Sum of ranks in column A,B	323 , 1003
Mann-Whitney U	70
Difference between medians	
Median of column A	4.100, n=22
Median of column B	11.90, n=29
Difference: Actual	7.800
Difference: Hodges-Lehmann	9.800

Table 24- Analytical data of Mann-Whitney test of the C2-C7 rectification angle severity score between two patient groups of A and B.

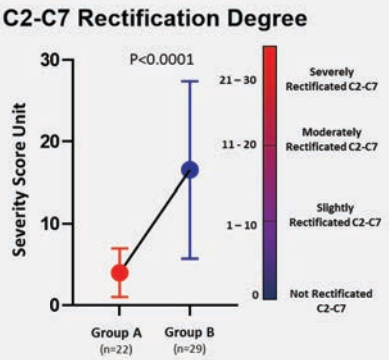


Figure 71- Scatter plot of the mean level of the C2-C7 rectification angle severity score in each group of the study. Individual points

Gaussian	Treatment Group B
Best-fit values	C2-C7 Rect. Cor.
Amplitude	165.0
Mean	211.8
SD	83.59
95% CI (profile likelihood)	
Amplitude	****
Mean	****
SD	****
Goodness of Fit	
Degrees of Freedom	26
R squared	0.6680
Sum of Squares	1091
Sy.x	6.478
Constraints	
SD	SD > 0
Number of points	
# of X values	29
# Y values analyzed	29

Table 25- Analytical data of Gaussian correlation test of the EASI levels vs. the C2-C7 rectification angle severity score in patients with severe Dermatitis.

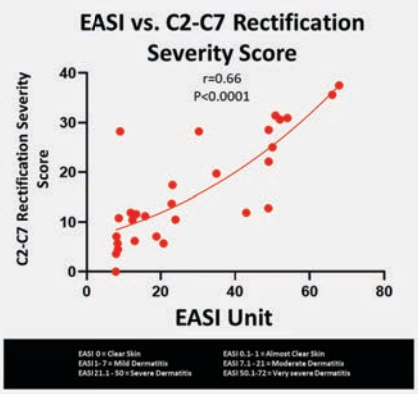


Figure 72- Scatter plot of the correlation between the EASI levels and the C2-C7 rectification angle severity score in patients with severe Dermatitis.

ix) Spondylolisthesis: Anterolisthesis and Retrolisthesis

Spondylolisthesis- the slippage of vertebra to forward or backwards- diagnosed in almost 87% of the patients in the study. The evaluation of data gathered from the spondylolisthesis observation presented in Figure 73. There was a significant difference (P<0.0001) between the severity level of spondylolisthesis in patients with mild EASI and the patients with severe EASI.

Table Analyzed	Antero/ Retro-listhesis
Column B	Group B
vs.	vs,
Column A	Group A
Mann Whitney test	
P value	<0,0001
Exact or approximate P value?	Exact
P value summary	****
Significantly different (P < 0.05)?	Yes
One- or two-tailed P value?	Two-tailed
Sum of ranks in column A,B	299,5 , 1027
Mann-Whitney U	46,50
Difference between medians	
Median of column A	1,000, n=22
Median of column B	3,000, n=29
Difference: Actual	2,000
Difference: Hodges-Lehmann	2,000

Table26 - Analytical data of Mann-Whitney test of the spondylolisthesis severity score between two patient groups of A and B.

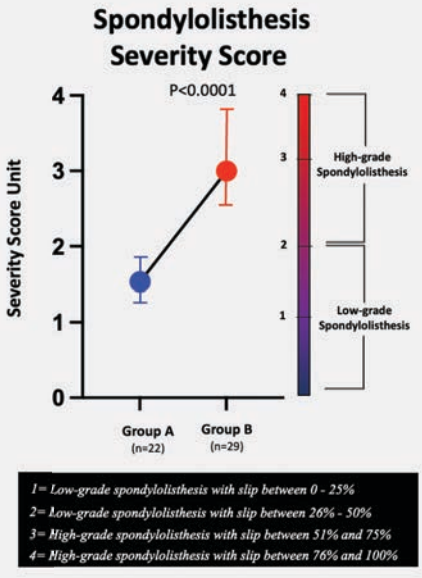


Figure 73- Scatter plot of the correlation between the EASI levels and the spondylolisthesis severity score in patients with severe Dermatitis.

In addition, the Gaussian correlation test of EASI levels and the severity level of spondylolisthesis clearly brings the result that there is a strong correlation (r= 0.85) between these two factors (Figure74).

Gaussian	
Best-fit values	
Amplitude	4,037
Mean	55,94
SD	40,13
95% CI (profile likelihood)	
Amplitude	3,795 to 4,393
Mean	48,37 to 75,07
SD	32,73 to 55,70
Goodness of Fit	
Degrees of Freedom	26
R squared	0,8508
Sum of Squares	3,426
Sy.x	0,3630
Constraints	
SD	SD > 0
Number of points	
# of X values	29
# Y values analyzed	29

Table 27- Analytical data of Gaussian correlation test of the EASI levels vs. the spondylolisthesis severity score in patients with severe Dermatitis.

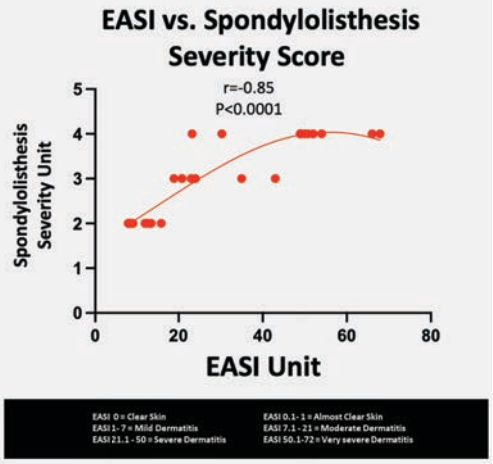
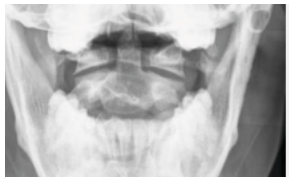


Figure 74 - Scatter plot of the correlation between the EASI levels and the spondylolisthesis severity score in patients with severe Dermatitis.

x) Analysis of the Conventional Anterior-posterior (AP) View of the Cervical Spine

Analysis of the conventional AP view of the spine has been divided into three sections: AP1: the anterior-posterior analysis of the C1- C2 segments; AP2: the anterior-posterior analysis of the C3-C5 segments; and AP3: the anterior-posterior analysis of the C5-C7 segments. (Figure 75)

- **AP1 (Conventional Anterior-Posterior Open Mouth X ray view 1)**



The anterior-posterior analysis of the cervical spine AP1 revealed a significant difference ($P<0.0001$) between the AP1 severity score in patients with low EASI level and patients with high EASI level (Figure 76). On-the other hand, no correlation was found between the AP1 severity score and the EASI level ($r=0.24$) (Figure 77)

Table Analyzed	Treatment Group
	AP1 Severity Sc.
Column B	Group B
vs.	vs.
Column A	Group A
Mann Whitney test	
P value	<0.0001
Exact or approximate P value?	Exact
P value summary	****
Significantly different (P < 0.05)?	Yes
One- or two-tailed P value?	Two-tailed
Sum of ranks in column A,B	376 , 950
Mann-Whitney U	123
Difference between medians	
Median of column A	0.000, n=22
Median of column B	1.000, n=29
Difference: Actual	1.000
Difference: Hodges-Lehmann	1.000

Table 28- Analytical data of Mann-Whitney test of the AP1 severity score between two patient groups of A and B.

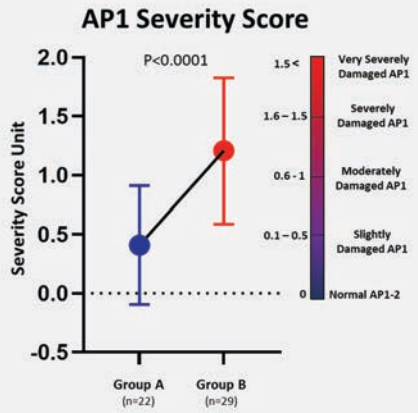


Figure 76- Scatter plot of the mean level of the AP1 rectification angle severity score in each group of the study.

Gaussian	Treatment Group B
Best-fit values	AP1 Sev. Cor.
Amplitude	1.932
Mean	98.94
SD	72.97
95% CI (profile likelihood)	
Amplitude	****
Mean	****
SD	26.28
Goodness of Fit	
Degrees of Freedom	26
R squared	0.2405
Sum of Squares	8.171
Sy.x	0.5606
Constraints	
SD	SD > 0
Number of points	
# of X values	29
# Y values analyzed	29

Table 29- Analytical data of Gaussian correlation test of the EASI levels vs. the AP1 severity score in patients with severe Dermatitis.

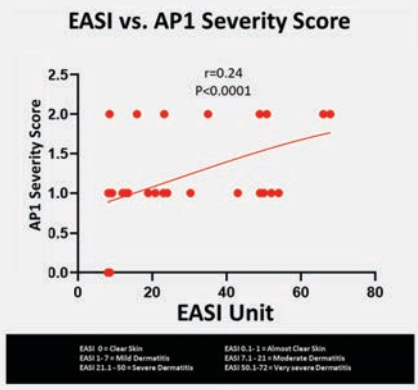


Figure 77. Scatter plot of the correlation between the EASI levels and the AP1 severity score in patients with severe Dermatitis.

- **AP2 (Conventional Anterior-Posterior X ray view 2)**

The conventional anterior-posterior analysis of the C3-C5 (AP2) allowed us to calculate the AP2 severity score in the patients. In the AP2 analysis, there was a significant difference (P<0.03) between the groups A and B (Figure 78), however, no correlation between AP2 severity score and EASI level (r=0. 43) was found. (Figure 79).

Table Analyzed	Treatment Group
	AP2 Severity Sc.
Column B	Group B
vs.	vs.
Column A	Group A
Mann Whitney test	
P value	0.0291
Exact or approximate P value?	Exact
P value summary	*
Significantly different (P < 0.05)?	Yes
One- or two-tailed P value?	Two-tailed
Sum of ranks in column A,B	467 , 859
Mann-Whitney U	214
Difference between medians	
Median of column A	1.000, n=22
Median of column B	1.000, n=29
Difference: Actual	0.000
Difference: Hodges-Lehmann	0.000

Table 30- Analytical data of Mann-Whitney test of the AP2 severity score between two patient groups of A and B.

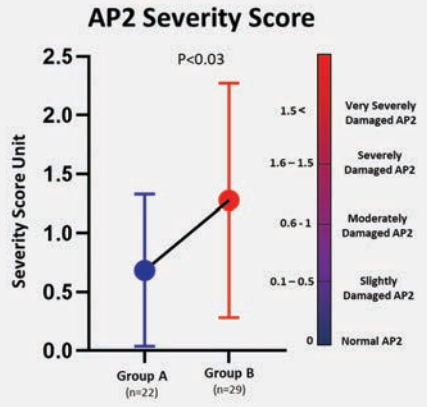
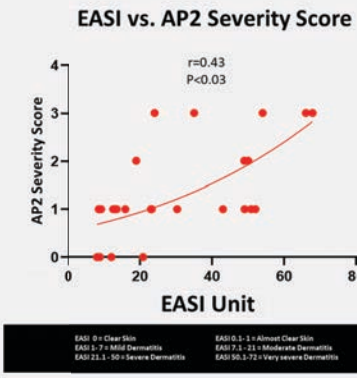


Figure 78- Scatter plot of the mean level of the AP2 rectification angle severity score in each group of the study.

Gaussian	Treatment Group B
Best-fit values	AP2 Sev. Cor.
Amplitude	20.97
Mean	263.9
SD	97.83
95% CI (profile likelihood)	
Amplitude	****
Mean	****
SD	****
Goodness of Fit	
Degrees of Freedom	26
R squared	0.4353
Sum of Squares	15.69
Sy.x	0.7769
Constraints	
SD	SD > 0
Number of points	
# of X values	29
# Y values analyzed	29

Table 31- Analytical data of Gaussian correlation test of the EASI levels vs. the AP2 severity score in patients with severe Dermatitis.



gure 79- Scatter plot of the corr :tween the EASI levels and the AP2 s ore in patients with severe Dermatiı

- **AP3 (Conventional Anterior-Posterior X ray view 3)**

Next, we analysed the conventional anteroposterior projection of cervical segments C5-C7 (AP3) (Figure 80). Next, we analysed the conventional anteroposterior projection of cervical segments C5-C7 (AP3) (Figure 80). There was not a significant difference between the AP3 levels in the patients of TG-A and TG-B (P<0.161) (Figure 81), or any correlations with the level of EASI (r=0.38) (Figure 82).

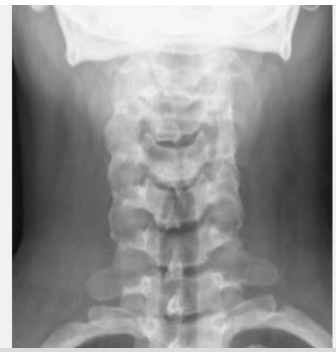


Figure 80- The AP2-AP3 projection of Cervical Spine.

Table Analyzed	Treatment Group
	AP3 Severity Sc.
Column B	Group B
vs.	vs.
Column A	Group A
Mann Whitney test	
P value	0.1610
Exact or approximate P value?	Exact
P value summary	ns
Significantly different (P < 0.05)?	No
One- or two-tailed P value?	Two-tailed
Sum of ranks in column A,B	501 , 825
Mann-Whitney U	248
Difference between medians	
Median of column A	0.000, n=22
Median of column B	1.000, n=29
Difference: Actual	1.000
Difference: Hodges-Lehmann	0.000

Table 32- Analytical data of Mann-Whitney test of the AP3 severity score between two patient groups of A and B.

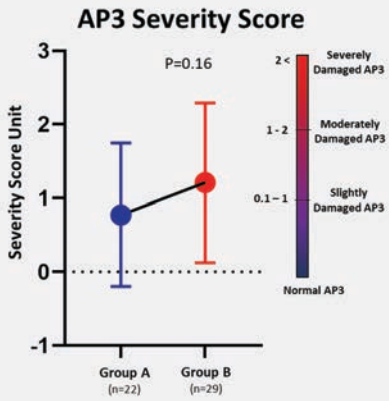


Figure 81- Scatter plot of the mean level of the AP3 rectification angle severity score in each group of the study.

Gaussian	Treatment Group B
Best-fit values	AP3 Sev. Cor.
Amplitude	2.795
Mean	16.57
SD	3.889
95% CI (profile likelihood)	
Amplitude	1.185 to 4.869
Mean	13.76
SD	2.215 to 9.504
Goodness of Fit	
Degrees of Freedom	26
R squared	-0.3845
Sum of Squares	45.35
Sy.x	1.321
Constraints	
SD	SD > 0
Number of points	
# of X values	29
# Y values analyzed	29

Table 33- Analytical data of Gaussian correlation test of the EASI levels vs. the AP3 severity score in patients with severe Dermatitis.

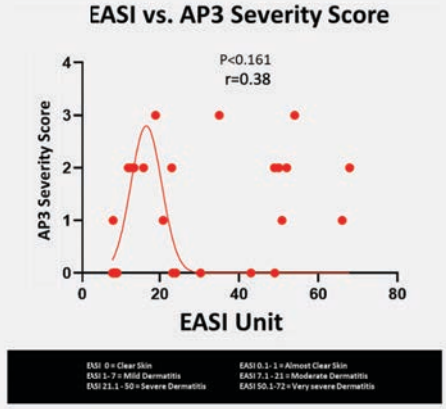


Figure 82- Scatter plot of the correlation between the EASI levels and the AP3 severity score in patients with severe Dermatitis.

B) Case Reports

In Figure 83 and Figure 84, clinical data are shown for a patient with dermatitis on the scalp and a patient with dermatitis on the neck, respectively. In addition, Figure 85 is presenting the data of a patient with dermatitis of the upper part of the face.

In addition, according to the Trigeminal nerve map (See Figure 27), the ophthalmic nerves have a great impact on inflammation of the skin around the eyes. [295–298] These illustrations may indicate the effect of spinal biomechanical correction on normalizing the patient's CGRP level and EASI score.

In Figure 89, analytical data of a 28-year-old patient diagnosed with dermatitis in the eyes area and biomechanical alterations in AT-AX of the cervical spine is presented. Interestingly, when decreasing the AT-AX severity score level through chiropractic SMT, we found a significant decrease in the CGRP level and, consequently, a significant reduction in the EASI level.

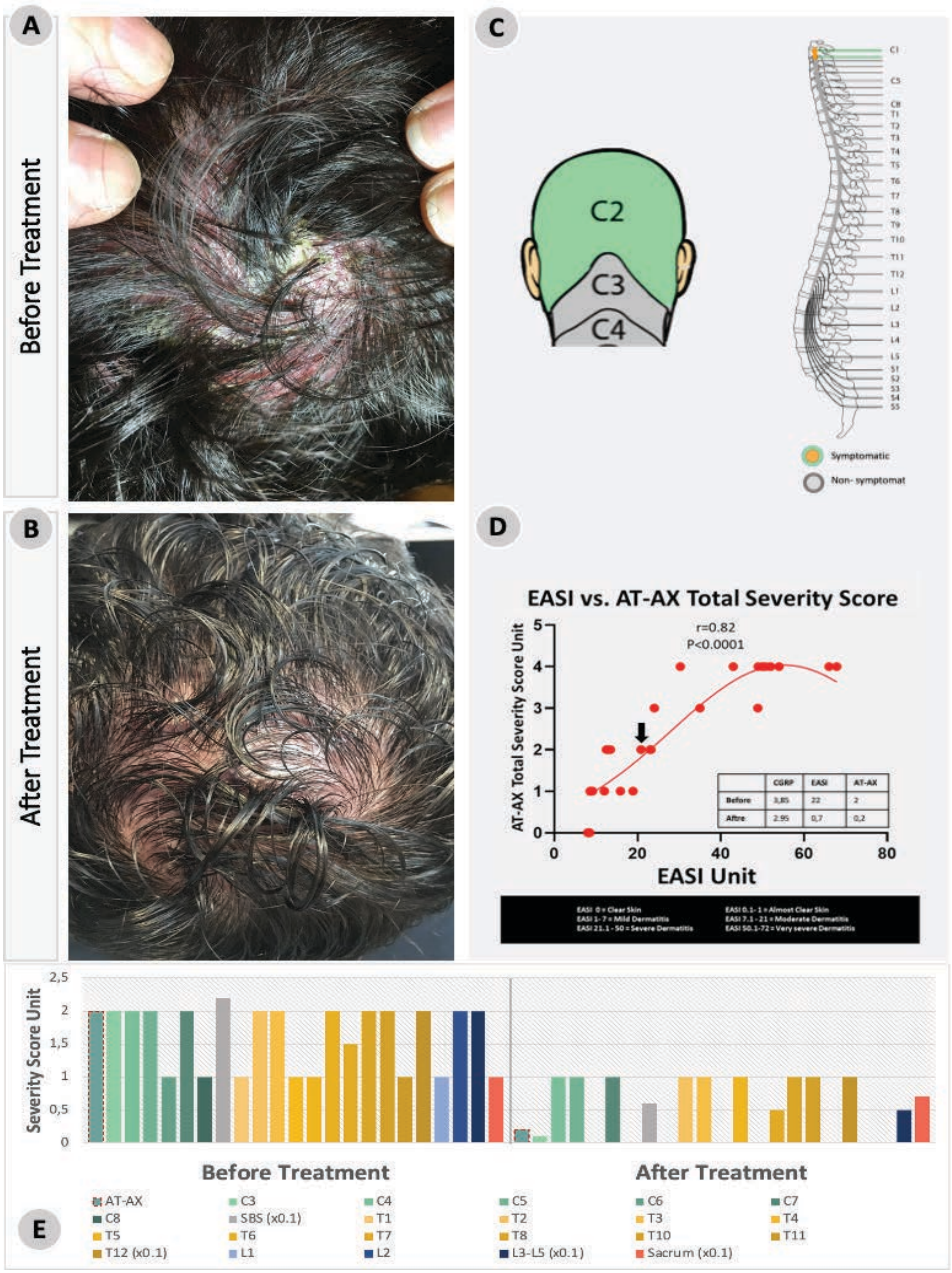


Figure 83- Case report 1: Analytical data obtained from a 41-year-old patient diagnosed with dermatitis in the scalp and SBA in AT-AX, before and afte the chiropractic treatment- (A) Patient's clinical picture before chiropractic treatment, and (B) a clinical picture of inflammated area after the chiropractic treatment. (C) a schematic of spinal cord highlighting C1-C2 and dermatome´s scalp section (D) Analytical graph indicating the correlation of EASI level and AT-AX severity scores, and, (E) Severity scores of different parts of the patient´s spine, before and after the chiropractic treatment.

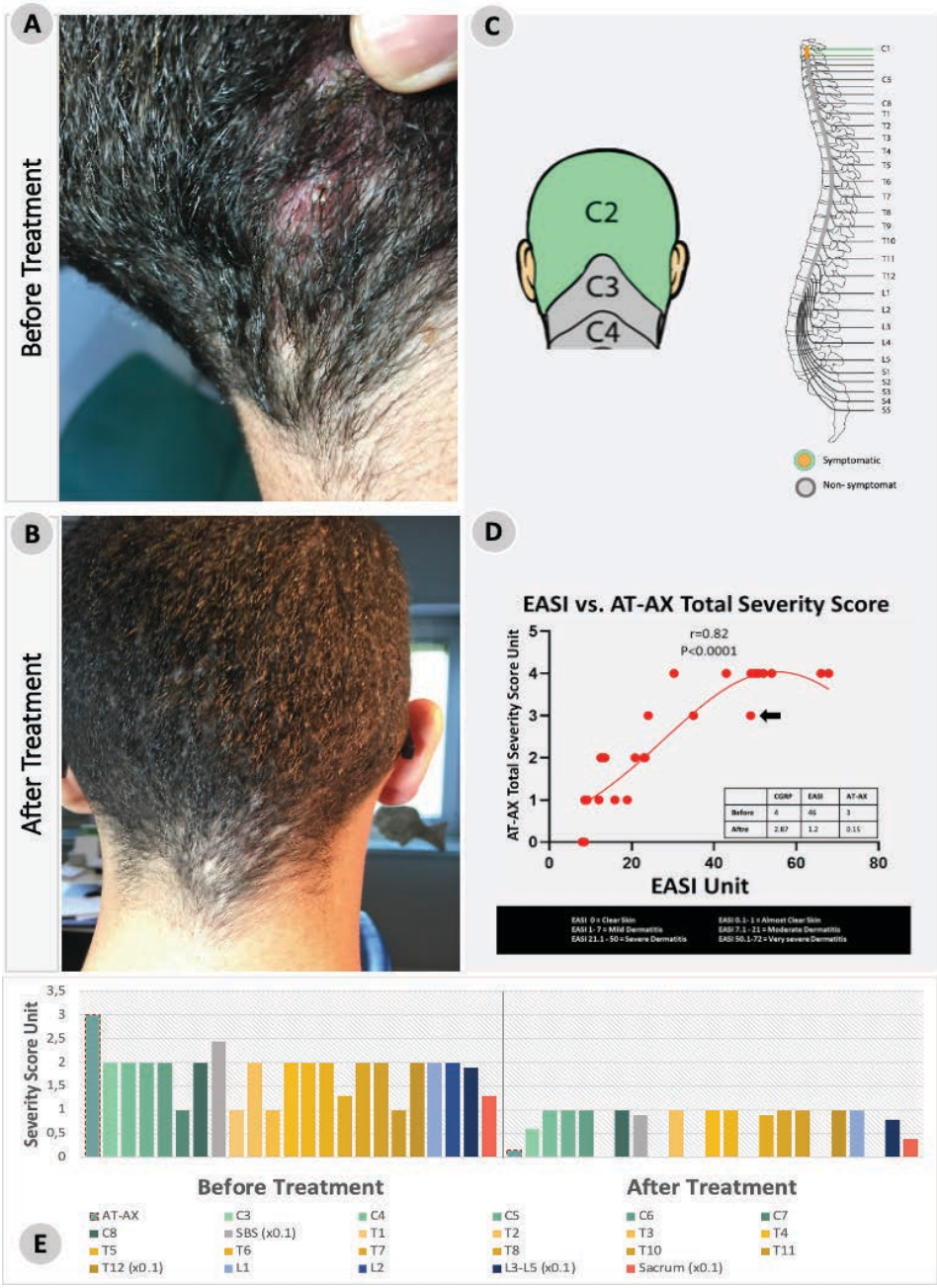


Figure 84- Case report 2: Analytical data obtained from a 24-year-old patient diagnosed with dermatitis in the neck and SBA in AT-AX, before and afte the chiropractic treatment- (A) Patient's clinical picture before chiropractic treatment, and (B) a clinical picture of inflammated area after the chiropractic treatment. (C) a schematic of spinal cord highlighting C1-C2 and dermatome´s scalp section (D) Analytical graph indicating the correlation of EASI level and AT-AX severity scores, and, (E) Severity scores of different parts of the patient´s spine, before and after the chiropractic treatment.

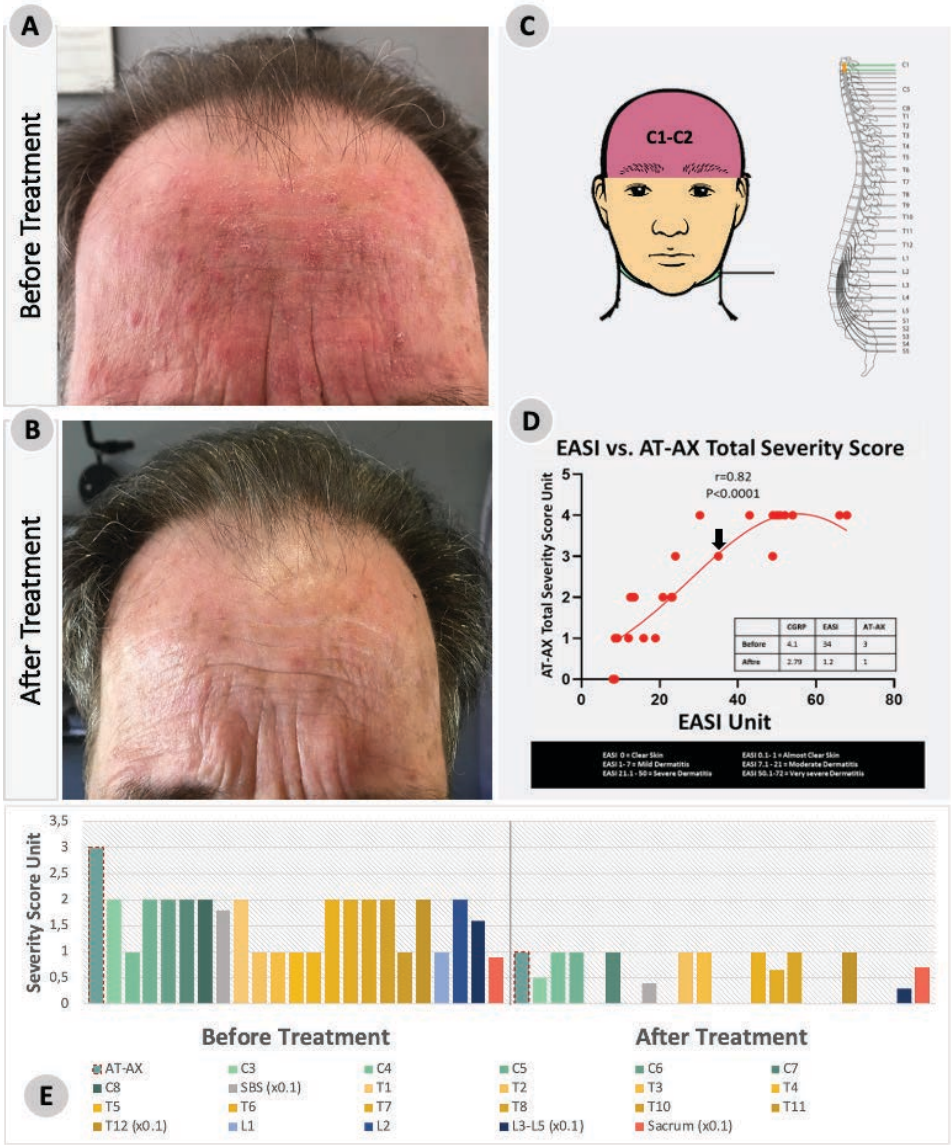


Figure 85- Case report 3: Analytical data obtained from a patient diagnosed with dermatitis in the upper face and SBA in AT-AX, before and afte the chiropractic treatment- (A) Patient's clinical picture before chiropractic treatment, and (B) a clinical picture of inflammated area after the chiropractic treatment. (C) a schematic of spinal cord highlighting C1-C2 and dermatome´s scalp section (D) Analytical graph indicating the correlation of EASI level and AT-AX severity scores, and, (E) Severity scores of different parts of the patient´s spine, before and after the chiropractic treatment.

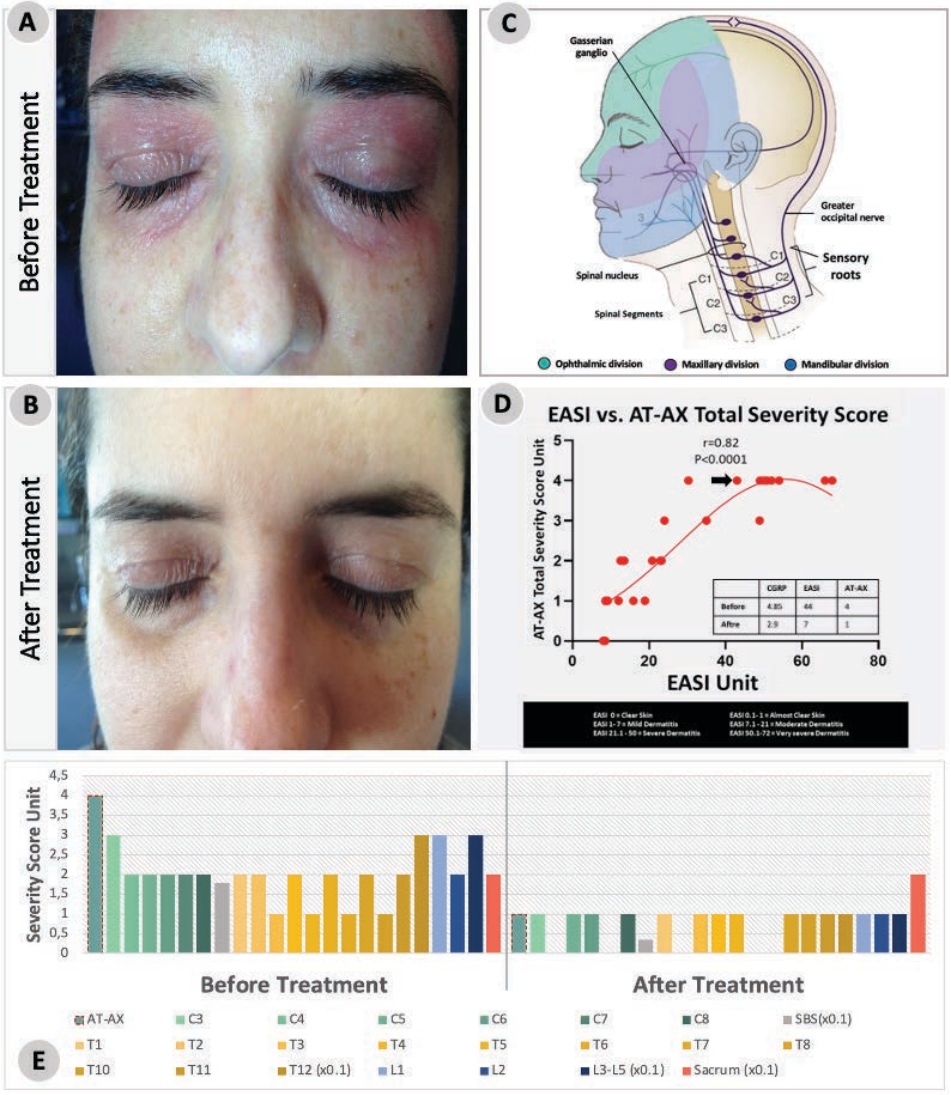


Figure 86- Case Report 4: Analytical data obtained from a 28 year old patient diagnosed with dermatitis in the eye area and spine biomechanical alteration, before and afte ther chiropractic treatment- (A) Patient's clinical picture before chiropractic treatment, and (B) a clinical picture of inflammated area after the chiropractic treatment. (C) Trigeminal nerves indicating the ophthalmic division, which is corresponded with the skin´s inflammatory processes in the eye area. (D) Analytical graph indicating the correlation of EASI level and AT-AX severity scores, and (E) Severity scores of different parts of the patient´s spine, before and after the chiropractic treatment.

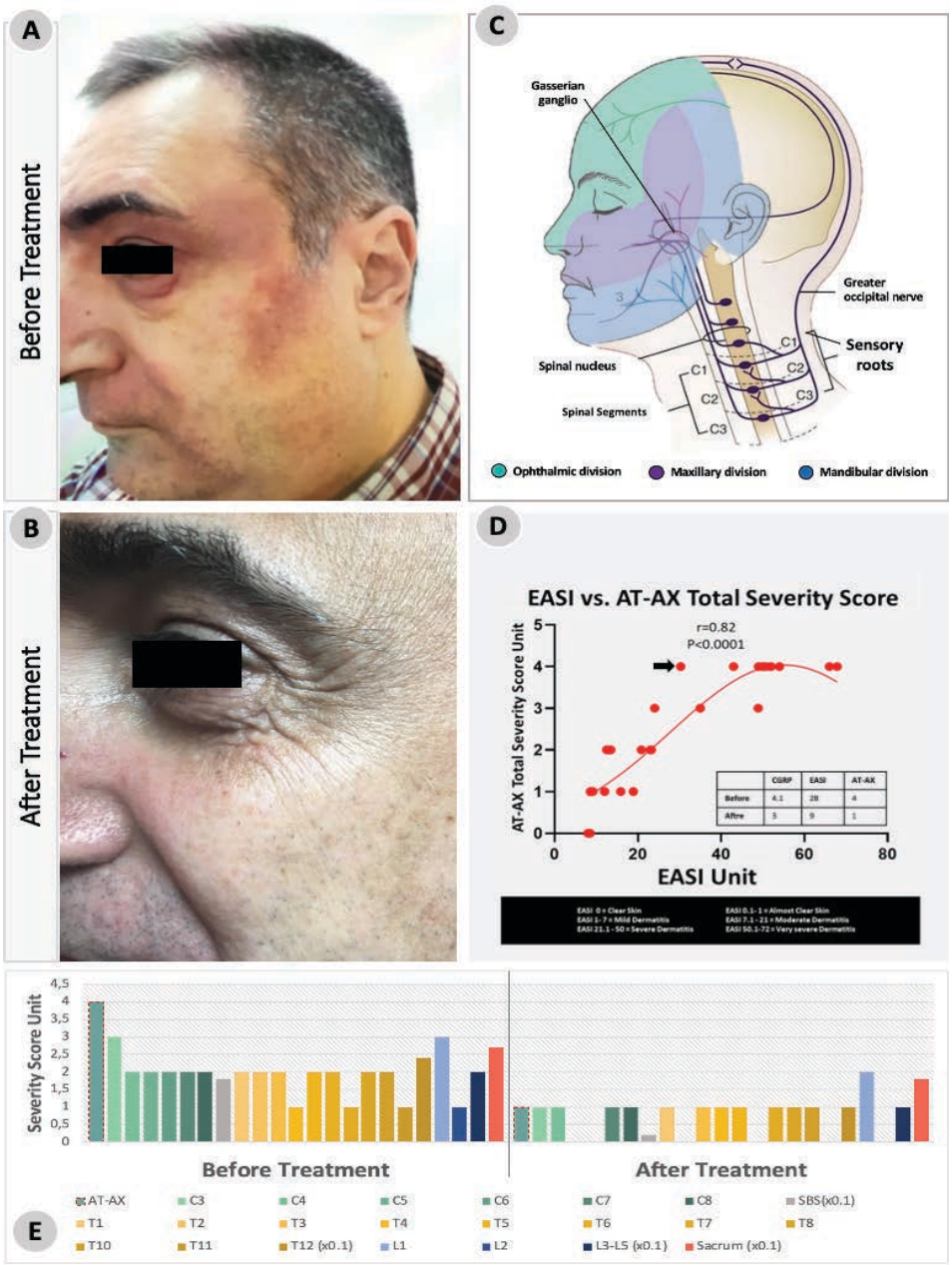


Figure 87- Case report 5: Analytical data obtained a patient diagnosed with dermatitis in the eye area and spine biomechanical alteration, before and after chiropractic treatment- (A) Patient's clinical picture before chiropractic treatment, and (B) a clinical picture of inflammated area after the chiropractic treatment. (C) Trigeminal nerves indicating the ophthalmic division, which is corresponded with the skin´s inflammatory processes in the eye area. (D) Analytical graph indicating the correlation of EASI level and AT-AX severity scores, and (E) Severity scores of different parts of the patient´s spine, before and after the chiropractic treatment.

Similarly, Figure 87, illustrates another patient with Dermatitis in the eye area. The patient demonstrated a high severity score in cervical spine, especially in C1 and C2. However, after chiropractic treatment the level of spine severity score decreased and following that, the CGRP level and EASI level reduced, significantly. This fact is evident when reviewing the state of patient's face, before and after the treatment.

In our study approximately 92% of the patients with alteration of cervical spine diagnosed by dermatitis in their face. Figure 88 presents a patient in our study with facial dermatitis. Additionally, she was diagnosed with cervical spine biomechanical alteration and altered CGRP level in the first visit. A summary of her data, before and after the chiropractic treatment, is presented in Figure 88.

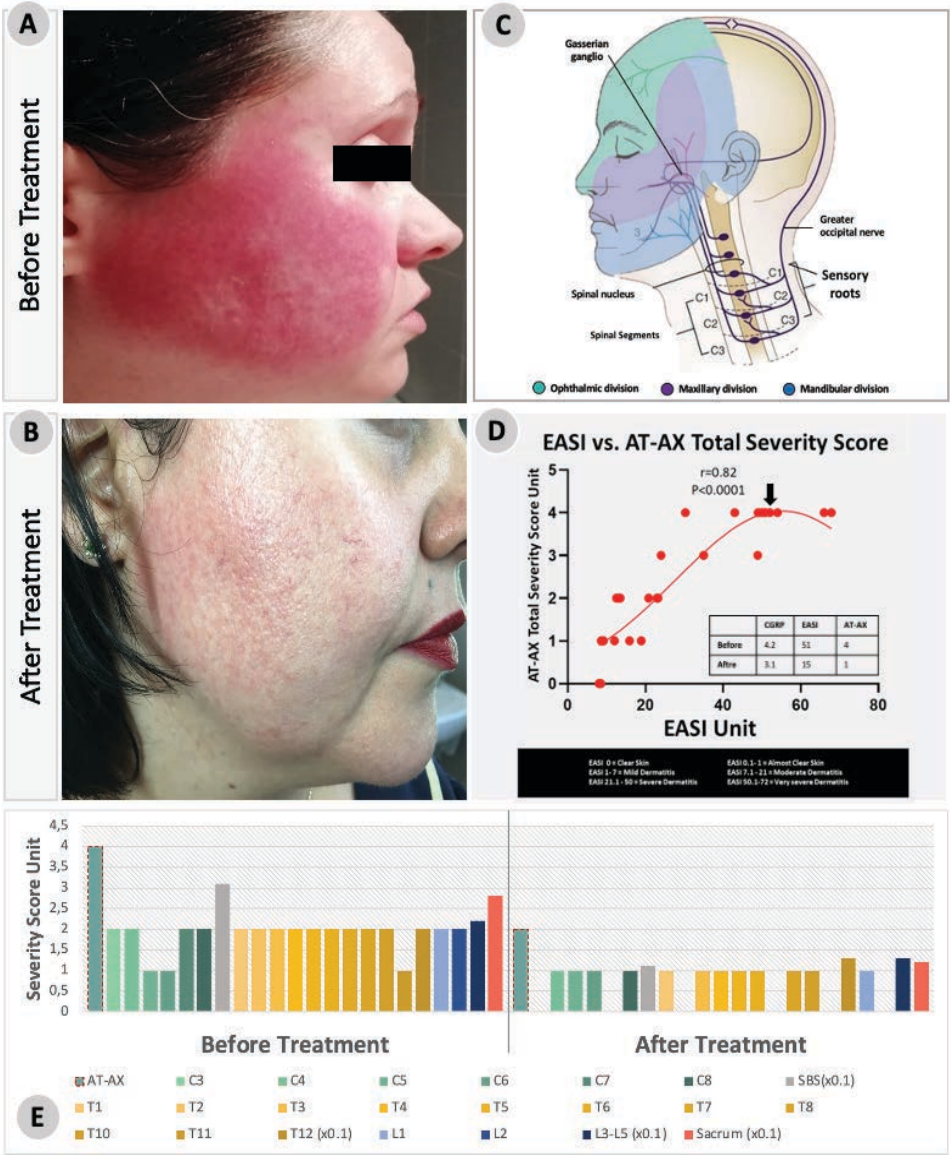


Figure 88- Case report 6: Dermatitis of the face. Analytical data obtained from a patient diagnosed with Dermatitis of the face and spine biomechanical alterations in cervical section, before and after the chiropractic treatment- (A) Patient's clinical picture before chiropractic treatment, and (B) a clinical picture of inflammated area after the chiropractic treatment. (C) Trigeminal nerves indicating the maxillary nerve, which is corresponded with the skin´s inflammatory processes in the cheek area. (D) Analytical graph indicating the correlation of EASI level and AT-AX severity scores, and (E) Severity scores of different parts of the patient´s spine, before and after the chiropractic treatment.

Moreover, Figure 89 presents clinical data of a 32-year-old woman with dermatitis of the ear diagnosed with alteration of the spine in cervical part, specifically in AT-AX. After the chiropractic treatment however, as the level of spine severity score reduced in the patient, CGRP level and EASI level nose-dived accordingly. A summary of severity scores, CGRP, and EASI levels along with pictures, before and after the treatment, are presented in Figure 89.

In addition, as mentioned before, trigeminal nerve is associated with neurogenic inflammation of the face and has an association with alterations in C1, C2, and C3. In Figure 90, a 7-year-old boy with Dermatitis in his chin area (Mandibular division) is presented. In the first visit, the patient was detected with a high cervical spine severity score (Cervical SpSS= 29), high EASI level (EASI =34), and altered CGRP level (CGRP= 3.4 pg/ml). When the spinal correction was made through 6 sessions of chiropractic, there was a significant improvement in all measured scores. This example, and more similar examples of this study, may explain the correlation between the EASI scores and AT-AX severity scores (r=0.82).

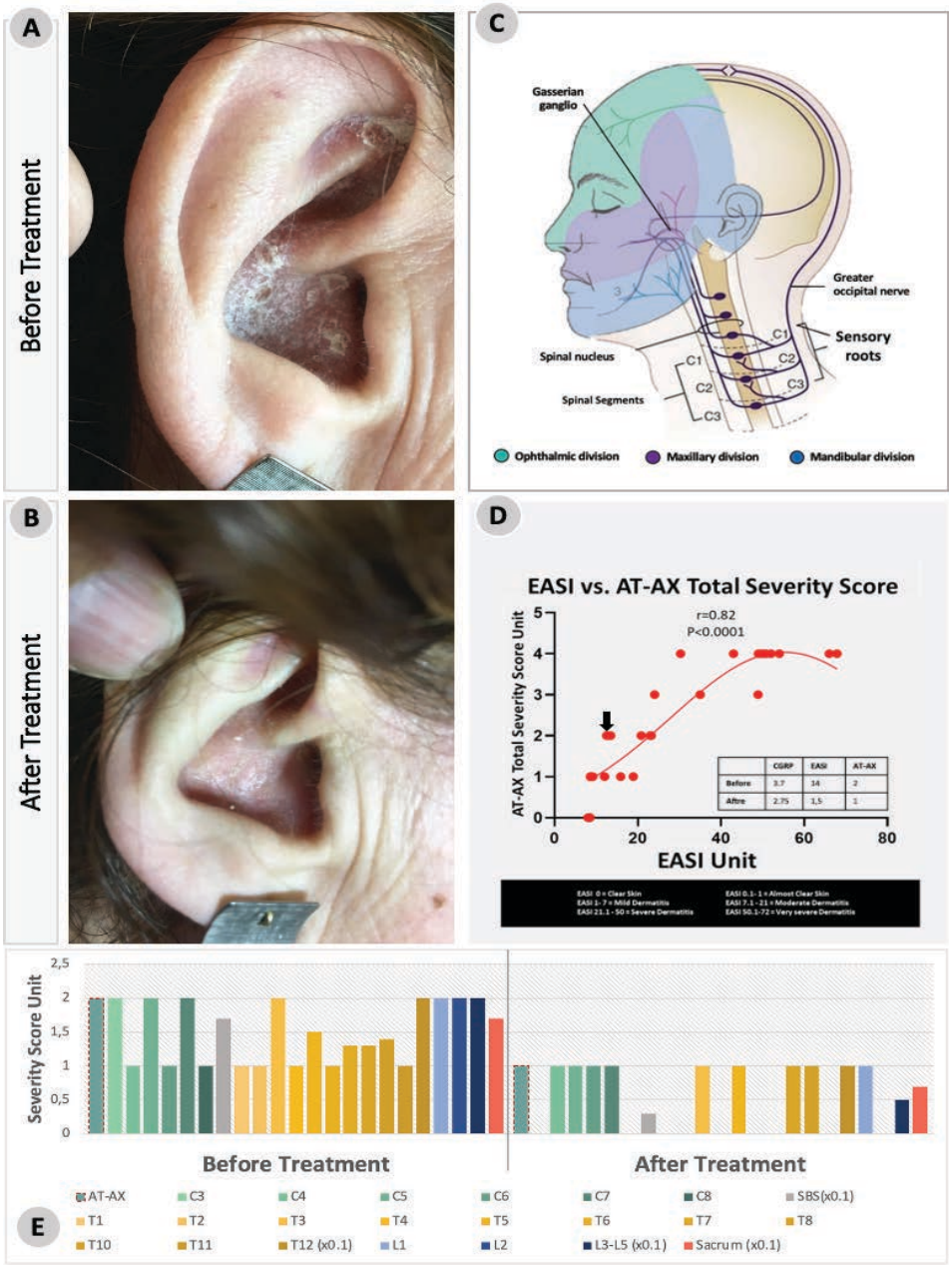


Figure 89- Case report 7- Dermatitis of the ear- Analytical data obtained from a patient diagnosed with dermatitis of the ear and SBA in cervical section, before and after the chiropractic treatment- (A) Patient's clinical picture before chiropractic treatment, and (B) a clinical picture of inflammated area after the chiropractic treatment. (C) Trigeminal nerves indicating the madibular nerve, which is corresponded with the skin´s inflammatory processes in the ear area. (D) Analytical graph indicating the correlation of EASI level and AT-AX severity scores, and (E) Severity scores of different parts of the patient´s spine, before and after the chiropractic treatment.

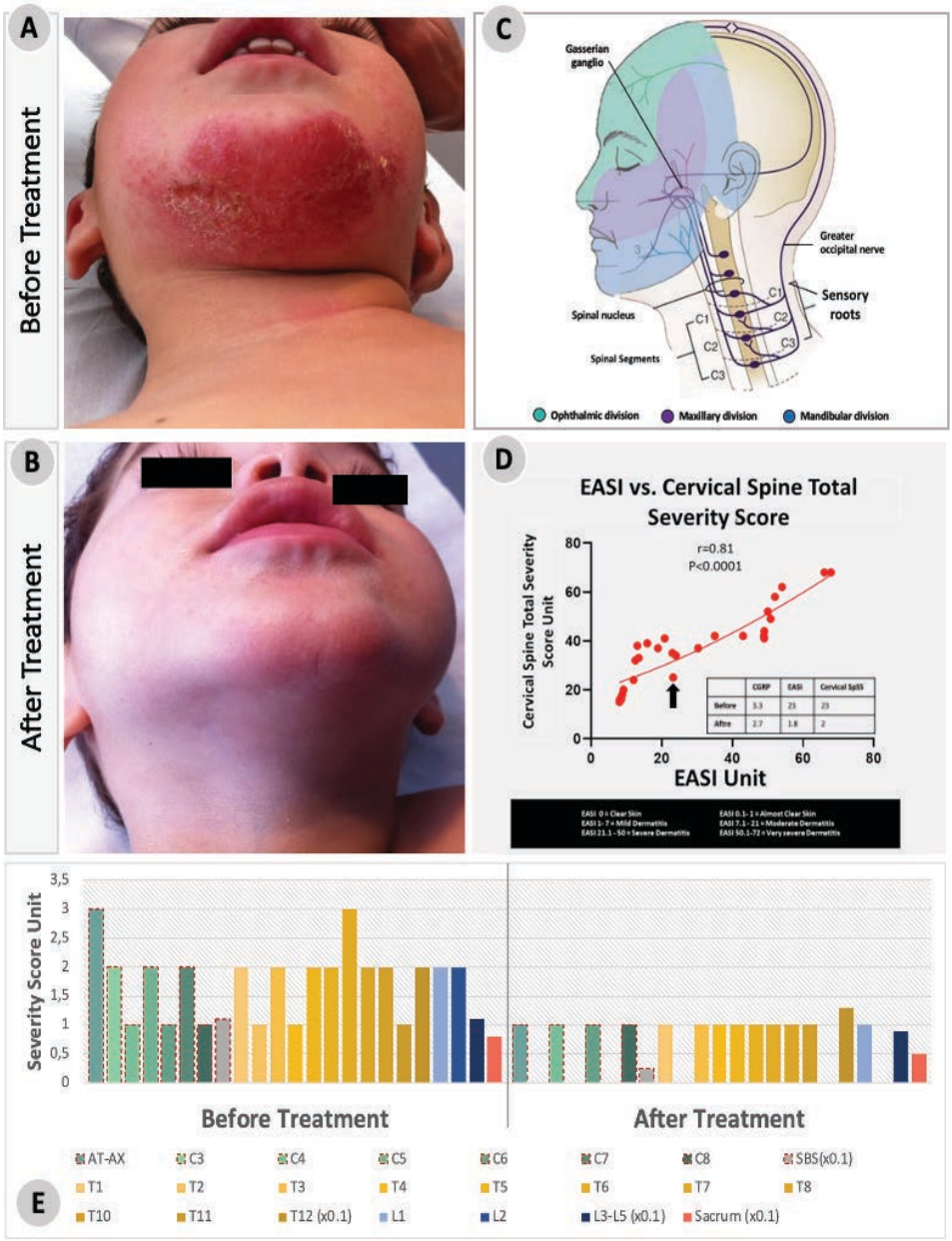


Figure 90- Case report 8: Dermatitis of the chin- Analytical data obtained from a patient diagnosed with dermatitis of the chin, SBS and SBA in cervical section, before and after the chiropractic treatment,- (A) Patient's clinical picture before chiropractic treatment, and (B) a clinical picture of inflammated area after the chiropractic treatment. (C) Trigeminal nerves indicating the madibular nerve, which is corresponded with the skin´s inflammatory processes in the chin area (D) Analytical graph indicating the correlation of EASI level and cervical SpSS, and (E) Severity scores of different parts of the patient´s spine, before and after the chiropractic treatment.

In addition, clinical data of a 68-year-old patient with dermatitis in the chest and inner part of the arm and sever SBA in the cervical section of the spine is presented in Figure 91. Also, in Figure 92, clinical data of a 59-year-old patient with dermatitis in the shoulder and outer part of the arm and sever SBA in the cervical section of the spine is presented, before and after the treatment. Both patients diagnosed by Spondylolistheses and cervical spine´s alteration.

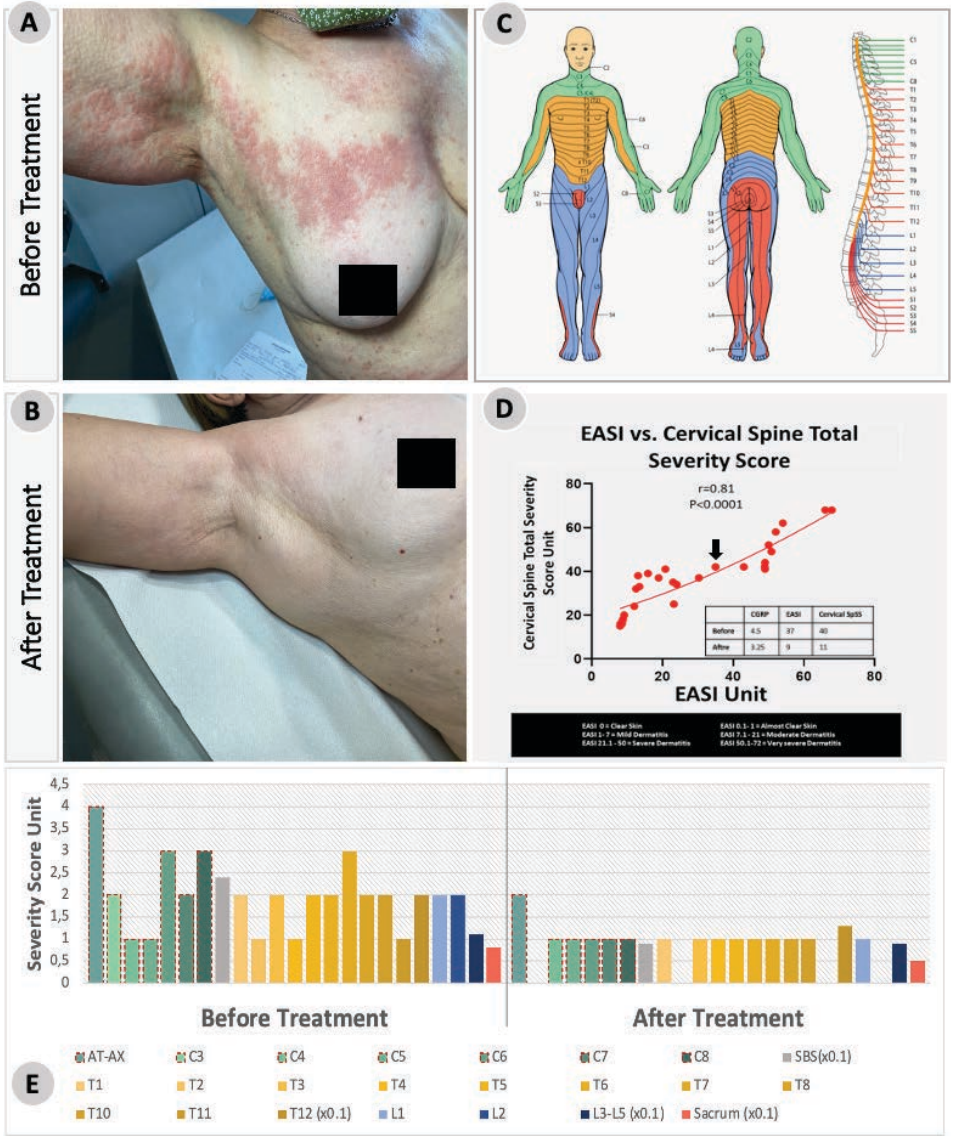


Figure 91- Case report 9- Dermatitis of the chest and inner part of the arm- Analytical data obtained from a patient diagnosed with dermatitis on the chest and arms and SBA in cervical section, before and after the chiropractic treatment- (A) Patient's clinical picture before chiropractic treatment, and (B) a clinical picture of inflammated area after the chiropractic treatment. (C) Netter´s dermatome map indicating the area of skin provided by cutaneous divisions of a single spinal nerve, (D) Analytical graph indicating the correlation of EASI level and Cervical SpSS, and (E) Severity scores of different parts of the patient´s spine, before and after the chiropractic treatment.

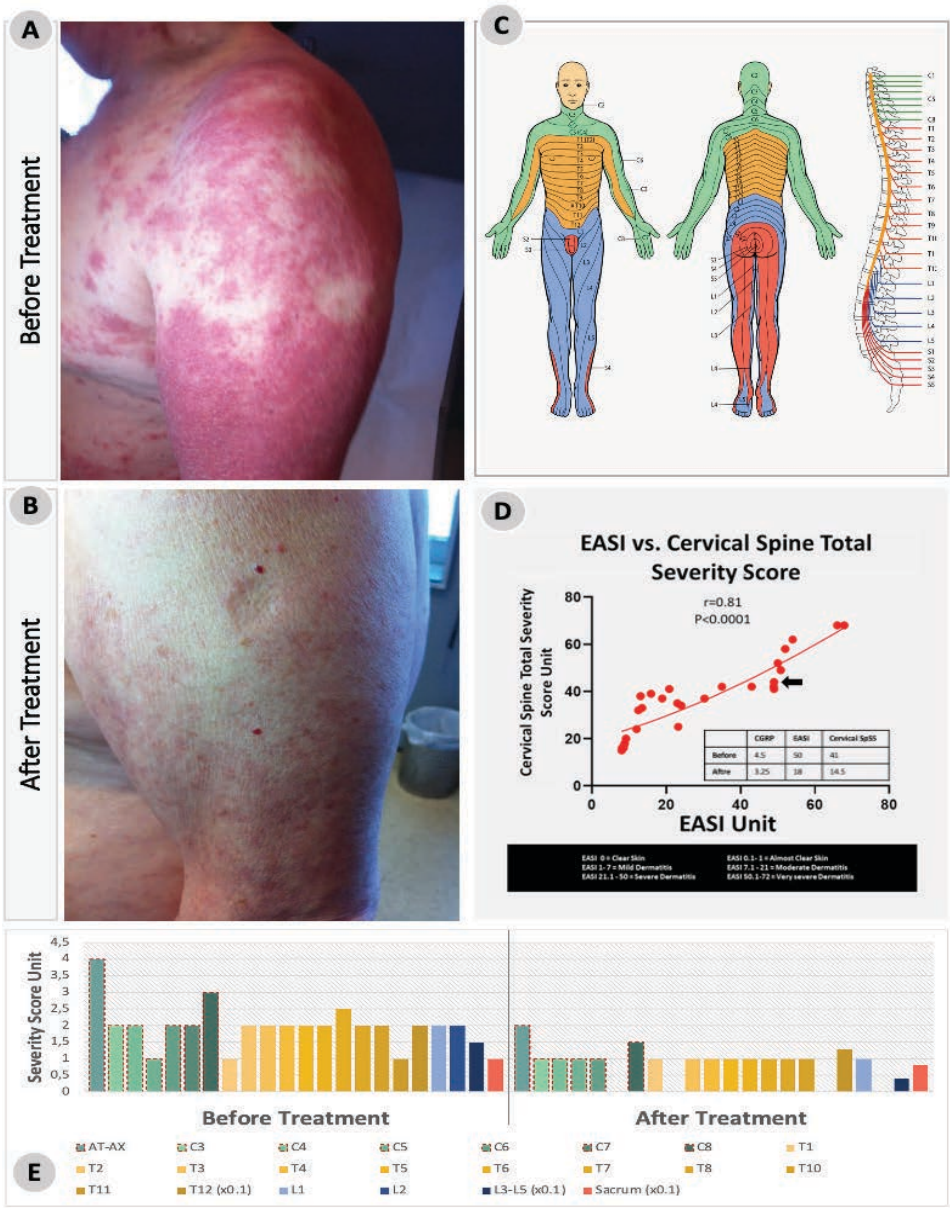


Figure 92- Case report 10: Dermatitis of the shoulder and outer part of the arm- Analytical data obtained from a patient diagnosed with dermatitis on the shoulder and outer part of the arm and severe SBA in cervical section, before and after the chiropractic treatment- (A) Patient's clinical picture before chiropractic treatment, and (B) a clinical picture of inflammated area after the chiropractic treatment. (C) Netter´s dermatome map indicating the area of skin provided by cutaneous divisions of a single spinal nerve, (D) Analytical graph indicating the correlation of EASI level and Cervical SpSS, and (E) Severity scores of different parts of the patient´s spine, before and after the chiropractic treatment.

4.2.2 Sagittal balance of the spine (SBS)

A) Analytical Data

Data collected from the sagittal (lateral) view radiographs revealed a significant difference (P<0.0001) between the level of SBS severity score between groups A and group B (Figure 93). In addition, the nonlinear Gaussian test of the SBS severity score and EASI level in the patients with high EASI level, revealed an important correlation (r=0.88) (Figure 94).

Table Analyzed	Treatment Group
	SBS Severity Sc.
Column B	Group B
vs.	vs.
Column A	Group A
Mann Whitney test	
P value	0.0001
Exact or approximate P value?	Exact
P value summary	***
Significantly different (P < 0.05)?	Yes
One- or two-tailed P value?	Two-tailed
Sum of ranks in column A,B	379 , 947
Mann-Whitney U	126
Difference between medians	
Median of column A	4.200, n=22
Median of column B	22.10, n=29
Difference: Actual	17.90
Difference: Hodges-Lehmann	18.15

Table 34- Analytical data of Mann-Whitney test of the SBS severity score between two patient groups of A and B.

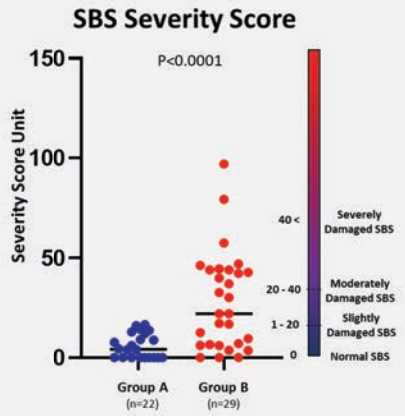


Figure 93- Scatter plot of the mean level of the SBS severity score in each group of the study. Individual points

Gaussian	Treatment Group B
Best-fit values	SBS Sev. Score
Amplitude	1602
Mean	250.4
SD	75.83
95% CI (profile likelihood)	
Amplitude	****
Mean	****
SD	****
Goodness of Fit	
Degrees of Freedom	26
R squared	0.8851
Sum of Squares	1918
Sy.x	8.589
Constraints	
SD	SD > 0
Number of points	
# of X values	29
# Y values analyzed	29

Table 35- Analytical data of Gaussian correlation test of the EASI levels vs. SBS severity score in patients with severe Dermatitis.

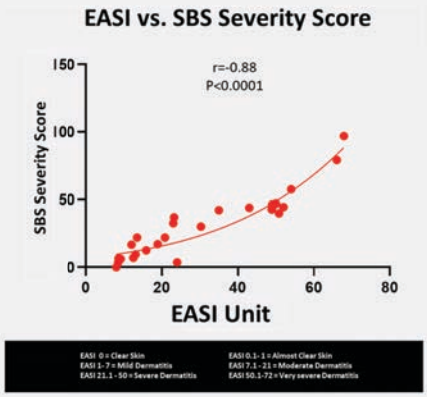


Figure 94- Scatter plot of the correlation between the EASI levels and SBS severity score in patients with severe Dermatitis.

B) Case reports

As previously mentioned, in our study, analysing the data collected from the X-Ray photography of the sagittal balance of the spine demonstrated that there is a significant correlation (r = 0.88) between the SBS severity score and the EASI level. Figure 95 and Figure 97 show two patient of our treatment group both diagnosed with alteration of sagittal spine balance. According to his data, a high severity score calculated in the cervical and lumbar sections that may resulted to neurogenic inflammation of the skin, and accordingly, manifested as dermatitis in the neck, upper side of the chest, arms and hands.

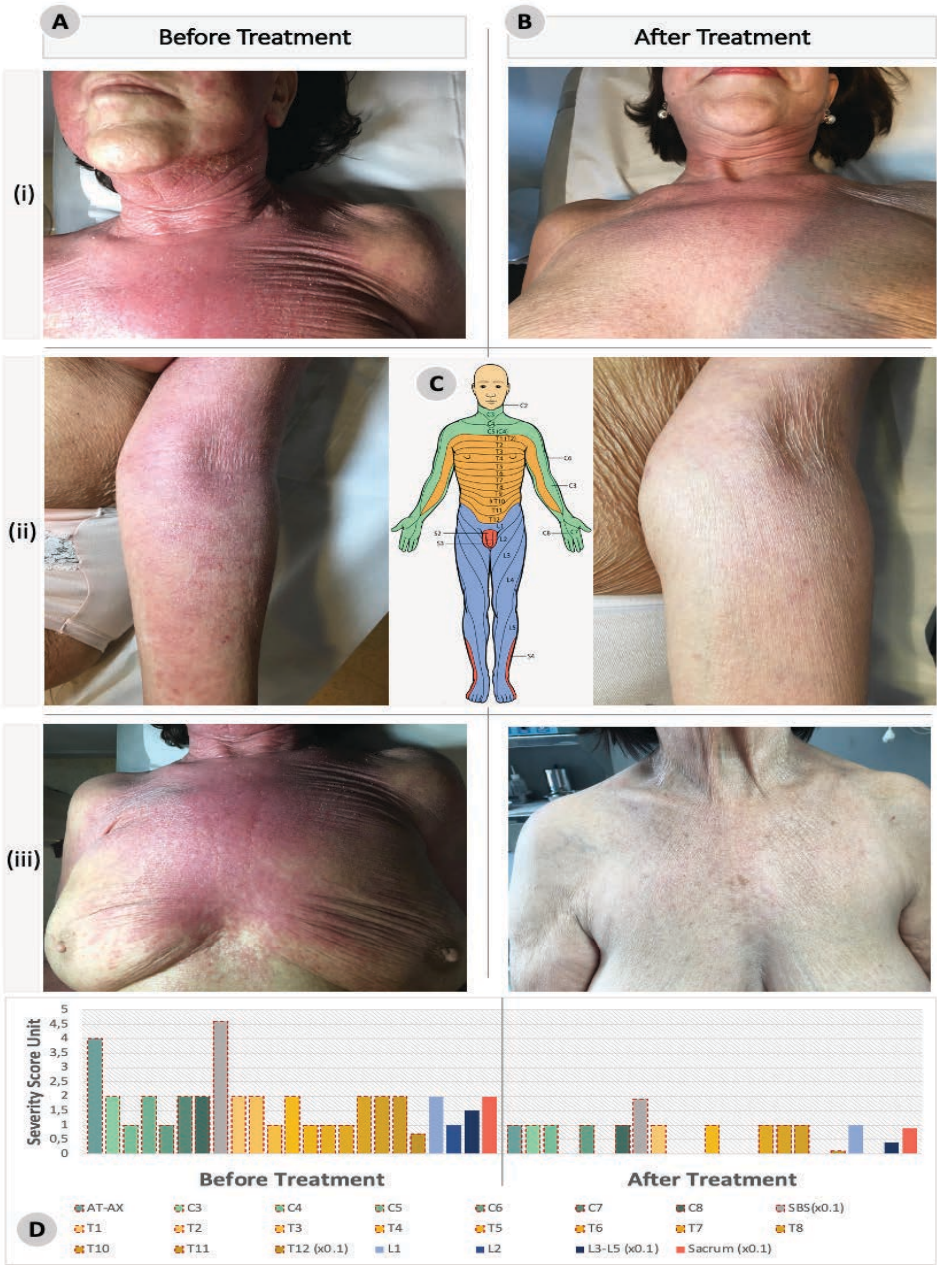
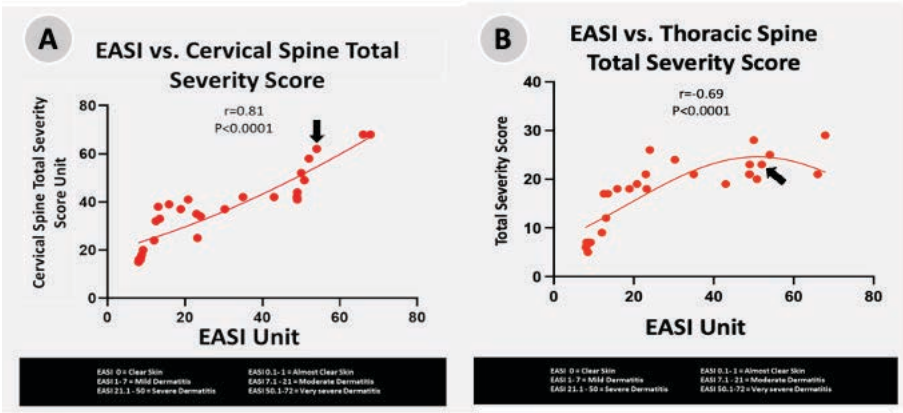


Figure 95- Case report 11: Dermatitis of the neck, chest and inner part of the arm - Analytical data obtained from a patient diagnosed with dermatitis on the neck, chest and inner part of the arm, and severe SBA in cervical and thoracic section, before and after the chiropractic treatment- (A) Patient's clinical picture before chiropractic treatment, and (B) a clinical picture of inflammated area after the chiropractic treatment. (C) Netter´s dermatome map indicating the area of skin provided by cutaneous divisions of a single spinal nerve, (D) Severity scores of different parts of the patient´s spine, before and after the chiropractic treatment.



	Before	After
CGRP	5.2	3.29
EASI	56	7
Cervical SpSS	60	17.6
Thoracic SpSS	23	8.2
SBS Sev. Score	52	14.5

Figure 96- Analytical data of the case report 11: Analytical graphs indicating the (A) correlation of EASI level and the cervical total SpSS and (B) correlation of EASI level and the total thoracic SpSS, (C) correlation of EASI level and the SBS Severity score, and (D) CGRP level, EASI score, Cervical SpSS, Thoracic SpSS, and SBS severity score, before and after the treatment, in the patient reffered in case report 11.

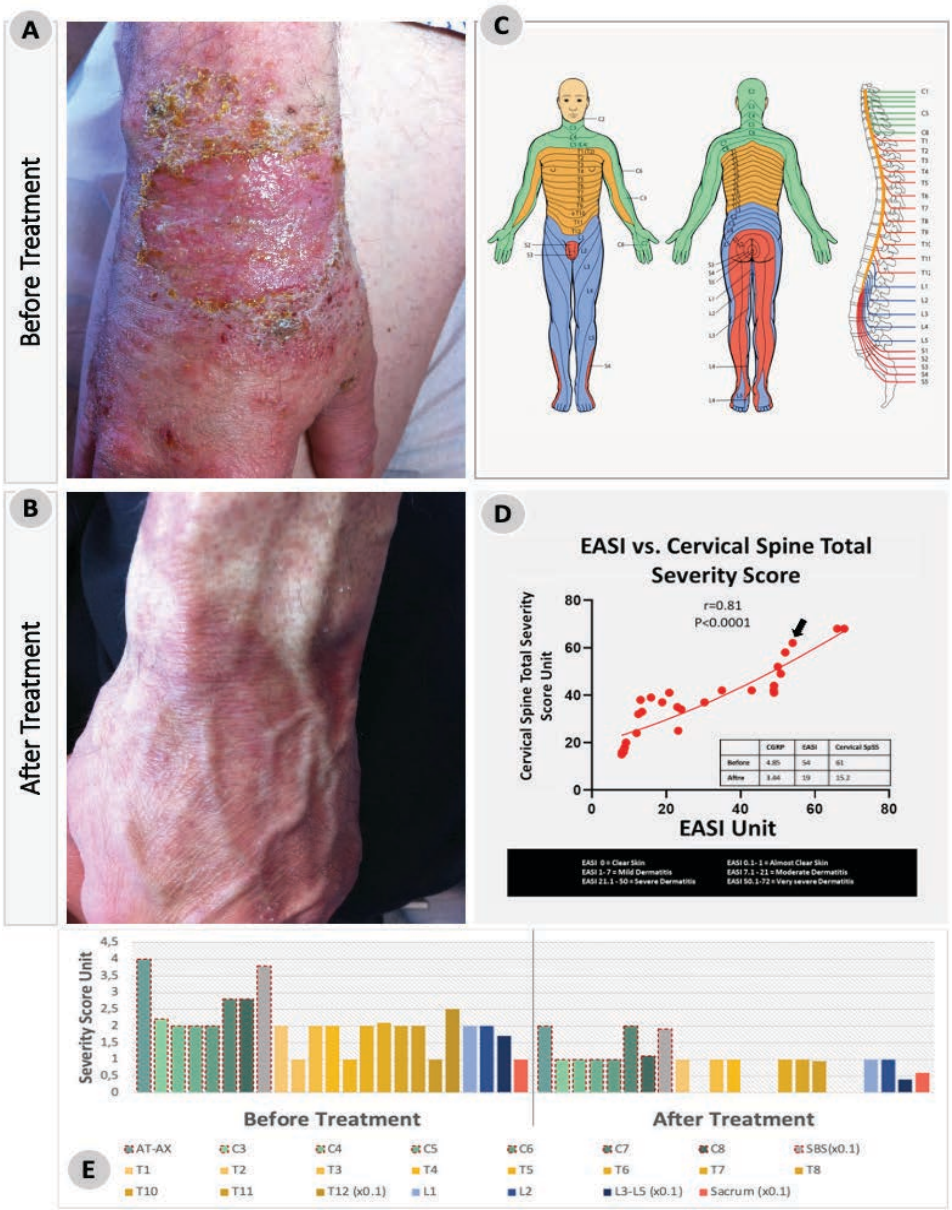


Figure 97- Case report 12: Dermatitis of the hand - Analytical data obtained from a patient diagnosed with dermatitis on the hand and severe SBA in cervical section, before and after the chiropractic treatment- (A) Patient's clinical picture before chiropractic treatment, and (B) a clinical picture of inflammated area after the chiropractic treatment. (C) Netter´s dermatome map indicating the area of skin provided by cutaneous divisions of a single spinal nerve, (D) Analytical graph indicating the correlation of EASI level and Cervical SpSS, and (E) Severity scores of different parts of the patient´s spine, before and after the chiropractic treatment.

4.2.3 Thoracic Spine Severity Score Analysis

A) Analytical Data

The thoracic spine consists of twelve vertebral segments (T1-T12) that shape the middle section of the spine. The result of the analysis in this section is based on the review of the radiographic lateral views of the patients' spine.

The result of this section is gathered from reviewing the lateral X-Ray photos of the patients' spine. As it is presented in Figure 98, there is a significant difference between Thoracic spine total severity score in patients with mild Dermatitis and patients with severe Dermatitis.

Table Analyzed	Thoracic Total
Column B	Group B
vs.	vs,
Column A	Group A
Mann Whitney test	
P value	<0,0001
Exact or approximate P value?	Exact
P value summary	****
Significantly different (P < 0.05)?	Yes
One- or two-tailed P value?	Two-tailed
Sum of ranks in column A,B	338 , 988
Mann-Whitney U	85
Difference between medians	
Median of column A	6,500, n=22
Median of column B	19,00, n=29
Difference: Actual	12,50
Difference: Hodges-Lehmann	12,00

Table36 - Analytical data of Mann-Whitney test of the Thoracic spine total severity score between two patient groups of A and B.

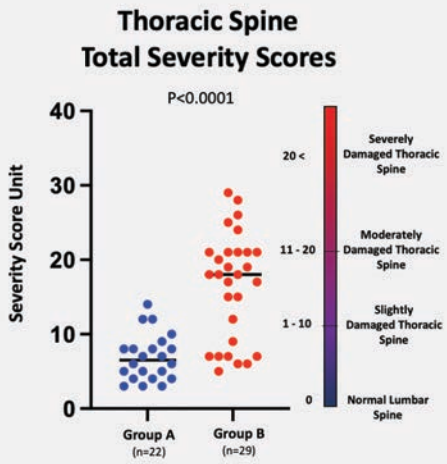


Figure 98- Scatter plot of the mean level of the Thoracic spine total severity score in each group of the study.

In addition, analysing those data using Gaussian non-linear test indicates us, that the correlation between Thoracic total severity scores and EASI levels are not meaningful. However, as the R value calculated so close to

the significant area, we strongly suggest further investigation on the correlation of EASI and Thoracic severity score, with a larger sample group. (Figure 99)

Gaussian	
Best-fit values	
Amplitude	24,60
Mean	50,94
SD	32,25
95% CI (profile likelihood)	
Amplitude	21,97 to 27,87
Mean	42,91 to 77,71
SD	24,69 to 52,64
Goodness of Fit	
Degrees of Freedom	26
R squared	0,6981
Sum of Squares	454,7
Sy.x	4,182
Constraints	
SD	SD > 0
Number of points	
# of X values	29
# Y values analyzed	29

Table37 - Analytical data of Gaussian correlation test of the EASI levels vs. Thoracis spine total severity score in patients with severe Dermatitis.

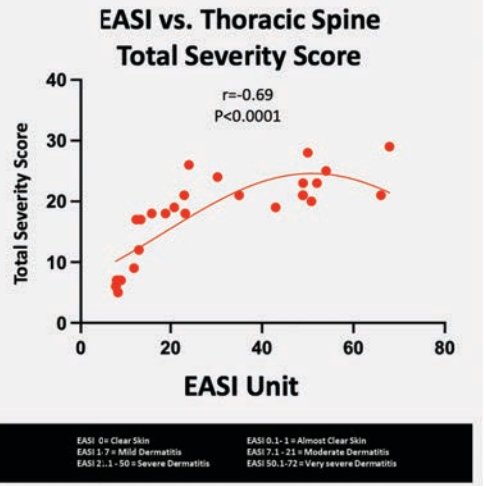


Figure 99- Scatter plot of the correlation between the EASI levels and Thoracis spine total severity score in patients with severe Dermatitis.

i) T1-T2 (Thoracic segments T1 and T2) Severity Score Analysis

By analysing the thoracic segments T1 and T2 in study patients, no significant difference (P<0.067) between two groups A and B was found. (Figure 100). Furthermore, there was no correlation (r=0.29) between T1-T2 severity score and the EASI levels (Figure 101).

Table Analyzed	Treatment Group
	T1-2 Severity Sc.
Column B	Group B
vs.	vs.
Column A	Group A
Mann Whitney test	
P value	0.0671
Exact or approximate P value?	Exact
P value summary	ns
Significantly different (P < 0.05)?	No
One- or two-tailed P value?	Two-tailed
Sum of ranks in column A,B	479 , 847
Mann-Whitney U	226
Difference between medians	
Median of column A	1.000, n=22
Median of column B	2.000, n=29
Difference: Actual	1.000
Difference: Hodges-Lehmann	1.000

Table 38- Analytical data of Mann-Whitney test of the T1-2 severity score between two patient groups of A and B.

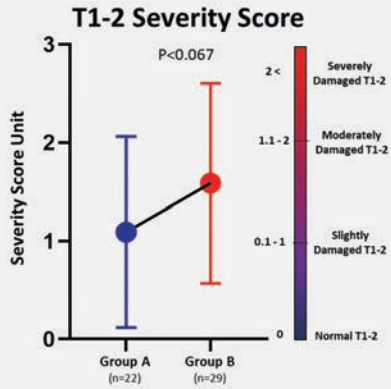


Figure 100- Scatter plot of the mean level of the T1-2 severity score Severity score in each group of the study.

Gaussian	Treatment Group B
Best-fit values	T1-2 Sev. Cor.
Amplitude	2.281
Mean	45.46
SD	28.27
95% CI (profile likelihood)	
Amplitude	1.710 to 2.965
Mean	35.08 to ???
SD	17.49 to ???
Goodness of Fit	
Degrees of Freedom	26
R squared	0.2922
Sum of Squares	20.55
Sy.x	0.8891
Constraints	
SD	SD > 0
Number of points	
# of X values	29
# Y values analyzed	29

Table 39- Analytical data of Gaussian correlation test of the EASI levels vs. T1-2 severity score in patients with severe Dermatitis.

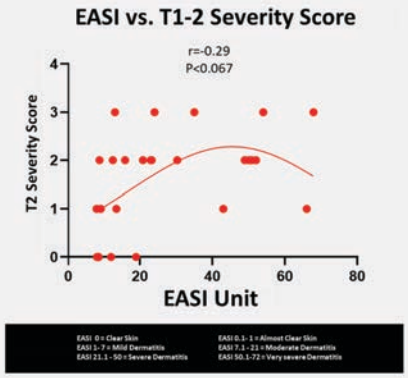


Figure 101- Scatter plot of the correlation between the EASI levels and T1-2 severity score in patients with severe Dermatitis.

ii) T3 (Thoracic segment T3) Severity Score Analysis

Calculation of Thoracic 3 severity scores are presented in Figure 102. There was a significant difference (P<0.04) between the T3 severity score in groups A and B; but there was no correlation between T3 severity score and EASI level (r=0.46) (Figure 103).

Table Analyzed	Treatment Group
	T3 Severity Sc.
Column B	Group B
vs.	vs.
Column A	Group A
Mann Whitney test	
P value	0.0389
Exact or approximate P value?	Exact
P value summary	*
Significantly different (P < 0.05)?	Yes
One- or two-tailed P value?	Two-tailed
Sum of ranks in column A,B	470.5 , 855.5
Mann-Whitney U	217.5
Difference between medians	
Median of column A	0.000, n=22
Median of column B	1.000, n=29
Difference: Actual	1.000
Difference: Hodges-Lehmann	1.000

Table 40- Analytical data of Mann-Whitney test of the T3 severity score between two patient groups of A and B.

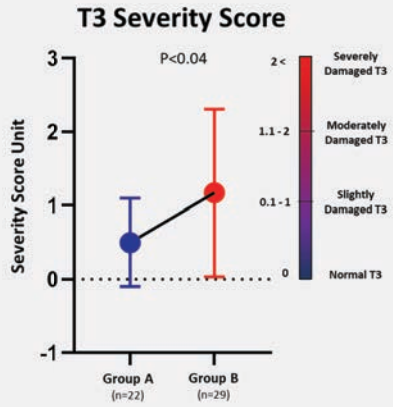


Figure 102- Scatter plot of the mean level of the T3 severity score Severity score in each group of the study.

Gaussian	Treatment Group B
Best-fit values	T3 Sev. Cor.
Amplitude	2.257
Mean	60.99
SD	29.52
95% CI (profile likelihood)	
Amplitude	1.620
Mean	42.47
SD	17.77
Goodness of Fit	
Degrees of Freedom	26
R squared	0.4641
Sum of Squares	19.37
Sy.x	0.8630
Constraints	
SD	SD > 0
Number of points	
# of X values	29
# Y values analyzed	29

Table 41- Analytical data of Gaussian correlation test of the EASI levels vs. T3 severity score in patients with severe Dermatitis.

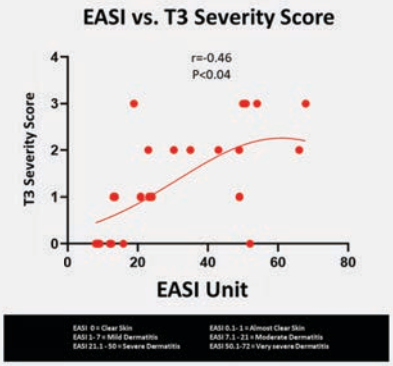


Figure 103- Scatter plot of the correlation between the EASI levels and T3 severity score in patients with severe Dermatitis.

iii) T4-T5 (Thoracic segments T4 and T5) Severity Score Analysis

The measurement of T4 and T5 severity score revealed a significant difference (P<0.04) between the two groups of patients, A and B. (Figure 104), however, there was no significant correlation between-EASI level and T4-T5 severity score (r=0.46) (Figure 105).

Table Analyzed	Treatment Group
	T4-5 Severity Sc.
Column B	Group B
vs.	vs.
Column A	Group A
Mann Whitney test	
P value	0.0105
Exact or approximate P value?	Exact
P value summary	*
Significantly different (P < 0.05)?	Yes
One- or two-tailed P value?	Two-tailed
Sum of ranks in column A,B	448 , 878
Mann-Whitney U	195
Difference between medians	
Median of column A	0.000, n=22
Median of column B	1.000, n=29
Difference: Actual	1.000
Difference: Hodges-Lehmann	1.000

Table 42. Analytical data of Mann-Whitney test of the T4-5 severity score between two patient groups of A and B.

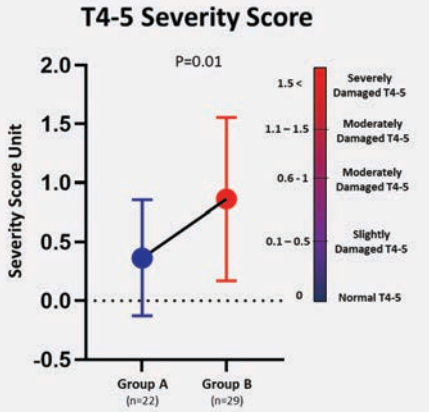


Figure 104. Scatter plot of the mean level of the T4-5 severity score Severity score in each group of the study.

Gaussian	Treatment Group B
Best-fit values	T4-5 Sev. Cor.
Amplitude	2.375
Mean	107.6
SD	54.17
95% CI (profile likelihood)	
Amplitude	****
Mean	47.33
SD	****
Goodness of Fit	
Degrees of Freedom	26
R squared	0.4459
Sum of Squares	7.452
Sy.x	0.5354
Constraints	
SD	SD > 0
Number of points	
# of X values	29
# Y values analyzed	29

Table 43. Analytical data of Gaussian correlation test of the EASI levels vs. T4-5 severity score in patients with severe Dermatitis.

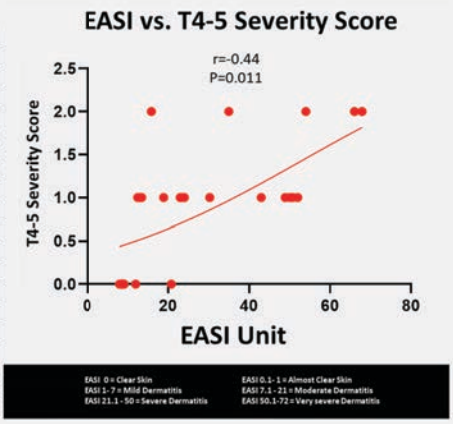


Figure 105. Scatter plot of the correlation between the EASI levels and T4-5 severity score in patients with severe Dermatitis.

Next, we analyzed the severity score of segments T6 to T9 and we have encountered a similar situation. There were significant differences between the T6 to T9 levels in each group, however, there was no correlation between these severity scores and EASI levels. These results are shown below in Figure 106- Figure 113.

iv) T6 (Thoracic segment T6) Severity Score Analysis

Table Analyzed	Treatment Group
	T6 Severity Sc.
Column B	Group B
vs.	vs.
Column A	Group A
Mann Whitney test	
P value	0.0105
Exact or approximate P value?	Exact
P value summary	*
Significantly different (P < 0.05)?	Yes
One- or two-tailed P value?	Two-tailed
Sum of ranks in column A,B	448 , 878
Mann-Whitney U	195
Difference between medians	
Median of column A	0.000, n=22
Median of column B	1.000, n=29
Difference: Actual	1.000
Difference: Hodges-Lehmann	1.000

Table 44- Analytical data of Mann-Whitney test of the T6 severity score between two patient groups of A and B.

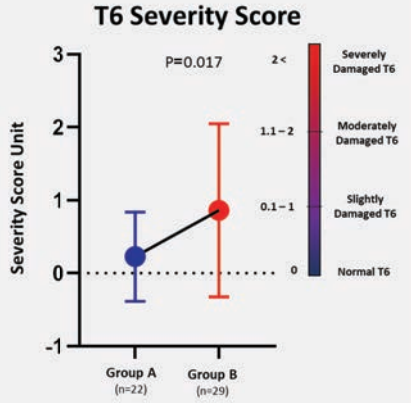


Figure 106- Scatter plot of the mean level of the T6 severity score Severity score in each group of the study.

Gaussian	Treatment Group B
Best-fit values	T6 Sev. Sc.
Amplitude	2.375
Mean	107.6
SD	54.17
95% CI (profile likelihood)	
Amplitude	****
Mean	47.33
SD	****
Goodness of Fit	
Degrees of Freedom	26
R squared	0.4459
Sum of Squares	7.452
Sy.x	0.5354
Constraints	
SD	SD > 0
Number of points	
# of X values	29
# Y values analyzed	29

Table 45- Analytical data of Gaussian correlation test of the EASI levels vs. T6 severity score in patients with severe Dermatitis.

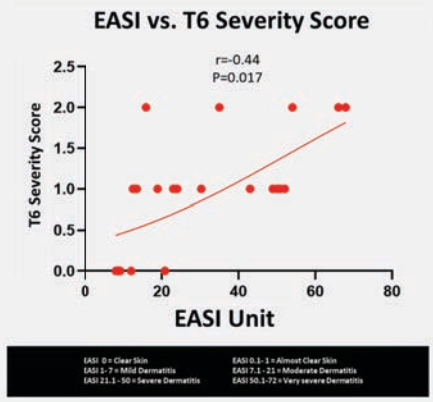


Figure 107- Scatter plot of the correlation between the EASI levels and T6 severity score in patients with severe Dermatitis.

v) T7 (Thoracic segment T7) Severity Score Analysis

Table Analyzed	Treatment Group
	T7 Severity Sc.
Column B	Group B
vs.	vs.
Column A	Group A
Mann Whitney test	
P value	0.0499
Exact or approximate P value?	Exact
P value summary	*
Significantly different (P < 0.05)?	Yes
One- or two-tailed P value?	Two-tailed
Sum of ranks in column A,B	470 , 856
Mann-Whitney U	217
Difference between medians	
Median of column A	1.000, n=22
Median of column B	2.000, n=29
Difference: Actual	1.000
Difference: Hodges-Lehmann	1.000

Table 46- Analytical data of Mann-Whitney test of the T7 severity score between two patient groups of A and B.

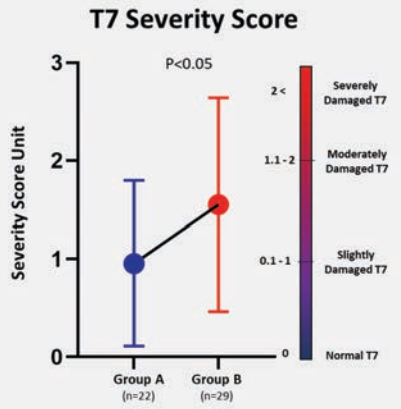


Figure 108- Scatter plot of the mean level of the T7 severity score Severity score in each group of the study.

Gaussian4.58	Treatment Group B
Best-fit values	T7 Sev. Cor.
Amplitude	2.513
Mean	60.64
SD	35.39
95% CI (profile likelihood)	
Amplitude	1.917
Mean	40.92
SD	20.77
Goodness of Fit	
Degrees of Freedom	26
R squared	0.4430
Sum of Squares	18.48
Sy.x	0.8430
Constraints	
SD	SD > 0
Number of points	
# of X values	29
# Y values analyzed	29

Table 47- Analytical data of Gaussian correlation test of the EASI levels vs. T7 severity score in patients with severe Dermatitis.

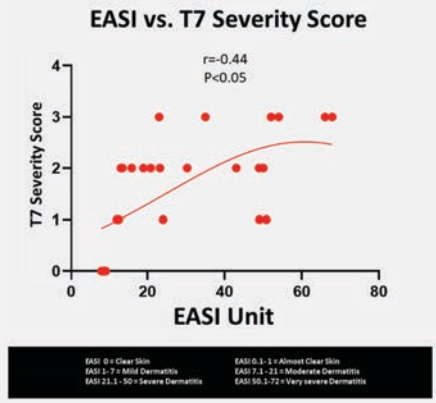


Figure 109- Scatter plot of the correlation between the EASI levels and T7 severity score in patients with severe Dermatitis.

vi) T8 (Thoracic segment T8) Severity Score Analysis

	Treatment Group
Table Analyzed	T8 Severity Sc.
Column B	Group B
vs.	vs.
Column A	Group A
Mann Whitney test	
P value	0.0114
Exact or approximate P value?	Exact
P value summary	*
Significantly different (P < 0.05)?	Yes
One- or two-tailed P value?	Two-tailed
Sum of ranks in column A,B	446.5 , 879.5
Mann-Whitney U	193.5
Difference between medians	
Median of column A	0.000, n=22
Median of column B	1.000, n=29
Difference: Actual	1.000
Difference: Hodges-Lehmann	1.000

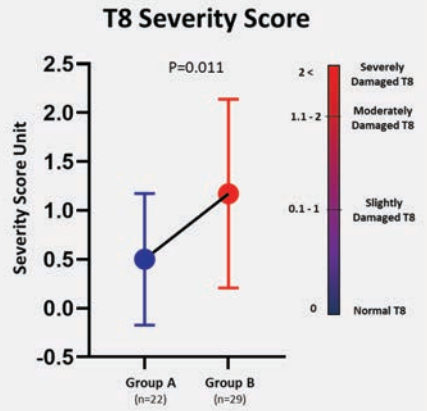


Table 48- Analytical data of Mann-Whitney test of the T8 severity score between two patient groups of A and B.

Figure 110- Scatter plot of the mean level of the T8 severity score Severity score in each group of the study.

Gaussian	Treatment Group B
Best-fit values	T8 Sev. Cor.
Amplitude	6039
Mean	731.9
SD	169.0
95% CI (profile likelihood)	
Amplitude	****
Mean	****
SD	****
Goodness of Fit	
Degrees of Freedom	26
R squared	0.4150
Sum of Squares	15.29
Sy.x	0.7668
Constraints	
SD	SD > 0
Number of points	
# of X values	29
# Y values analyzed	29

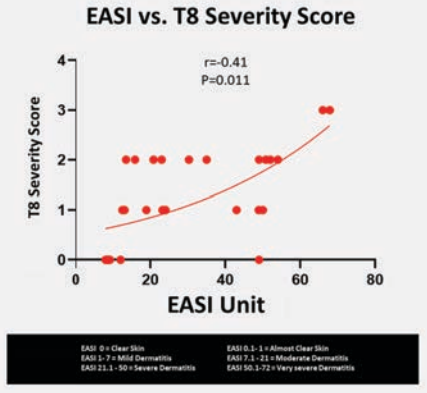


Table 49. Analytical data of Gaussian correlation test of the EASI levels vs. T8 severity score in patients with severe Dermatitis.

Figure 111. Scatter plot of the correlation between the EASI levels and T8 severity score in patients with severe Dermatitis.

vii) T9 (Thoracic segment T9) Severity Score Analysis

Analysis of the T9 data gathered from 51 patients demonstrated a significant difference between groups A and B (Figure 112). In addition, there was a slight correlation between T9 severity score and EASI levels. (Figure 113)

Table Analyzed	Treatment Group
	T9 Severity Sc.
Column B	Group B
vs.	vs.
Column A	Group A
Mann Whitney test	
P value	0.0012
Exact or approximate P value?	Exact
P value summary	**
Significantly different (P < 0.05)?	Yes
One- or two-tailed P value?	Two-tailed
Sum of ranks in column A,B	410.5 , 915.5
Mann-Whitney U	157.5
Difference between medians	
Median of column A	1.000, n=22
Median of column B	2.000, n=29
Difference: Actual	1.000
Difference: Hodges-Lehmann	1.000

Table 50- Analytical data of Mann-Whitney test of the T9 severity score between two patient groups of A and B.

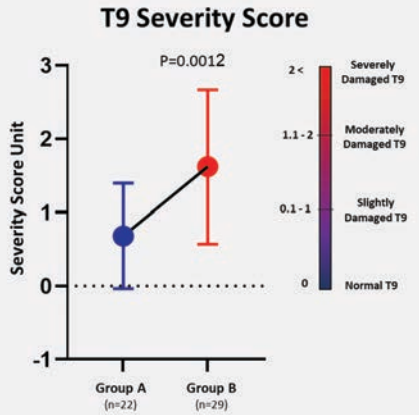


Figure 112- Scatter plot of the mean level of the T9 severity score Severity score in each group of the study.

Gaussian	Treatment Group B
Best-fit values	T9 Sev. Cor.
Amplitude	2.776
Mean	60.14
SD	32.43
95% CI (profile likelihood)	
Amplitude	2.303 to 18.38
Mean	46.34 to 248.0
SD	22.72 to 98.88
Goodness of Fit	
Degrees of Freedom	26
R squared	0.6507
Sum of Squares	10.77
Sy.x	0.6436
Constraints	
SD	SD > 0
Number of points	
# of X values	29
# Y values analyzed	29

Table 51- Analytical data of Gaussian correlation test of the EASI levels vs. T9 severity score in patients with severe Dermatitis.

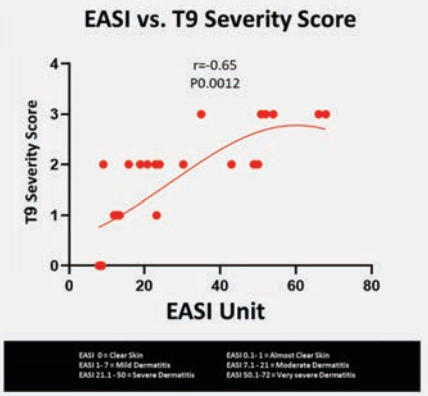


Figure 113- Scatter plot of the correlation between the EASI levels and T9 severity score in patients with severe Dermatitis.

viii) T10 (Thoracic segment T10) Severity Score Analysis

Analysis of the T10 severity score data, gathered from the study patients, demonstrated a significant difference between groups A and B (Figure 114). Additionally, unlike the T1-T9 segments, we found a strong correlation between T10 severity score and EASI levels (r= 0.87) (Figure 115).

	Treatment Group
Table Analyzed	T10 Severity Sc.
Column B	Group B
vs.	vs.
Column A	Group A
Mann Whitney test	
P value	<0.0001
Exact or approximate P value?	Exact
P value summary	****
Significantly different (P < 0.05)?	Yes
One- or two-tailed P value?	Two-tailed
Sum of ranks in column A,B	358.5 , 967.5
Mann-Whitney U	105.5
Difference between medians	
Median of column A	2.000, n=22
Median of column B	3.000, n=29
Difference: Actual	1.000
Difference: Hodges-Lehmann	2.000

Table 52- Analytical data of Mann-Whitney test of the T10 severity score between two patient groups of A and B.

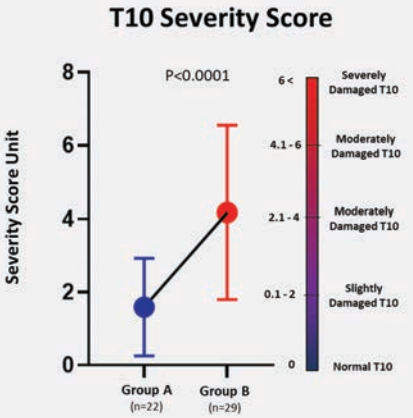


Figure 114- Scatter plot of the mean level of the T10 severity score Severity score in each group of the study.

Gaussian	Treatment Group B
Best-fit values	T10 Sev. Cor.
Amplitude	8.294
Mean	75.35
SD	39.34
95% CI (profile likelihood)	
Amplitude	6.992 to 20.41
Mean	59.28 to 158.4
SD	29.81 to 71.58
Goodness of Fit	
Degrees of Freedom	26
R squared	0.8722
Sum of Squares	20.21
Sy.x	0.8816
Constraints	
SD	SD > 0
Number of points	
# of X values	29
# Y values analyzed	29

Table 53- Analytical data of Gaussian correlation test of the EASI levels vs. T10 severity score in patients with severe Dermatitis.

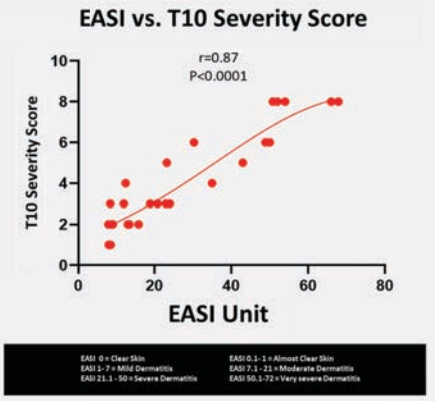


Figure 115- Scatter plot of the correlation between the EASI levels and T10 severity score in patients with severe Dermatitis.

ix) T11 (Thoracic segment T11) Severity Score Analysis

When analyzing the T11, we found a slightly significant difference (P<0.045) between groups A and B (Figure 116). In addition, there was a modest correlation (r=0.61) between T11 severity score and the EASI levels. (Figure 117).

Table Analyzed	Treatment Group
	T 11 Severity Sc.
Column B	Group B
vs.	vs.
Column A	Group A
Mann Whitney test	
P value	0.0422
Exact or approximate P value?	Exact
P value summary	*
Significantly different (P < 0.05)?	Yes
One- or two-tailed P value?	Two-tailed
Sum of ranks in column A,B	474 , 852
Mann-Whitney U	221
Difference between medians	
Median of column A	0.000, n=22
Median of column B	1.000, n=29
Difference: Actual	1.000
Difference: Hodges-Lehmann	0.000

Table 54- Analytical data of Mann-Whitney test of the T11 severity score between two patient groups of A and B.

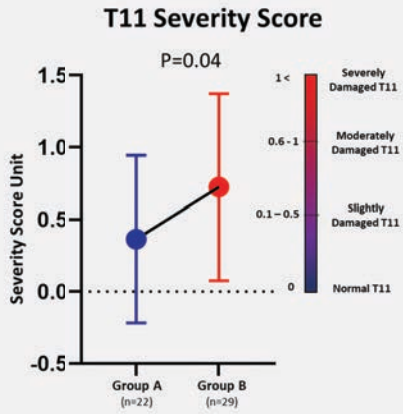


Figure 116- Scatter plot of the mean level of the T11 severity score Severity score in each group of the study.

Gaussian	Treatment Group B
Best-fit values	T11 Sev. Cor.
Amplitude	4.467
Mean	141.3
SD	56.73
95% CI (profile likelihood)	
Amplitude	****
Mean	****
SD	****
Goodness of Fit	
Degrees of Freedom	26
R squared	0.6180
Sum of Squares	4.505
Sy.x	0.4163
Constraints	
SD	SD > 0
Number of points	
# of X values	29
# Y values analyzed	29

Table 55. Analytical data of Gaussian correlation test of the EASI levels vs. T11 severity score in patients with severe Dermatitis.

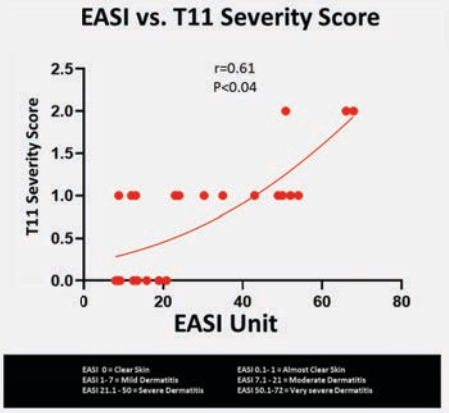


Figure 117. Scatter plot of the correlation between the EASI levels and T11 severity score in patients with severe Dermatitis.

x) T12 (Thoracic segment T12) Severity Score Analysis

The analysis of the last thoracic vertebra, T12 that, although there was significant difference (P<0.0001) between groups A and B (Figure 118), there was no correlation (r=0.32) between T12 severity score and the EASI levels (Figure 119).

Table Analyzed	Treatment Group
	T12 Severity Score
Column B	Group B
vs.	vs.
Column A	Group A
Mann Whitney test	
P value	<0.0001
Exact or approximate P value?	Exact
P value summary	****
Significantly different (P < 0.05)?	Yes
One- or two-tailed P value?	Two-tailed
Sum of ranks in column A,B	350 , 976
Mann-Whitney U	97
Difference between medians	
Median of column A	18.75, n=22
Median of column B	36.50, n=29
Difference: Actual	17.75
Difference: Hodges-Lehmann	14.60

Table 56- Analytical data of Mann-Whitney test of the T12 severity score between two patient groups of A and B.

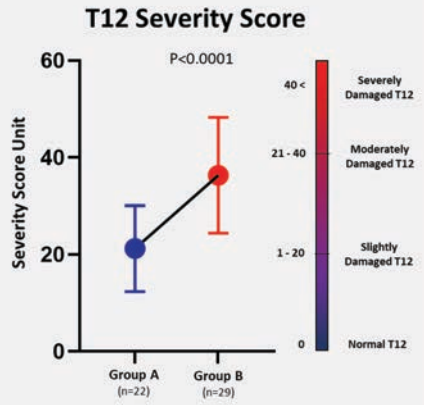


Figure 118- Scatter plot of the mean level of the T12 severity score Severity score in each group of the study. Individual values

Gaussian	Treatment Group B
Best-fit values	T12 Sev. Cor.
Amplitude	63.24
Mean	144.3
SD	109.8
95% CI (profile likelihood)	
Amplitude	****
Mean	****
SD	****
Goodness of Fit	
Degrees of Freedom	26
R squared	0.3239
Sum of Squares	2709
Sy.x	10.21
Constraints	
SD	SD > 0
Number of points	
# of X values	29
# Y values analyzed	29

Table 57. Analytical data of Gaussian correlation test of the EASI levels vs. T12 severity score in patients with severe Dermatitis.

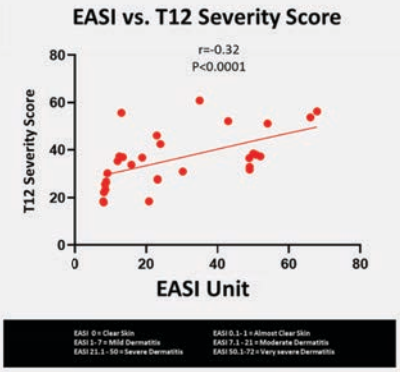


Figure 119. Scatter plot of the correlation between the EASI levels and T12 severity score in patients with severe Dermatitis.

All in all, the data provided in the previous section showed a strong correlation between T10 severity score and EASI levels (r= 0.87)

B) Case Reports

According to Netter´s Dermatome map, cautious nerve fibres innervated from thoracic spine, have a great impact on the human skin in trunk and arms area. (Figure 28) In Figure 120, Figure 121, and Figure 122, analysis of data and clinical pictures of a patients with dermatitis in trunk and inner part of the arm, dermatitis in the back, and dermatitis of the abdomen, are presented respectively. As presented through these figures, when correcting the SBA in the thoracic section through chiropractic treatment and reducing the level of thoracic spine severity scores, the level of CGRP is reduced, and accordingly, the level of EASI score has been decreased.

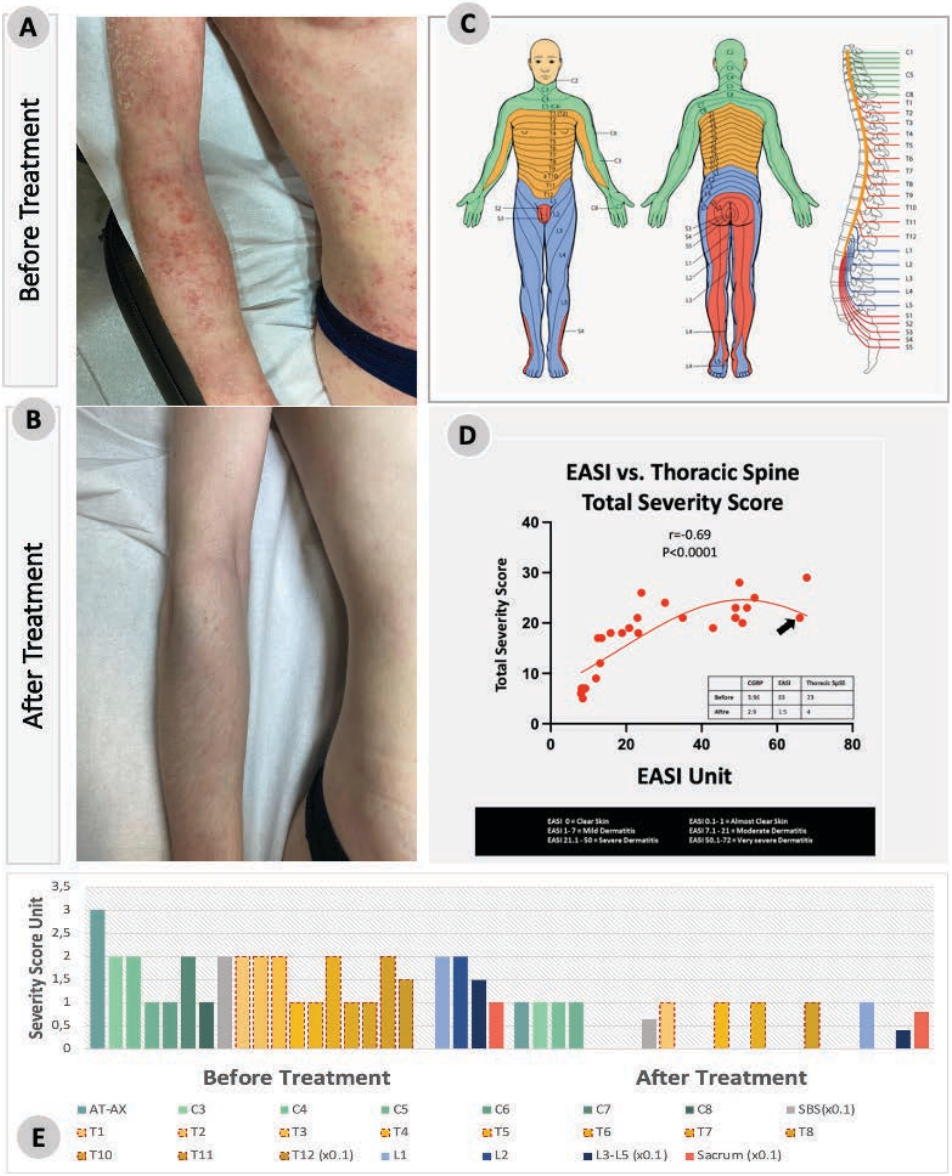


Figure 120- Case report 13: Dermatitis of the inner part of the arm and trunk- Analytical data obtained from a patient diagnosed with dermatitis on the inner part of the arm and trunk, and severe SBA in thoracic section, before and after the chiropractic treatment- (A) Patient's clinical picture before chiropractic treatment, and (B) a clinical picture of inflammated area after the chiropractic treatment. (C) Netter´s dermatome map indicating the area of skin provided by cutaneous divisions of a single spinal nerve, (D) Analytical graph indicating the correlation of EASI level and the total thoracic SpSS, and (E) Severity scores of different parts of the patient´s spine, before and after the chiropractic treatment.

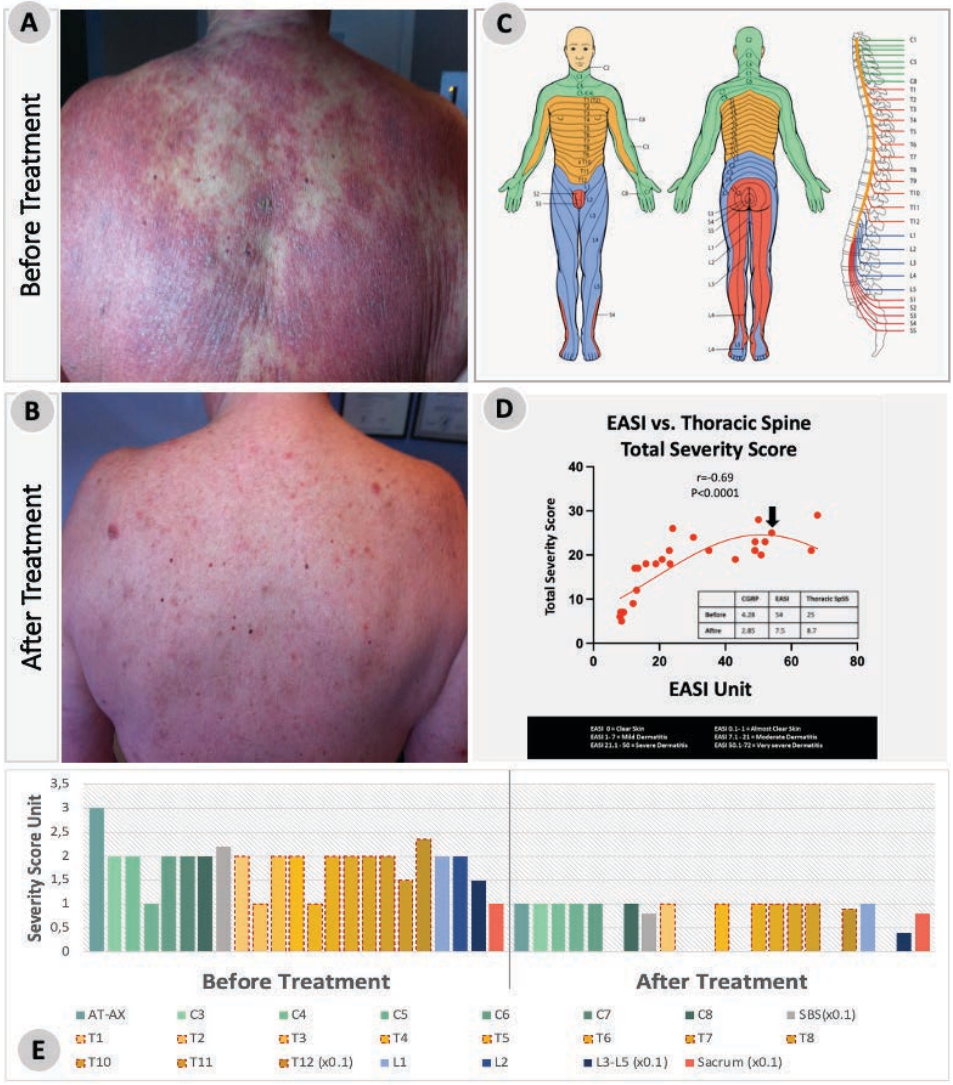


Figure 121- Case report 14: Dermatitis of the back- Analytical data obtained from a patient diagnosed with dermatitis on back, and severe SBA in thoracic section, before and after the chiropractic treatment- (A) Patient's clinical picture before chiropractic treatment, and (B) a clinical picture of inflammated area after the chiropractic treatment. (C) Netter´s dermatome map indicating the area of skin provided by cutaneous divisions of a single spinal nerve, (D) Analytical graph indicating the correlation of EASI level and the total thoracic SpSS, and (E) Severity scores of different parts of the patient´s spine, before and after the chiropractic treatment.

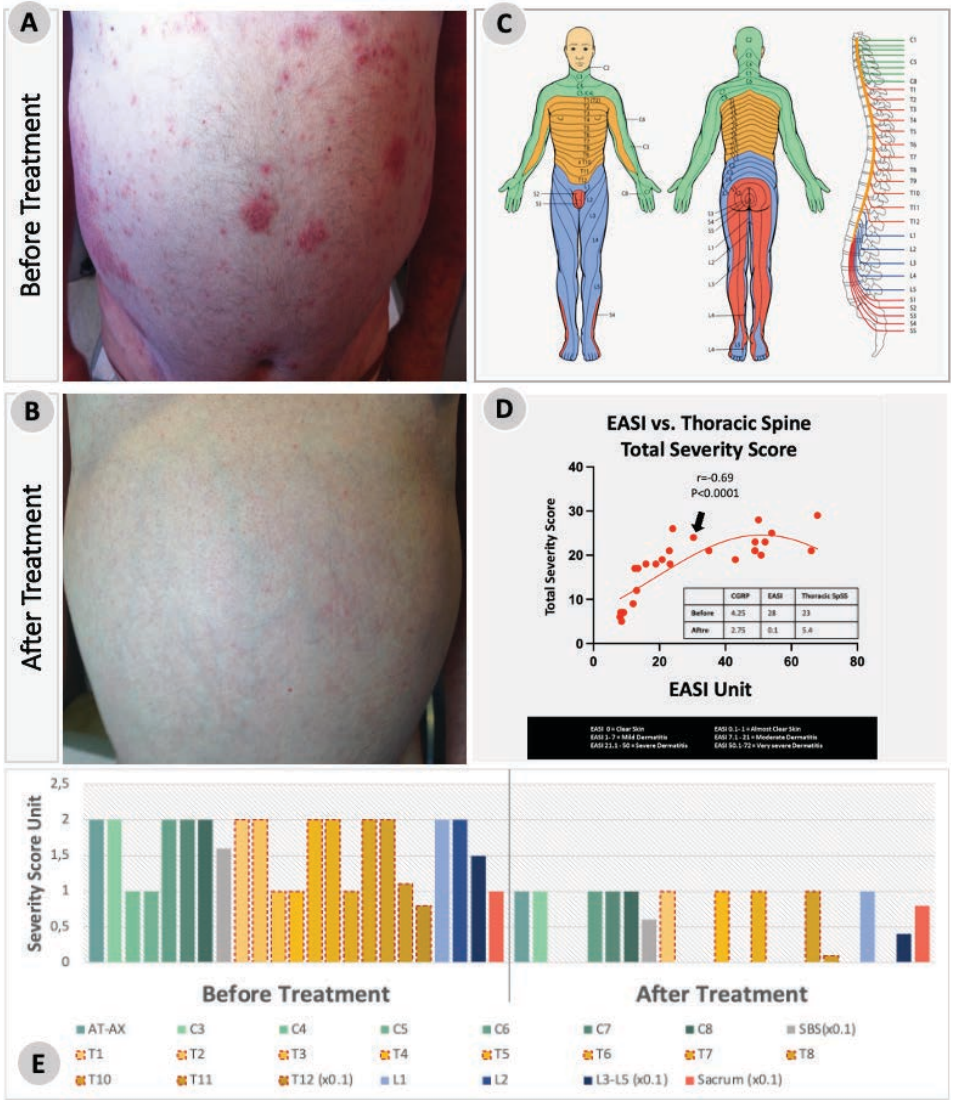


Figure 122- Case report 15: Dermatitis of the abdomen- Analytical data obtained from a patient diagnosed with dermatitis on the abdomen, and severe SBA in thoracic section, before and after the chiropractic treatment- (A) Patient's clinical picture before chiropractic treatment, and (B) a clinical picture of inflammated area after the chiropractic treatment. (C) Netter´s dermatome map indicating the area of skin provided by cutaneous divisions of a single spinal nerve, (D) Analytical graph indicating the correlation of EASI level and the total thoracic SpSS, and (E) Severity scores of different parts of the patient´s spine, before and after the chiropractic treatment.

4.2.4 Lumbar Spine Segments Severity Score Analysis

A) Analytical Data

The lumbar spine segments are located at the bottom of the spine, between the thoracic and the sacral segments. It is structured by five separate vertebrae that are the largest vertebrae in the human spine. The lumbar segments help the spine to support its structure. To facilitate the analysis, we divided the lumbar segments in two groups of segments: Lumbar 1 - Lumbar 2 (L1-L2) and Lumbar 3 -Lumbar 5 (L3-L5).

As it is presented in Figure123 , there is a significant difference in the situation of Lumbar spine in patients with mild Dermatitis and patients with severe Dermatitis. Moreover, correlation between the level of EASI levels and Lumbar spine total severity score is presented in Figure 124. As it is indicated, the r square of non-linear test is calculated 0.697 that is very close to the significant area (minimum significancy: r=0.70). Nevertheless, statistically we cannot take it as a meaningful correlation, and we suggest further studies on the correlation of Lumbar spine and Dermatitis.

Table Analyzed	Lumbar Total
	Treatment Group
Column B	Group B
vs.	vs,
Column A	Group A
Mann Whitney test	
P value	<0,0001
Exact or approximate P value?	Exact
P value summary	****
Significantly different (P < 0.05)?	Yes
One- or two-tailed P value?	Two-tailed
Sum of ranks in column A,B	263 , 1063
Mann-Whitney U	10
Difference between medians	
Median of column A	79,00, n=22
Median of column B	99,00, n=29
Difference: Actual	20,00
Difference: Hodges-Lehmann	20,00

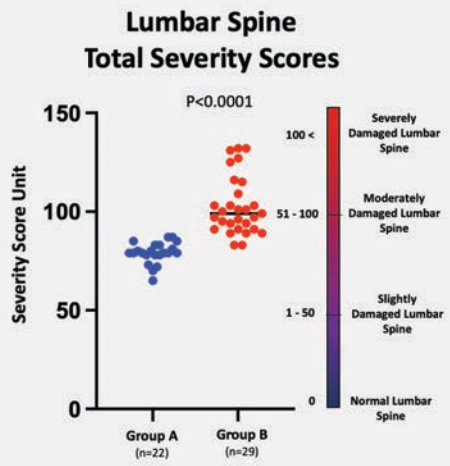


Table58 - Analytical data of Mann-Whitney test of the Lumbar Spine Total severity score between two patient groups of A and B.

Figure123 - Scatter plot of the mean level of the Lumbar Spine Total severity score Severity score in each group of the study. Individual values

Gaussian	Lumbar Total Score
Best-fit values	
Amplitude	5868
Mean	1389
SD	477,8
95% CI (profile likelihood)	
Amplitude	
Mean	64,28
SD	
Goodness of Fit	
Degrees of Freedom	26
R squared	0,6978
Sum of Squares	1835
Sy.x	8,400
Constraints	
SD	SD > 0
Number of points	
# of X values	29
# Y values analyzed	29

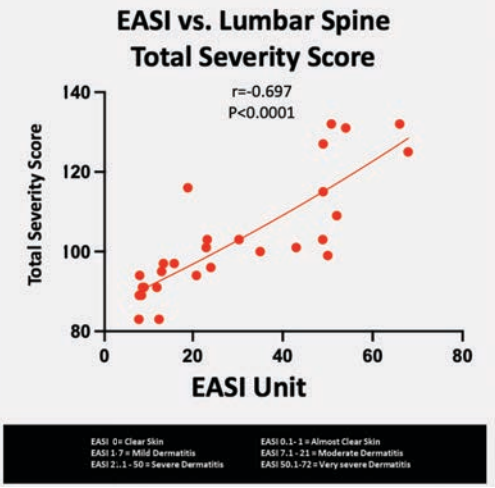


Table59 - Analytical data of Gaussian correlation test of the EASI levels vs. Lumbar

Figure 124- Scatter plot of the correlation between the EASI levels and Lumbar Spine

Spine Total severity score in patients with severe Dermatitis.

Total severity score in patients with severe Dermatitis.

i) L1-L2 (Lumbar spine segments L1 - L2) Severity Score Analysis

Analysis of the data collected from L1 and L2 showed a significant difference between the severity score level in both groups A and B (P=0.0021). (Figure 125). The nonlinear Gaussian test of the L1 severity score and EASI level in the patients, indicated a good correlation between those data sets (r=0.81). (Figure 126).

Table Analyzed	Lumbar 1
	Treatment Group
Column B	Group B
vs.	vs,
Column A	Group A
Mann Whitney test	
P value	0,0021
Exact or approximate P value?	Exact
P value summary	**
Significantly different (P < 0.05)?	Yes
One- or two-tailed P value?	Two-tailed
Sum of ranks in column A,B	416 , 910
Mann-Whitney U	163
Difference between medians	
Median of column A	2,000, n=22
Median of column B	4,000, n=29
Difference: Actual	2,000
Difference: Hodges-Lehmann	2,000

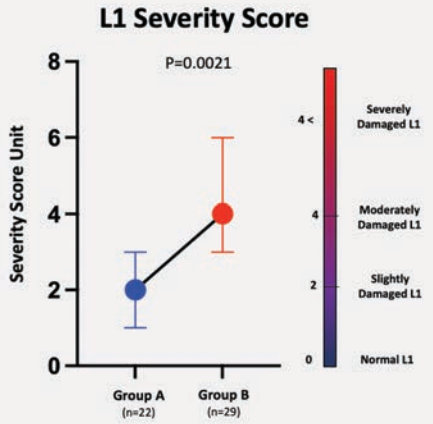


Table 60. Analytical data of Mann-Whitney test of the L1 severity score between two patient groups of A and B.

Figure 125. Scatter plot of the mean level of the L1 severity score Severity score in each group of the study.

Gaussian	
Best-fit values	
Amplitude	7,790
Mean	79,74
SD	48,11
95% CI (profile likelihood)	
Amplitude	6,447
Mean	57,15
SD	33,52
Goodness of Fit	
Degrees of Freedom	26
R squared	0,8138
Sum of Squares	19,93
Sy.x	0,8754
Constraints	
SD	SD > 0
Number of points	
# of X values	29
# Y values analyzed	29

Table 61. Analytical data of Gaussian correlation test of the EASI levels vs. L1 severity score in patients with severe Dermatitis.

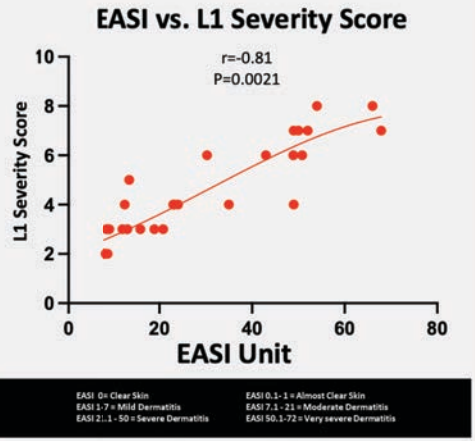


Figure 126. Scatter plot of the correlation between the EASI levels and L1 severity score in patients with severe Dermatitis.

In addition, similar results obtained from the analysis of Lumbar 2 severity scores. Figure 127 clearly presents a significant difference ($P<0.0001$) between the levels of L2 in patients with mild and severe Dermatitis (Figure 127). Moreover, as it is presented in Figure 128, there is a correlation between the level of EASI in patients with severe Dermatitis and their L2 severity score ($r= 0.70$).

Table Analyzed	Lumbar 2
	Treatment Group
Column B	Group B
vs.	vs,
Column A	Group A
Mann Whitney test	
P value	<0,0001
Exact or approximate P value?	Exact
P value summary	****
Significantly different (P < 0.05)?	Yes
One- or two-tailed P value?	Two-tailed
Sum of ranks in column A,B	375,5 , 950,5
Mann-Whitney U	122,5
Difference between medians	
Median of column A	1,500, n=22
Median of column B	3,000, n=29
Difference: Actual	1,500
Difference: Hodges-Lehmann	1,000

Table62 - Analytical data of Mann-Whitney test of the L2 severity score between two patient groups of A and B.

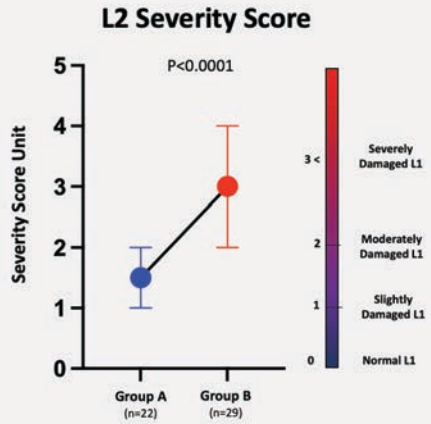


Figure 127- Scatter plot of the mean level of the L2 severity score Severity score in each group of the study.

Gaussian	
Best-fit values	
Amplitude	4,041
Mean	52,26
SD	35,79
95% CI (profile likelihood)	
Amplitude	3,659 to 4,622
Mean	43,91 to 83,02
SD	27,44 to 59,87
Goodness of Fit	
Degrees of Freedom	26
R squared	0,7019
Sum of Squares	9,498
Sy.x	0,6044
Constraints	
SD	SD > 0
Number of points	
# of X values	29
# Y values analyzed	29

Table63 - Analytical data of Gaussian correlation test of the EASI levels vs. 2 severity score in patients with severe Dermatitis.

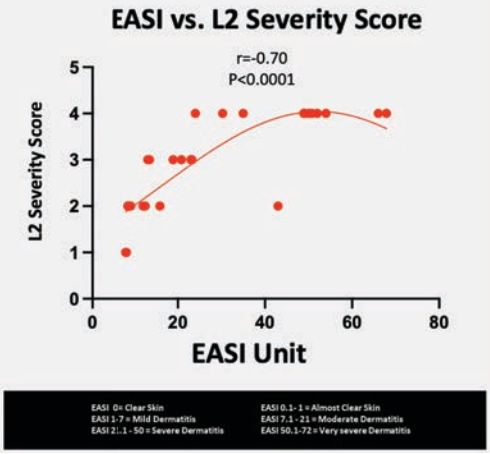


Figure 128- Scatter plot of the correlation between the EASI levels and 2 severity score in patients with severe Dermatitis.

ii) L3-L5 (Lumbar segments L3-L5) Severity Score Analysis

The scatter mean-plot of the severity score of the L3-L5 region is presented in Figure 129. There is a significant difference (P<0.0001) between the L3-L5 severity score between groups A and B (Figure 129). However, there was no correlation between the L3-L5 severity score and the EASI level (r=0.43) (Figure 130).

Table Analyzed	Treatment Group
	L3-5 Severity Sc.
Column B	Group B
vs.	vs.
Column A	Group A
Mann Whitney test	
P value	<0.0001
Exact or approximate P value?	Exact
P value summary	****
Significantly different (P < 0.05)?	Yes
One- or two-tailed P value?	Two-tailed
Sum of ranks in column A,B	337 , 989
Mann-Whitney U	84
Difference between medians	
Median of column A	44.00, n=22
Median of column B	63.40, n=29
Difference: Actual	19.40
Difference: Hodges-Lehmann	20.60

Table 64. Analytical data of Mann-Whitney test of the L3-5 severity score between two patient groups of A and B.

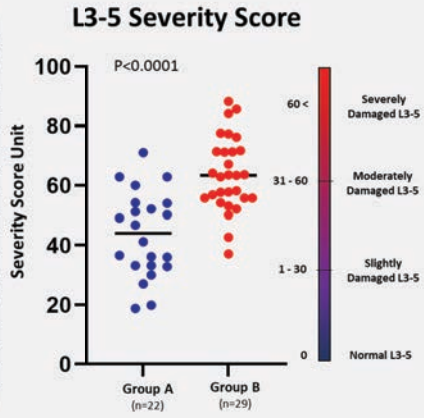


Figure 129. Scatter mean-plot of the level of the L3-5 severity score Severity score in each group of the study. Individual points,

Gaussian	Treatment Group B
Best-fit values	L3-5 Sev. Cor.
Amplitude	
Mean	3387
SD	724.2
95% CI (profile likelihood)	
Amplitude	(Very wide)
Mean	****
SD	****
Goodness of Fit	
Degrees of Freedom	26
R squared	0.4343
Sum of Squares	2430
Sy.x	9.668
Constraints	
SD	SD > 0
Number of points	
# of X values	29
# Y values analyzed	29

Table 65- Analytical data of Gaussian correlation test of the EASI levels vs. L3-5 severity score in patients with severe Dermatitis.

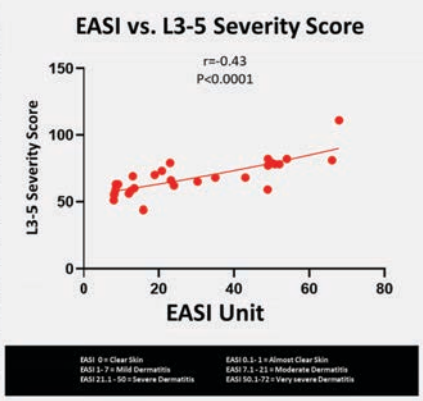


Figure 130. Scatter plot of the correlation between the EASI levels and L3-5 severity score in patients with severe Dermatitis.

B) Case Reports

According to the Netter´s Dermatome, neuron fibres initiating from the lumbar section have a direct and indirect impact on the situation of inflammatory process in the lower parts of the human body such as legs and feet (Figure 28). (225) Accordingly, data from a patient with alteration of spine in L1 and L2 is presented in Figure 131. The altered CGRP level due to the neurogenic inflammation in this patient may initiated from alteration of their spine. This fact becomes clearer by reviewing the data after the chiropractic adjustment. This example demonstrates that by correcting the condition of lumbar and thoracic spine in this patient, the level of CGRP and the level of EASI decreased and resulted to a better quality of skin, decrease in itching sensation, and of course, a better quality of life.

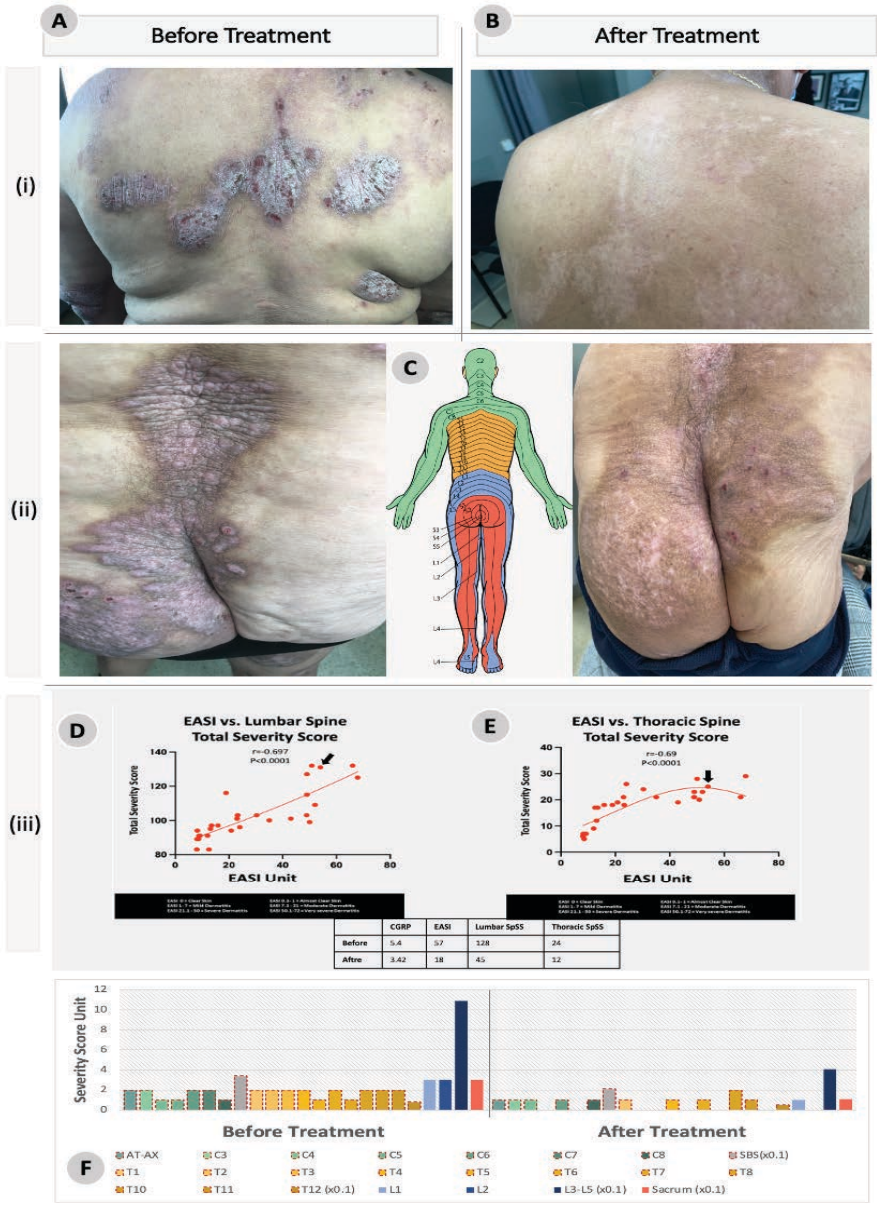


Figure 131- Case report 16: Dermatitis of the back in both upper and lower parts of the trunk, - Analytical data obtained from a patient diagnosed with dermatitis upper and lower parts of the trunk, and severe SBA in lumbar and thoracic sections, before and after the chiropractic treatment- (A) Patient's clinical picture before chiropractic treatment, and (B) a clinical picture of inflammated area after the chiropractic treatment. (C) Netter´s dermatome map indicating the area of skin provided by cutaneous divisions of a single spinal nerve, (D) Analytical graphs indicating the correlation of EASI level and the lumbar spine total SpSS and (E) correlation of EASI level and the total thoracic SpSS (F) Severity scores of different parts of the patient´s spine, before and after the chiropractic treatment.

In our study, although the results could not indicate a significant correlation between the EASI scores and SBA in lumbar spine (r= 0.697), almost all of the patients with dermatitis in legs and/or feet diagnosed with SBA in lumbar spine. In addition, chiropractic treatment in those patients provided a significant decrease in the level of EAS in patients with dermatitis of the legs and feet. (See Figure 132 and Figure 133)

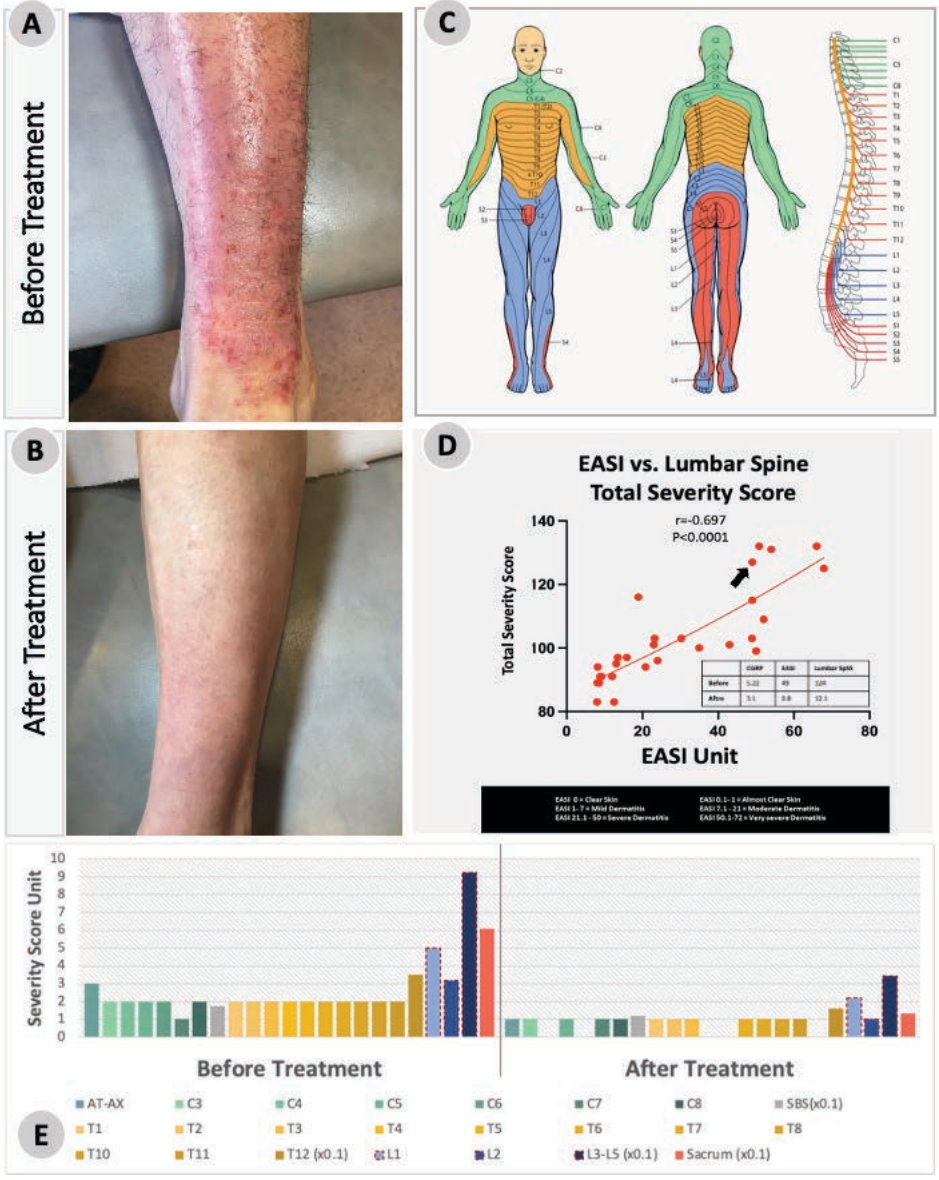


Figure 132- Case report 17: Dermatitis of the legs- Analytical data obtained from a patient diagnosed with dermatitis on the legs and severe SBA in lumbar section, before and after the chiropractic treatment- (A) Patient's clinical picture before chiropractic treatment, and (B) a clinical picture of inflammated area after the chiropractic treatment. (C) Netter´s dermatome map indicating the area of skin provided by cutaneous divisions of a single spinal nerve, (D) Analytical graph indicating the correlation of EASI level and the total lumbar SpSS, and (E) Severity scores of different parts of the patient´s spine, before and after the chiropractic treatment.

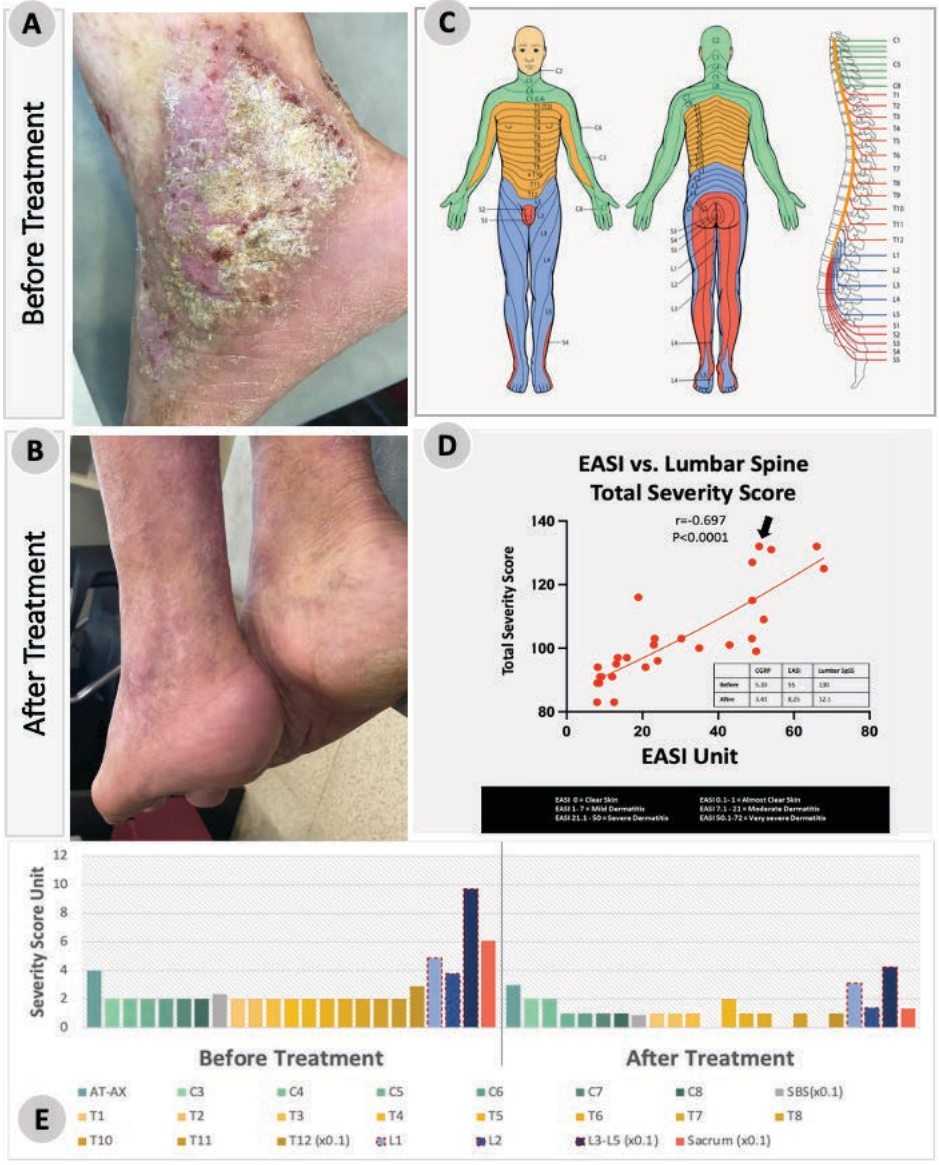


Figure 133- Case report 18: Dermatitis of the feet- Analytical data obtained from a patient diagnosed with dermatitis on the feet and severe SBA in lumbar section, before and after the chiropractic treatment- (A) Patient's clinical picture before chiropractic treatment, and (B) a clinical picture of inflammated area after the chiropractic treatment. (C) Netter´s dermatome map indicating the area of skin provided by cutaneous divisions of a single spinal nerve, (D) Analytical graph indicating the correlation of EASI level and the total lumbar SpSS, and (E) Severity scores of different parts of the patient´s spine, before and after the chiropractic treatment.

4.2.5 Sacral and Coccyx

A) Analytical Data

The sacrum and coccyx (S-C) are different from other parts of human spine 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.

Results gathered from analyzing the S-C severity score, showed a significant difference (P<0.0001) in between two groups of A and B but (Figure 134), the correlation between this variable and EASI level was not significant (r=0.61). (Figure 135)

Table Analyzed	Treatment Group
	S-C Severity Score
Column B	Group B
vs.	vs.
Column A	Group A
Mann Whitney test	
P value	<0.0001
Exact or approximate P value?	Exact
P value summary	****
Significantly different (P < 0.05)?	Yes
One- or two-tailed P value?	Two-tailed
Sum of ranks in column A,B	325.5 , 949.5
Mann-Whitney U	94.50
Difference between medians	
Median of column A	55.00, n=22
Median of column B	66.00, n=29
Difference: Actual	11.00
Difference: Hodges-Lehmann	13.80

Table 66. Analytical data of Mann-Whitney test of the S-C severity score between two patient groups of A and B.

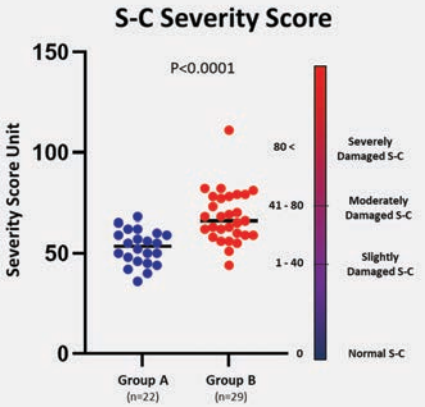


Figure 134. Scatter mean-plot of the level of the S-C severity score Severity score in each group of the study.

Gaussian	Treatment Group B
Best-fit values	S-C Sev. Cor.
Amplitude	183668
Mean	2151
SD	533.5
95% CI (profile likelihood)	
Amplitude	****
Mean	****
SD	****
Goodness of Fit	
Degrees of Freedom	26
R squared	0.6129
Sum of Squares	1837
Sy.x	8.406
Constraints	
SD	SD > 0
Number of points	
# of X values	29
# Y values analyzed	29

Table 67. Analytical data of Gaussian correlation test of the EASI levels vs. S-C SBA severity score in patients with severe Dermatitis.

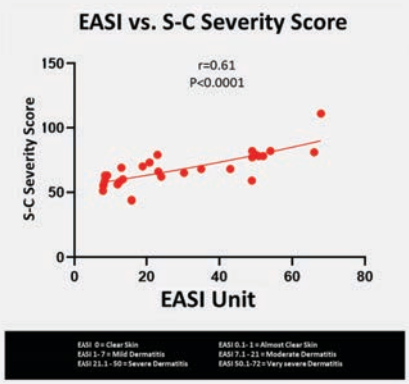


Figure 135. Scatter plot of the correlation between the EASI levels and S-C SBA severity score in patients with severe Dermatitis.

B) Case reports

In Figure 136, Figure 137, and Figure 138 for example, show the manifestation of dermatitis in the anus, vulva, penis, and penis scrotum.

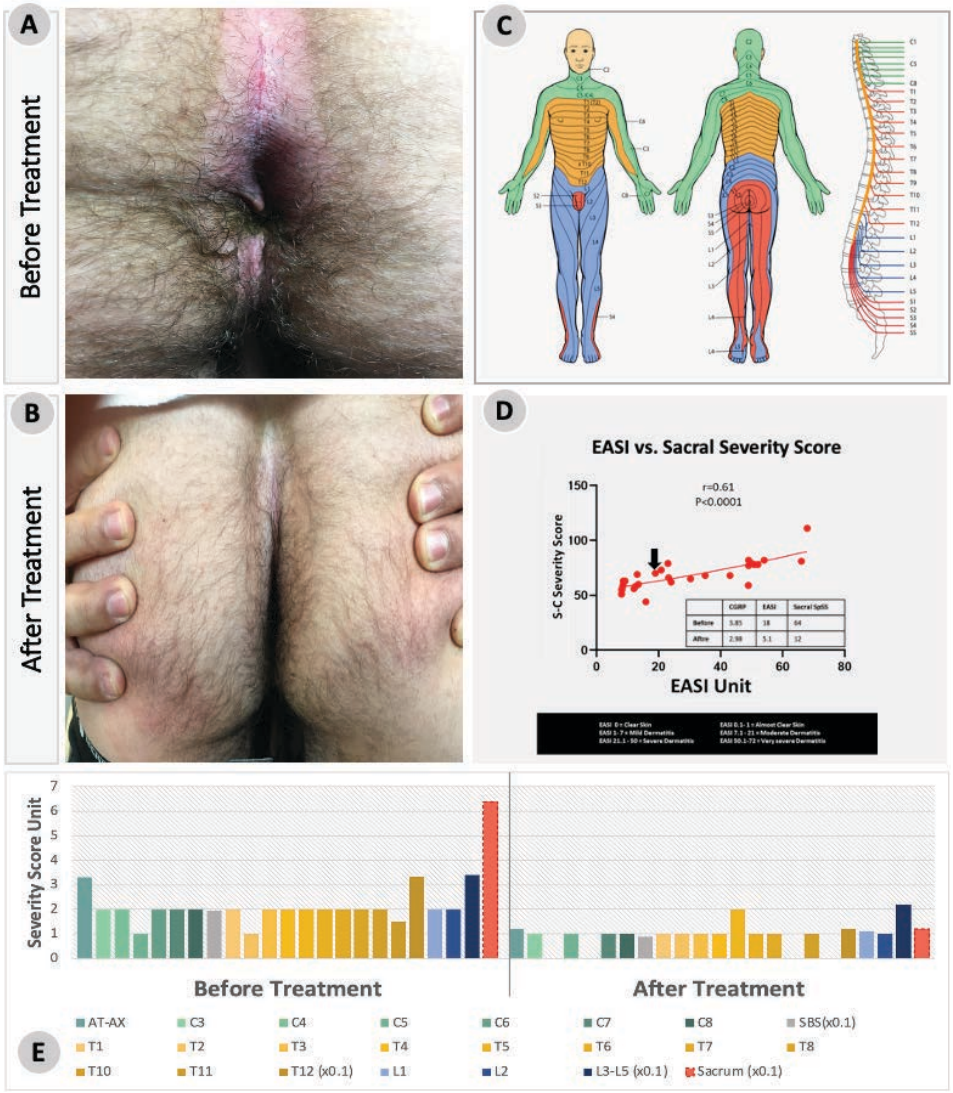


Figure 136- Case report 19: Dermatitis of the anus- Analytical data obtained from a patient diagnosed with dermatitis on the anus and severe SBA in the sacral section, before and after the chiropractic treatment- (A) Patient's clinical picture before chiropractic treatment, and (B) a clinical picture of inflammated area after the chiropractic treatment. (C) Netter´s dermatome map indicating the area of skin provided by cutaneous divisions of a single spinal nerve, (D) Analytical graph indicating the correlation of EASI level and the total sacral SpSS, and (E) Severity scores of different parts of the patient´s spine, before and after the chiropractic treatment.

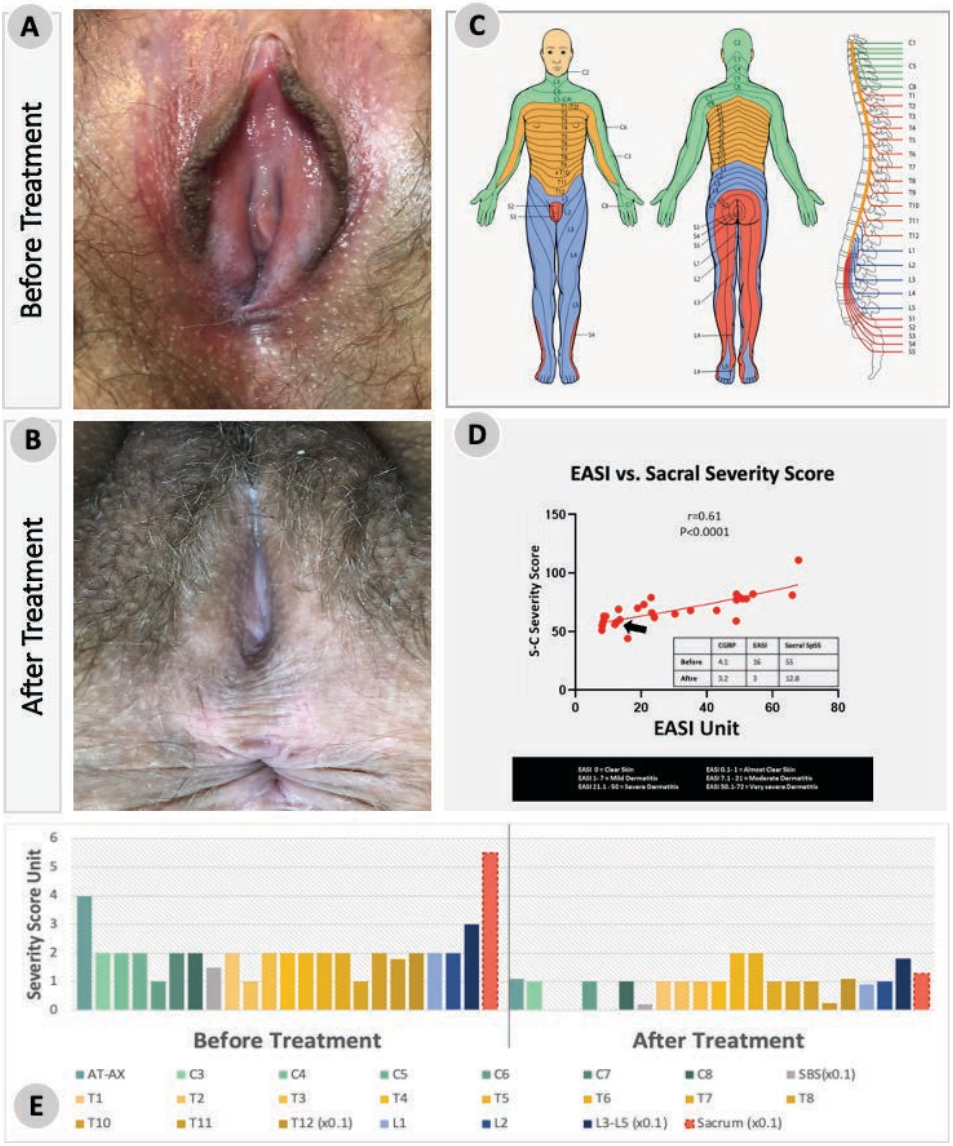


Figure 137- Case report 20: Dermatitis of the vulva (vulvitis)- Analytical data obtained from a patient diagnosed with vulvitis and severe SBA in the sacral section, before and after the chiropractic treatment- (A) Patient's clinical picture before chiropractic treatment, and (B) a clinical picture of inflammated area after the chiropractic treatment. (C) Netter´s dermatome map indicating the area of skin provided by cutaneous divisions of a single spinal nerve, (D) Analytical graph indicating the correlation of EASI level and the total sacral SpSS, and (E) Severity scores of different parts of the patient´s spine, before and after the chiropractic treatment.

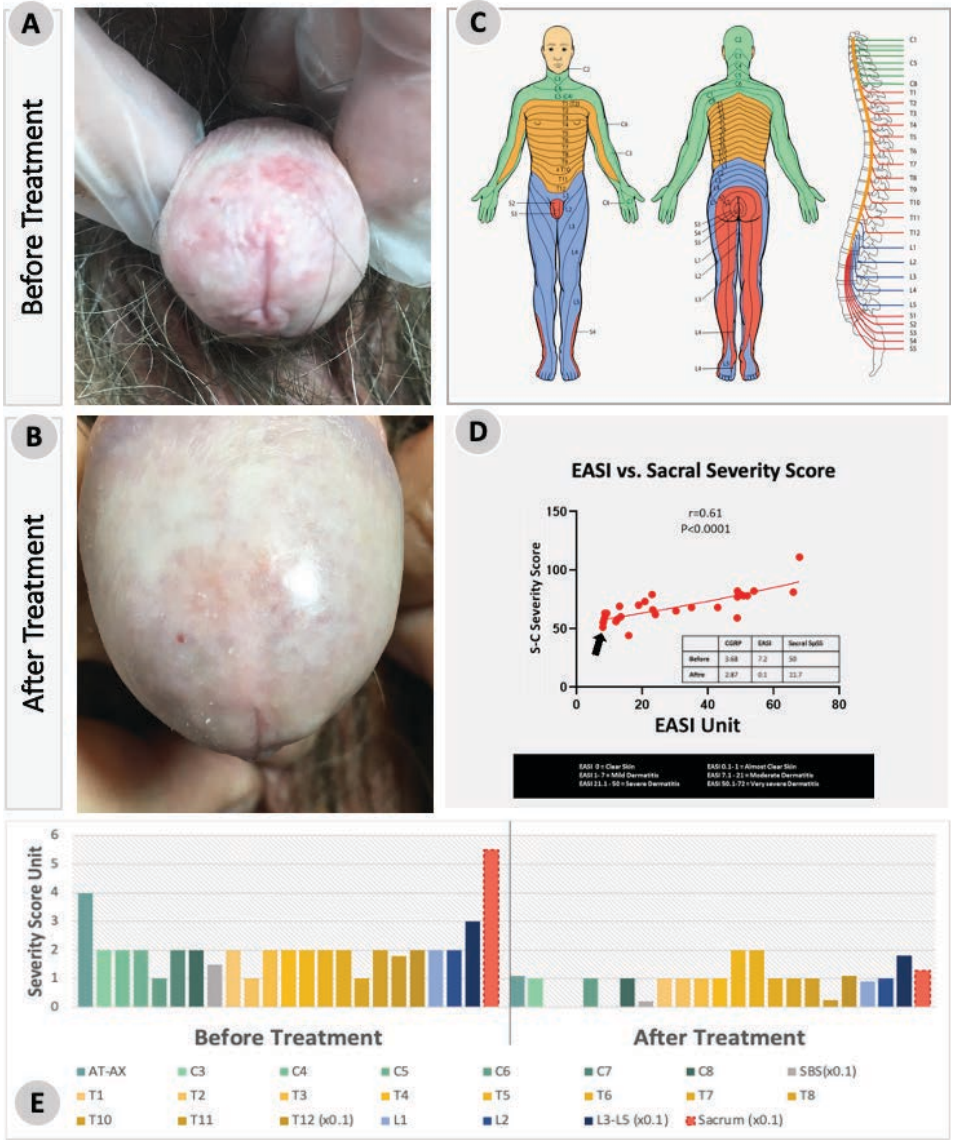


Figure 138- Case report 21: Dermatitis of the penis- Analytical data obtained from a patient diagnosed with dermatitis on the penis and severe SBA in the sacral section, before and after the chiropractic treatment- (A) Patient's clinical picture before chiropractic treatment, and (B) a clinical picture of inflammated area after the chiropractic treatment. (C) Netter´s dermatome map indicating the area of skin provided by cutaneous divisions of a single spinal nerve, (D) Analytical graph indicating the correlation of EASI level and the total sacral SpSS, and (E) Severity scores of different parts of the patient´s spine, before and after the chiropractic treatment.

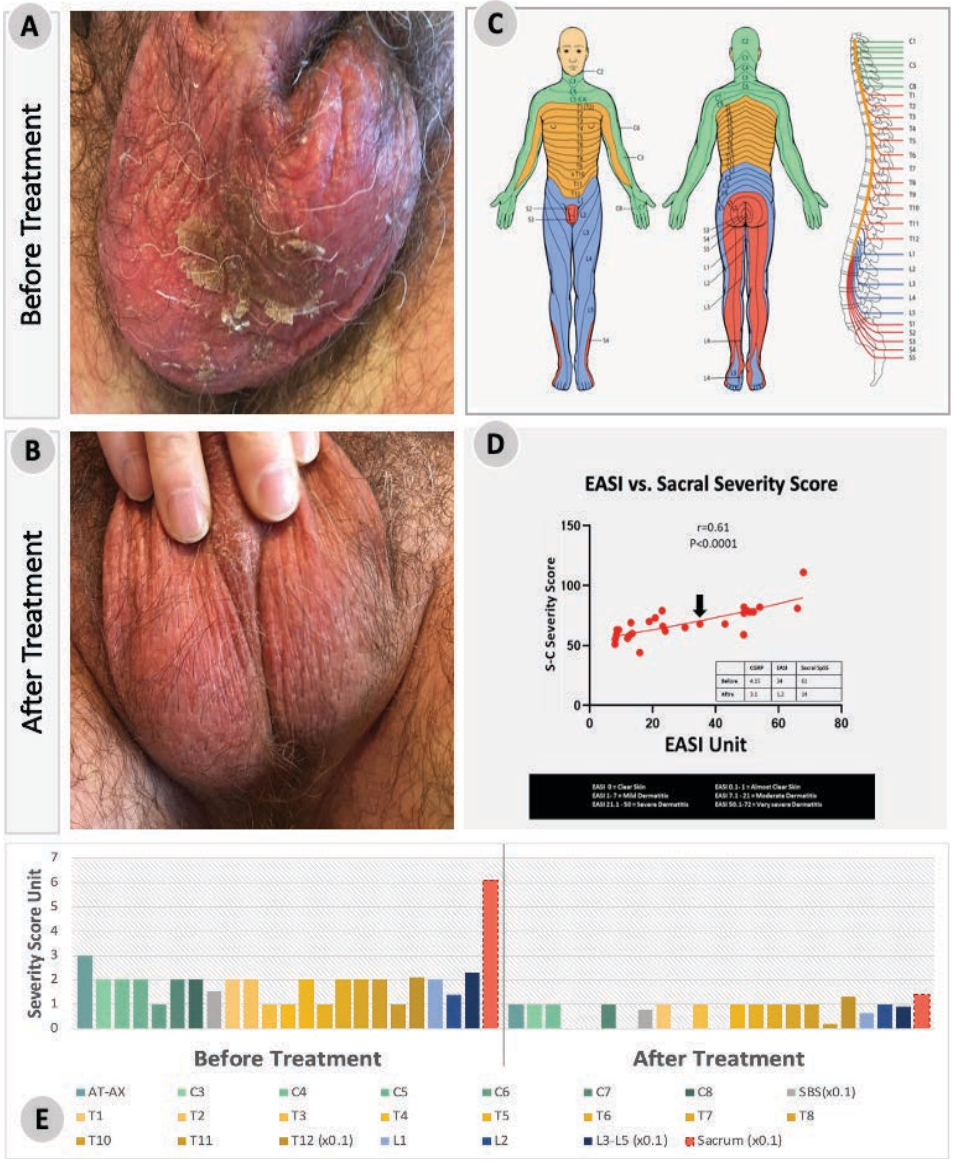


Figure 139- Case report 22: Dermatitis of the scrotum- Analytical data obtained from a patient diagnosed with dermatitis in the scritum and severe SBA in the sacral section, before and after the chiropractic treatment- (A) Patient's clinical picture before chiropractic treatment, and (B) a clinical picture of inflammated area after the chiropractic treatment. (C) Netter´s dermatome map indicating the area of skin provided by cutaneous divisions of a single spinal nerve, (D) Analytical graph indicating the correlation of EASI level and the total sacral SpSS, and (E) Severity scores of different parts of the patient´s spine, before and after the chiropractic treatment.

4.2.6 Summary of the spine severity score evaluation

The results presented above may be indicative of a correlation between the altered biomechanics of different spinal segments and the altered state of the skin.

When reviewing all the data collected from the radiographic spinal examination of the study patients, we found that the EASI levels in the patients suffering from Dermatitis were significantly correlated with SBA in the Atlas- Axis (AT- AX) (r=0.82), in the cervical spine (r=0.91), in the sagittal balance of the spine SBS (r=0.88), in Spondylolisthesis (r=0.85), in T10 (r=0.87), in L1 (r=0.81), and L2 (r=0.70).

4.3 Calcitonin Gene Related Peptide (CGRP) and Dermatitis

As we discussed earlier, pressure and strains on the vertebrae lead to SBA and subsequent inflammation, called neurogenic inflammation. [38,48,181] Neurogenic inflammation is a local inflammatory response characterized by enhanced vascular absorption mast cells degranulation, and neuropeptides release. It has already been found that there are quantitative differences in the level of neuropeptides between clinically normal skin and altered cutaneous neuropeptide expression in Dermatitis patients, which contribute to the pathogenesis of the disease. [299–301]

Another question we wanted to answer in this study was: "**Is there any correlation between the level of CGRP and the severity level of Dermatitis?**"

To answer this question, the level of calcitonin gene-related peptide (CGRP) in patients suffering from Dermatitis has been analyzed following the first visit of the dermatologist (before any treatments).

As shown in Figure 140, there was a significant difference (P<0.0001) in the level of CGRP between the two groups of patients, A and B (with high and respectively mild dermatitis) EASI scores.

	Treatment Group
Table Analyzed	CGRP First Visit
Column B	Group B
vs.	vs.
Column A	Group A
Mann Whitney test	
P value	<0.0001
Exact or approximate P value?	Exact
P value summary	****
Significantly different (P < 0.05)?	Yes
One- or two-tailed P value?	Two-tailed
Sum of ranks in column A,B	233.5 , 1093
Mann-Whitney U	2.500
Difference between medians	
Median of column A	3.100, n=22
Median of column B	4.500, n=29
Difference: Actual	1.400
Difference: Hodges-Lehmann	1.200

Table 68- Analytical data of Mann-Whitney test of the CGRP between two groups of A and B.

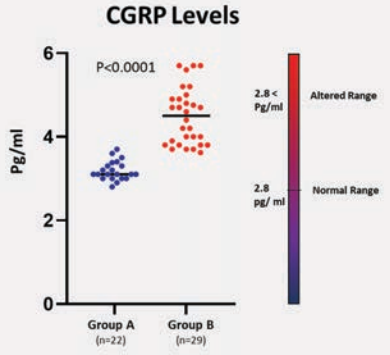


Figure 140- Scatter plot of the patient's CGRP level in each subgroup of the treatment group.

4.3.1 Correlation of the CGRP levels and EASI Scores

Analyzing the CGRP levels and EASI scores showed a strong correlation between the plasma CGRP level in the of patients with high EASI score. (r=0.83) (Figure 141).

	CGRP
Gaussian	
Best-fit values	
Amplitude	6.358
Mean	123.3
SD	115.4
95% CI (profile likelihood)	
Amplitude	5.269
Mean	62.49
SD	65.19
Goodness of Fit	
Degrees of Freedom	26
R squared	0.8308
Sum of Squares	2.129
Sy.x	0.2862
Constraints	
SD	SD > 0
Number of points	
# of X values	29
# Y values analyzed	29

Table 69- Analytical data of Gaussian correlation test of the EASI levels vs. CGRP levels in patients with severe Dermatitis.

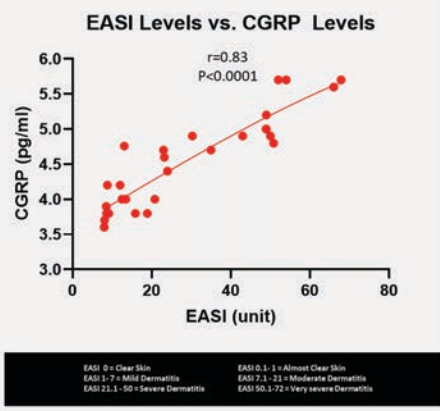


Figure 141- Scatter plot of the correlation between the EASI levels and CGRP levels in patients with severe Dermatitis.

4.3.2 Correlation of the CGRP levels and Spine Severity Scores

The correlation of CGRP levels with spine severity scores is shown in Figure 142. The Gaussian test between these two factors showed a good correlation between the plasma CGRP level and spinal biomechanical alterations (SBA) severity score (r=0.70).

	Group B
Gaussian	CGRP Vs. Spine Scores
Best-fit values	
Amplitude	41282
Mean	40.44
SD	9.622
95% CI (profile likelihood)	
Amplitude	****
Mean	****
SD	****
Goodness of Fit	
Degrees of Freedom	26
R squared	0.7075
Sum of Squares	2428
Sy.x	9.664
Constraints	
SD	SD > 0
Number of points	
# of X values	29
# Y values analyzed	29

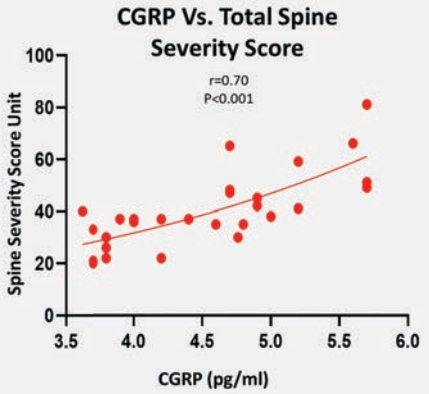


Table 70. Analytical data of Gaussian correlation test of the CGRP levels versus Spine Total severity score in patients with severe Dermatitis.

Figure 142. Scatter plot of the correlation between the CGRP levels versus Spine Total severity score in patients with severe Dermatitis.

Previously, in section 5.2 we showed that the spinal biomechanical alterations (SBA) in some areas correlated with the EASI score (AT-AX, Cervical Spine, SBS, and the Thoracic 10). This time, we examined those parts against CGRP levels to see if there is any correlation between the level of CGRP and spine severity score in those areas.

The results presented in Figure 143 demonstrate a good correlation (r=0.70) between the level of AT-AX severity score and the level of CGRP in patients with severe Dermatitis.

	Group B
Gaussian	CGRP Vs. AT- AX
Best-fit values	
Amplitude	3.931
Mean	5.524
SD	1.016
95% CI (profile likelihood)	
Amplitude	3.298 to 6.900
Mean	5.181 to 7.662
SD	0.7319 to 2.106
Goodness of Fit	
Degrees of Freedom	26
R squared	0.6768
Sum of Squares	19.33
Sy.x	0.8622
Constraints	
SD	SD > 0
Number of points	
# of X values	29
# Y values analyzed	29

Table 71. Analytical data of Gaussian correlation test of the CGRP levels versus AT-AX severity score in patients with severe Dermatitis.

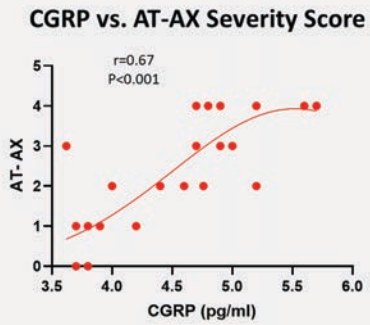


Figure 143. Scatter plot of the correlation between the CGRP levels versus AT-AX severity score in patients with severe Dermatitis.

In addition, as presented in Figure 144, there is good correlation between the cervical spine total severity score and the plasma CGRP level.

	Group B
Gaussian	CGRP vs Cervical Sp. Total
Best-fit values	
Amplitude	5.933
Mean	5.391
SD	0.9318
95% CI (profile likelihood)	
Amplitude	5.339 to 6.555
Mean	5.201 to 5.773
SD	0.7679 to 1.219
Goodness of Fit	
Degrees of Freedom	26
R squared	0.8395
Sum of Squares	18.81
Sy.x	0.8506
Constraints	
SD	SD > 0
Number of points	
# of X values	29
# Y values analyzed	29

Table 72. Analytical data of Gaussian correlation test of the CGRP levels versus Cervical Spine Total severity score in patients with severe Dermatitis.

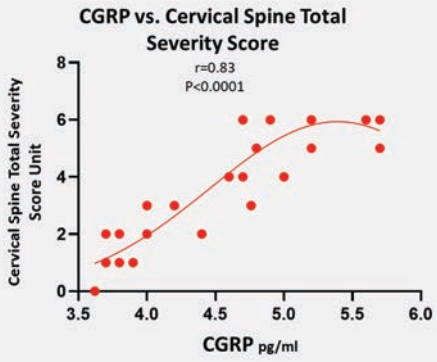


Figure 144. Scatter plot of the correlation between the CGRP levels versus Cervical Spine Total severity score in patients with severe Dermatitis.

The results of the correlation test between the plasma CGRP level and SBS (Sagittal Spinal Balance) severity score is presented in Figure145 and indicates a good correlation (r=0.74) between the CGRP level and the SBS severity scores in patients with severe Dermatitis.

Gaussian	Group B
Best-fit values	CGRP vs. Spondylolisthesis Severity Score
Amplitude	4,081
Mean	5,410
SD	1,424
95% CI (profile likelihood)	
Amplitude	3,823 to 4,425
Mean	5,156 to 6,040
SD	1,167 to 1,967
Goodness of Fit	
Degrees of Freedom	26
R squared	0,8188
Sum of Squares	4,111
Sy.x	0,3977
Constraints	
SD	SD > 0
Number of points	
# of X values	29
# Y values analyzed	29

Table 73 - Analytical data of Gaussian correlation test of the CGRP levels versus Spondylolisthesis severity score in patients with severe Dermatitis.

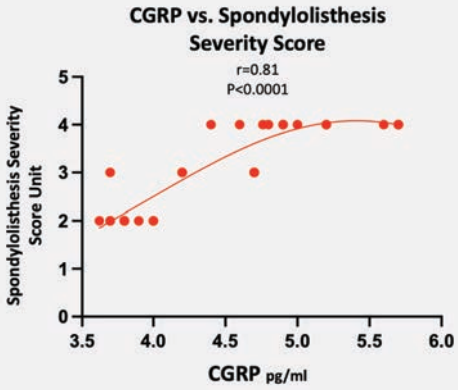


Figure 145 - Scatter plot of the correlation between the CGRP levels versus Spondylolisthesis severity score in patients with severe Dermatitis.

The results of the correlation test between the level of CGRP and SBS severity score is presented in Figure 146, and it is indicating a good correlation (r=0.74) between the level of CGRP and the level of SBS severity scores in patients with severe Dermatitis.

	Group B
Gaussian	CGRP vs SBS
Best-fit values	
Amplitude	63.45
Mean	5.688
SD	0.8536
95% CI (profile likelihood)	
Amplitude	51.66 to 196.8
Mean	5.352 to 8.467
SD	0.5652 to 1.943
Goodness of Fit	
Degrees of Freedom	26
R squared	0.7460
Sum of Squares	4526
Sy.x	13.19
Constraints	
SD	SD > 0
Number of points	
# of X values	29
# Y values analyzed	29

Table 74. Analytical data of Gaussian correlation test of the CGRP levels versus SBS severity score in patients with severe Dermatitis.

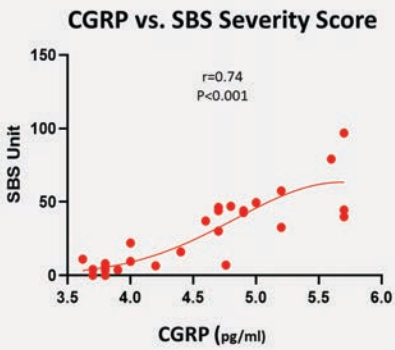


Figure 146. Scatter plot of the correlation between the CGRP levels versus SBS severity score in patients with severe Dermatitis.

Similarly, there is a good correlation (r=0.70) between the level of CGRP and Thoracic 10 (T10) severity score, presented in Figure 147.

	Group B
Gaussian	CGRP vs T10
Best-fit values	
Amplitude	13.91
Mean	8.007
SD	2.195
95% CI (profile likelihood)	
Amplitude	
Mean	5.618
SD	1.072
Goodness of Fit	
Degrees of Freedom	26
R squared	0.7076
Sum of Squares	46.24
Sy.x	1.334
Constraints	
SD	SD > 0
Number of points	
# of X values	29
# Y values analyzed	29

Table 75- Analytical data of Gaussian correlation test of the CGRP levels versus T10 severity score in patients with severe Dermatitis.

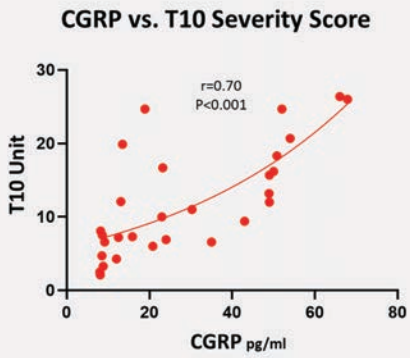


Figure 147- Scatter plot of the correlation between the CGRP levels versus T10 severity score in patients with severe Dermatitis.

In addition, the non-linear Gaussian test indicates a meaningful correlation (r= 0.71) between CGRP levels and Lumbar 1 severity scores. (See Figure 148)

Gaussian	
Best-fit values	
Amplitude	7,004
Mean	5,905
SD	1,493
95% CI (profile likelihood)	
Amplitude	5,946
Mean	5,307
SD	1,039
Goodness of Fit	
Degrees of Freedom	26
R squared	0,7162
Sum of Squares	30,38
Sy.x	1,081
Constraints	
SD	SD > 0
Number of points	
# of X values	29
# Y values analyzed	29

Table 76 - Analytical data of Gaussian correlation test of the CGRP levels versus Lumbar 1 severity score in patients with severe Dermatitis.

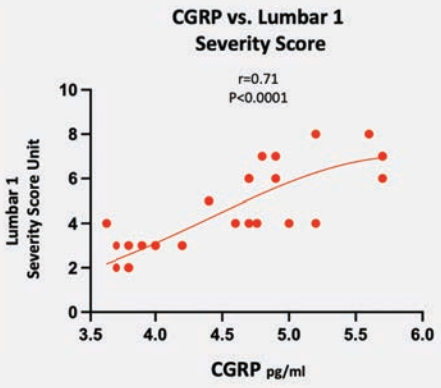


Figure 148- Scatter plot of the correlation between the CGRP levels versus Lumbar 1 severity score in patients with severe Dermatitis.

As well as Lumbar 1, analysis of the data obtained from Lumbar 2 presents a meaningful correlation (r= 0.74) with the level of CGRP in patients with severe Dermatitis. (See Figure 149)

Gaussian	
Best-fit values	
Amplitude	4,045
Mean	5,377
SD	1,295
95% CI (profile likelihood)	
Amplitude	3,693 to 4,545
Mean	5,099 to 6,196
SD	1,030 to 1,947
Goodness of Fit	
Degrees of Freedom	26
R squared	0,7473
Sum of Squares	7,825
Sy.x	0,5486
Constraints	
SD	SD > 0
Number of points	
# of X values	29
# Y values analyzed	29

Table 77 - Analytical data of Gaussian correlation test of the CGRP levels versus Lumbar 2 severity score in patients with severe Dermatitis.

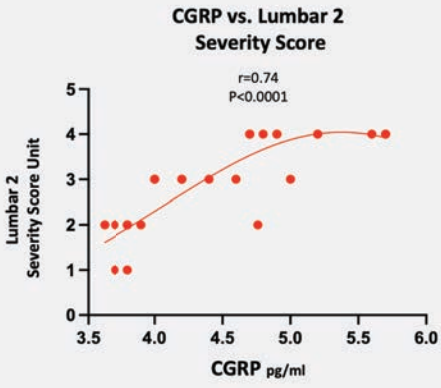


Figure 149- Scatter plot of the correlation between the CGRP levels versus Lumbar 2 severity score in patients with severe Dermatitis.

Overall, when reviewing all the data obtained from the study patients and summarizing them in graphs, we observed that the improvement in the plasma CGRP level correlates with the improvement in the EASI level and the improvement in the SBA severity score.
It suggests that spinal biomechanical alterations (SBA) may contribute to the release of neuropeptides, including CGRP, from sensory nerves endings. Increase of plasma CGRP results in neurogenic inflammation of the skin and contributes to dermatological disorders such as dermatitis.

4.3 The control group of patients receiving only pharmacological treatment

A) Analytical Data

To determine the role of this chiropractic treatment we used a control group of 22 patients (Group C) suffering from dermatitis that they only received the same pharmacological treatment consisting of the compound cream. However, they did not undertake chiropractic treatment. The same as the treatment group, analysis of the CGRP, the EASI level, and the spine severity score have been carried out.
In order to determine if the patients in control group can be used, first we compare both groups (treatment group and control group) in different aspects such as spine severity score, EASI and CGRP levels. As presented in Figure 150 to Figure 152, there is no significant differences between the levels of spine severity score, EASI, and CGRP in the two groups. These figures indicate to us that the two groups are similar and can be used to evaluate the chiropractic treatment.

	Treatment G vs. Control G
Table Analyzed	Spine Severity Score
Column B	Control Group
vs.	vs.
Column A	Treatment Group
Mann Whitney test	
P value	0.5931
Exact or approximate P value?	Exact
P value summary	ns
Significantly different (P < 0.05)?	No
One- or two-tailed P value?	Two-tailed
Sum of ranks in column A,B	1721 , 835.5
Mann-Whitney U	495.5
Difference between medians	
Median of column A	30.00, n=49
Median of column B	28.00, n=22
Difference: Actual	-2.000
Difference: Hodges-Lehmann	2.000

Table 78. Analytical data of Mann-Whitney test of the spine severity scores between two groups of treatment and control.

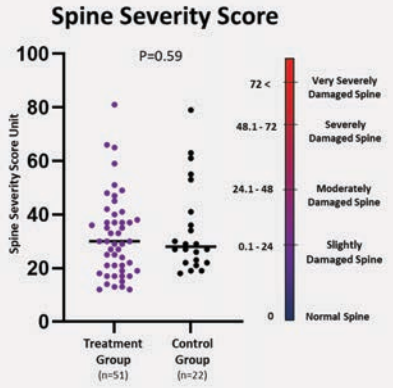


Figure 150. Scatter plot of the patient's spine severity score in the treatment and control group.

	Treatment G vs. Control G
Table Analyzed	EASI Levels
Column B	Control Group
vs.	vs.
Column A	Treatment Group
Mann Whitney test	
P value	0.9453
Exact or approximate P value?	Exact
P value summary	ns
Significantly different (P < 0.05)?	No
One- or two-tailed P value?	Two-tailed
Sum of ranks in column A,B	1881 , 820
Mann-Whitney U	555
Difference between medians	
Median of column A	13.10, n=51
Median of column B	14.60, n=22
Difference: Actual	1.500
Difference: Hodges-Lehmann	0.2000

Table 79. Analytical data of Mann-Whitney test of the EASI levels between two groups of treatment and control.

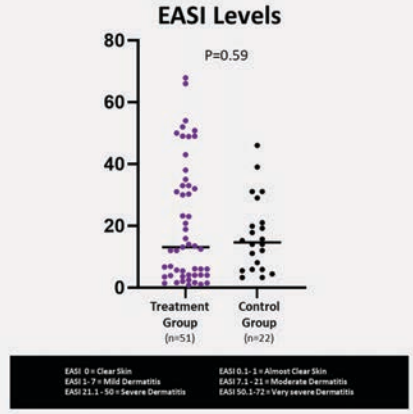


Figure 151. Scatter plot of the patient's EASI levels in the treatment and control group.

	Treatment G vs. Control G
Table Analyzed	CGRP Tret vs Contr
Column B	CGRP Control Before
vs.	vs.
Column A	CGRP Treatment Before
Mann Whitney test	
P value	0.6434
Exact or approximate P value?	Exact
P value summary	ns
Significantly different (P < 0.05)?	No
One- or two-tailed P value?	Two-tailed
Sum of ranks in column A,B	1926 , 775
Mann-Whitney U	522
Difference between medians	
Median of column A	3.800, n=51
Median of column B	3.615, n=22
Difference: Actual	-0.1850
Difference: Hodges-Lehmann	-0.08500

Table 80. Analytical data of Mann-Whitney test of the CGRP levels between two groups of treatment and control.

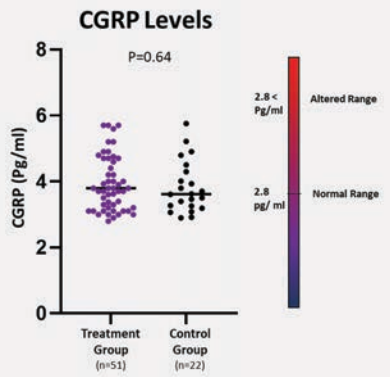


Figure 152. Scatter plot of the patient's CGRP levels in the treatment and control group.

Therefore, in none of the mentioned aspects (Spine severity score, EASI or CGRP) there were no significant differences between patients in treatment group and the control group.

4.3.2 Evaluation of the CGRP levels in the control group (Group C)

The level of CGRP has been evaluated before and after the pharmacological treatment for the control group. Figure 153 clearly shows that there is no significant difference (P=0.53) between the level of CGRP before and after the usage of the pharmacological treatment.

	Group C
Table Analyzed	CGRP before aft Cream
Column B	After
vs.	vs.
Column A	Before
Mann Whitney test	
P value	0.5337
Exact or approximate P value?	Exact
P value summary	ns
Significantly different (P < 0.05)?	No
One- or two-tailed P value?	Two-tailed
Sum of ranks in column A,B	522 , 468
Mann-Whitney U	215
Difference between medians	
Median of column A	3.615, n=22
Median of column B	3.400, n=22
Difference: Actual	-0.2150
Difference: Hodges-Lehmann	-0.1100

Table 81. Analytical data of Mann-Whitney test of the CGRP before using the cream and 3 months after using the cream in the control group.

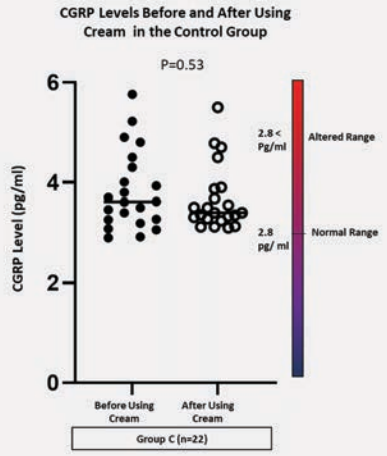


Figure 153. Scatter plot of the patient's CGRP level in the control group, before using the cream and 3 months after using the cream.

4.3.2 Evaluation of EASI levels in the control group (Group C)

After using the compound cream (as the usual treatment for Dermatitis) for two weeks, all patients in the control group (group C) improve their symptomatology of Dermatitis and they become cured. As shown in Figure 154, the level of EASI in patients of this control group decreases after 2 weeks of using the cream (as it prescribes for 2 weeks). However, after 3 months, the initial symptomatology returned and the levels of EASI were similar to the ones at the beginning, before any treatment.

A

	Control Group
Table Analyzed	EASI Before vs EASI After
Column B	EASI After 3 months
vs.	vs.
Column A	EASI Before Treatment
Mann Whitney test	
P value	0.4528
Exact or approximate P value?	Exact
P value summary	ns
Significantly different (P < 0.05)?	No
One- or two-tailed P value?	Two-tailed
Sum of ranks in column A,B	527.5 , 462.5
Mann-Whitney U	209.5
Difference between medians	
Median of column A	14.60, n=22
Median of column B	11.15, n=22
Difference: Actual	-3.450
Difference: Hodges-Lehmann	-1.900

B

	Control Group
Table Analyzed	EASI Before vs After 2 Weeks
Column B	EASI After 2 weeks
vs.	vs.
Column A	EASI Before
Mann Whitney test	
P value	0.0057
Exact or approximate P value?	Exact
P value summary	**
Significantly different (P < 0.05)?	Yes
One- or two-tailed P value?	Two-tailed
Sum of ranks in column A,B	611 , 379
Mann-Whitney U	126
Difference between medians	
Median of column A	14.60, n=22
Median of column B	6.800, n=22
Difference: Actual	-7.800
Difference: Hodges-Lehmann	-7.500

C

	Control Group
Table Analyzed	2 Weeks vs 3 Months
Column B	EASI After 3 months
vs.	vs.
Column A	EASI After 2 weeks
Mann Whitney test	
P value	0.0228
Exact or approximate P value?	Exact
P value summary	*
Significantly different (P < 0.05)?	Yes
One- or two-tailed P value?	Two-tailed
Sum of ranks in column A,B	398.5 , 591.5
Mann-Whitney U	145.5
Difference between medians	
Median of column A	6.800, n=22
Median of column B	11.15, n=22
Difference: Actual	4.350
Difference: Hodges-Lehmann	3.750

Table 82- Analytical data of Mann-Whitney test of the EASI levels before treatment versus EASI levels after 3 months (A), before treatment versus EASI levels after 2 weeks (B), after 2 weeks versus after 3 months (C) in the control group

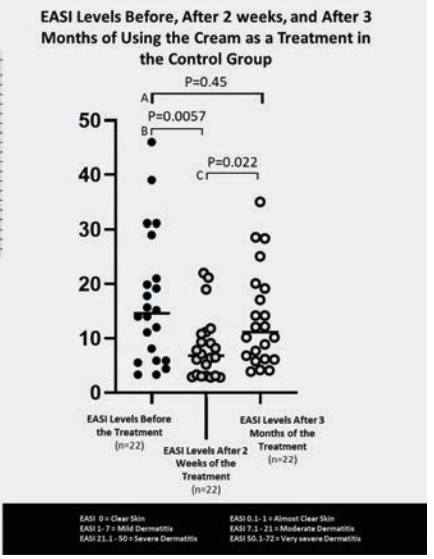


Figure 154. Scatter plot of the patient's EASI level in the control group, before treatment, after 2 weeks, and after 3 months in the control group.

4.4 Results of the TG (Treatment Group) - Group of patients treated with chiropractic STM)

The results of the treatment group TG (n=51), who beside using the topical cream, underwent chiropractic treatment, indicate a significant difference between EASI level before and after the chiropractic STM, after 3 months. (Figure 155).

	Treatment Group
Table Analyzed	EASI Before vs EASI After
Column B	EASI After
vs.	vs.
Column A	EASI Before
Mann Whitney test	
P value	<0.0001
Exact or approximate P value?	Exact
P value summary	****
Significantly different (P < 0.05)?	Yes
One- or two-tailed P value?	Two-tailed
Sum of ranks in column A,B	3591 , 1662
Mann-Whitney U	336
Difference between medians	
Median of column A	7.400, n=51
Median of column B	1.000, n=51
Difference: Actual	-6.400
Difference: Hodges-Lehmann	-6.200

Table 83- Analytical data of Mann-Whitney test of the EASI levels before chiropractic treatment versus CGRP levels after chiropractic treatment in 3 months after the first visit.

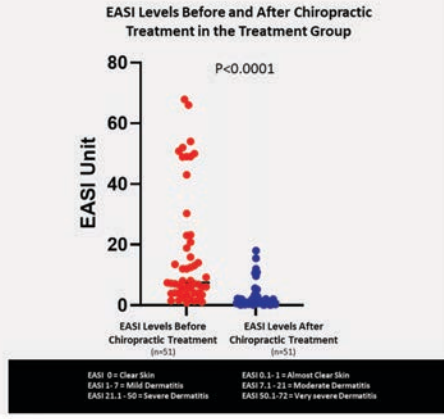


Figure 155-Scatter plot of the patient's EASI level in the treatment group, before chiropractic treatment, and after 3 months of the chiropractic treatment.

In addition, plasma CGRP level has also normalized after the chiropractic treatment in the 51 patients of the treatment group (Figure 156). In more detail, we can clearly see that there is a significant difference between the level of CGRP in patients before and after the chiropractic treatment (See Figure157).

	Treatment Group
Table Analyzed	CGRP Before/ After Chiropractic treatment
Column B	CGRP After
vs.	vs.
Column A	CGRP Before
Mann Whitney test	
P value	<0.0001
Exact or approximate P value?	Exact
P value summary	****
Significantly different (P < 0.05)?	Yes
One- or two-tailed P value?	Two-tailed
Sum of ranks in column A,B	3727 , 1526
Mann-Whitney U	200
Difference between medians	
Median of column A	3.800, n=51
Median of column B	2.800, n=51
Difference: Actual	-1.000
Difference: Hodges-Lehmann	-1.000

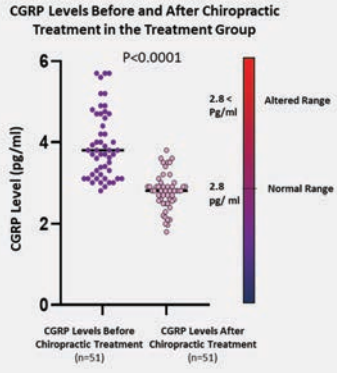


Table 84- Analytical data of Mann-Whitney test of the CGRP levels before chiropractic treatment versus CGRP levels after chiropractic treatment in 3 months after the first visit

Figure 156- Scatter plot of the patient's CGRP level in the treatment group, before chiropractic treatment, 3 months after the chiropractic treatment.

A

Table Analyzed	CGRP Group A Before/ After
Column B	After
vs.	vs.
Column A	Before
Mann Whitney test	
P value	<0.0001
Exact or approximate P value?	Exact
P value summary	****
Significantly different (P < 0.05)?	Yes
One- or two-tailed P value?	Two-tailed
Sum of ranks in column A,B	667.5 , 322.5
Mann-Whitney U	69.50
Difference between medians	
Median of column A	3.100, n=22
Median of column B	2.800, n=22
Difference: Actual	-0.3000
Difference: Hodges-Lehmann	-0.4000

B

Table Analyzed	CGRP Group B Before/ After
Column B	After
vs.	vs.
Column A	Before
Mann Whitney test	
P value	<0.0001
Exact or approximate P value?	Exact
P value summary	****
Significantly different (P < 0.05)?	Yes
One- or two-tailed P value?	Two-tailed
Sum of ranks in column A,B	1276 , 435
Mann-Whitney U	0
Difference between medians	
Median of column A	4.400, n=29
Median of column B	2.800, n=29
Difference: Actual	-1.600
Difference: Hodges-Lehmann	-1.700

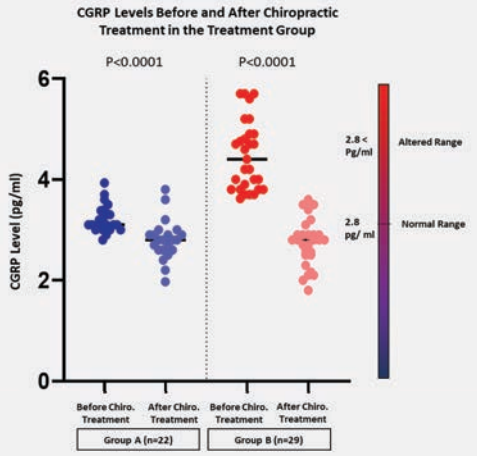


Table 85 - Analytical data of Mann-Whitney test of the CGRP levels before chiropractic treatment versus CGRP levels after chiropractic treatment in 3 months after the first visit.

Figure 157 - Scatter plot of the patient's CGRP level in group A and B, before chiropractic treatment, and 3 months after the chiropractic treatment.

Additionally, we studied the differences in EASI level and CGRP level, before and after the chiropractic treatment [(EASI/CGRP Before) - (EASI/CGRP After)]. The result showed a good correlation between changes in EASI level and changes in plasma CGRP level, before and after chiropractic STM. (Figure 158)

	CGRP/ EASI Before / Aftre Differences Correlation
Gaussian	
Best-fit values	
Amplitude	3.188
Mean	69.64
SD	42.39
95% CI (profile likelihood)	
Amplitude	2.389
Mean	40.46
SD	23.32
Goodness of Fit	
Degrees of Freedom	26
R squared	0.7049
Sum of Squares	5.336
Sy.x	0.4530
Constraints	
SD	SD > 0
Number of points	
# of X values	29
# Y values analyzed	29

Table 86- Analytical data of Gaussian correlation test of the differences of CGRP and EASI levels before and after the chiropractic treatment.

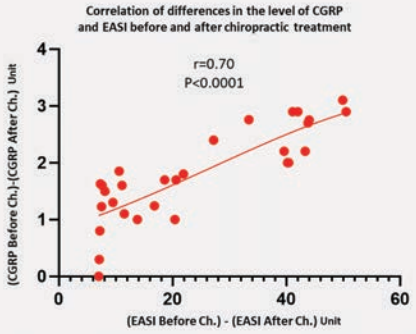
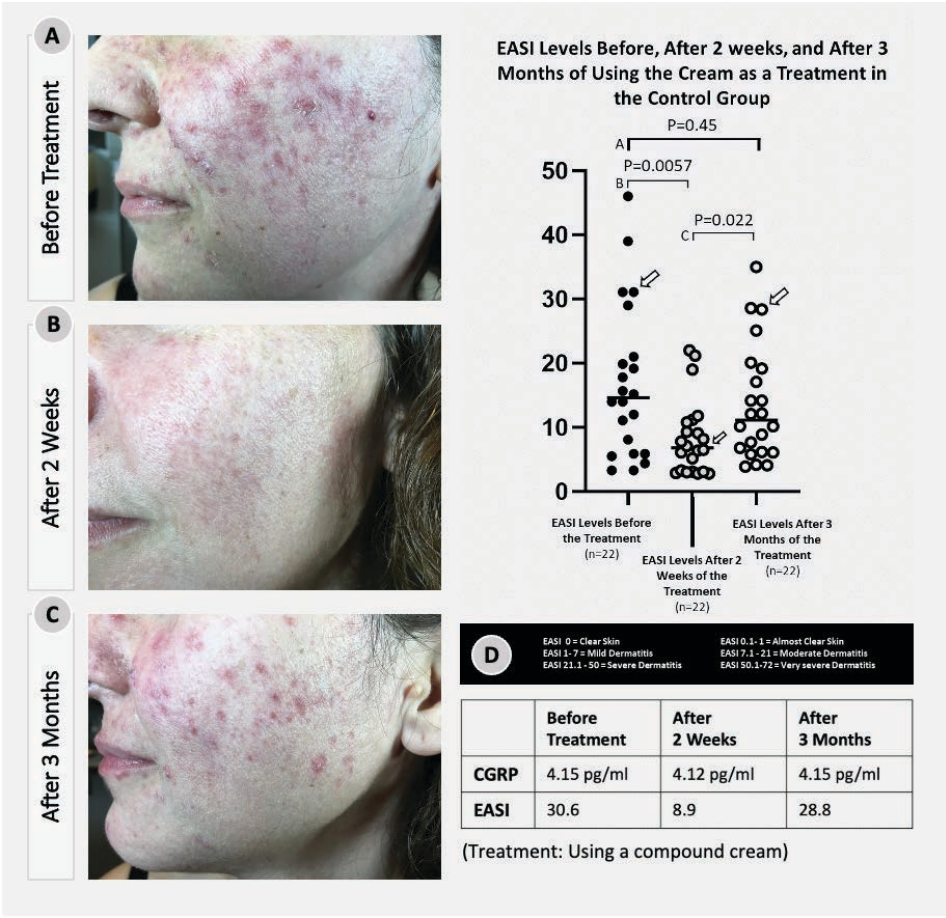


Figure 158. Scatter plot of the correlation between the differences of CGRP and EASI levels before and after the chiropractic treatment.

B) Case report

As a case report from the control group, Figure 159 shows a 31-year-old woman with dermatitis of the face. As clearly presented, although the level of EASI decreased after 2 weeks of using the compound cream, the level of CGRP did not have a significant change. Therefore, after 3 months the Dermatitis symptoms showed up again and the level of EASI increased significantly.



	Before Treatment	After 2 Weeks	After 3 Months
CGRP	4.15 pg/ml	4.12 pg/ml	4.15 pg/ml
EASI	30.6	8.9	28.8

(Treatment: Using a compound cream)

Figure 159- Case report 23: Data obtained from a 31-year-old patient of the control group presenting the situation of her skin (A) before using the compound cream, (B) after completing the use of cream-2 weeks-, and (C) after 3 months of starting the treatment. (D) CGRP and EASI level of the exact patient indicating the change of EASI after 2 weeks and 3 months.

CHAPTER 5:
DISCUSSION

This study is designed to determine the relationship between spinal biomechanical alterations and dermatitis by focusing on the level of CGRP in patients' plasma. The link between the peripheral sensory neurons irritation and neurogenic inflammatory response has been contemplated, studied, and described in many papers. [15,302–361] However, the main role player of this mechanism remains unknown. [305,332,336] The correlation of neurogenic inflammation and many other chronic diseases has been demonstrated in various studies. Itching [332–342], Asthma [15,325–331], eyes inflammation [315–324], migraine [308–314], Psoriasis [362–369], Rosacea [370–377] and Sleep Apnea [308–318,378], are some examples of them.

A. Treatment Group

In this section, we presented the data obtained from the patients in the treatment group (TG), who in underwent chiropractic treatment.

Chiropractic spinal manipulation therapy (SMT) has been shown to be an effective adjunct treatment for neurogenic-related conditions and chronic pain, such as cystitis [379–382] and migraine [383–388]. In 1999, Eldred et al. published a case study describing the surprising beneficial effect of chiropractic treatment on a patient with acute atopic eczema.[389]

In 2004, Takeda Y. and Arai S. published a large study investigating the spinal condition of 1,028 atopic dermatitis patients and bronchial asthma patients, to consider the relationship between allergic disease and spinal misalignments. They found that "vertebral misalignment is a common and characteristic finding in patients with atopic dermatitis and bronchial asthma and concluded, on behalf of their results, that chronic nerve compression, secondary to vertebral deformity (misalignment), in the

thoracic spine may have "a significant effect on the immune function of atopic dermatitis and bronchial asthma patients."[390]

Our results are consistent with their findings and support the hypothesis of our study, which focuses primarily on the role of CGRP in the production of skin inflammation in the form of dermatitis.

Below we will discuss our study results of the plasma CGRP level, EASI level and Spine Severity Score in study patients before and after treatment. By using the term 'spine severity score' we refer to the score of chronic SBA and subsequent spinal degenerating changes, detected by radiographic analysis.

5.1 CGRP Level, EASI level, and Spine Severity Score

As mentioned in section two, the main objective of this thesis was to determine if the quantification of the spinal biomechanical alterations (SBA) correlates with the quantification of the Dermatitis lesions. The results show a correlation between the severity level of Dermatitis (EASI level) and the spine severity score in patients suffering from Dermatitis. Analysis of the data in the 73 patients revealed that in most cases ($r = 0.76$) an increase in the EASI level was correlated with an increase in the severity score of the spine. This is in line with the findings of the study of Takeda et al. mentioned above. [390] In addition, a study by Han et al. published in 2015 tried to identify dermatological conditions following spinal cord injury and examined these conditions in relation to various characteristics of spinal cord injuries. They reported that 64% of patients with spinal cord injuries had dermatitis and suggested that more research might be needed in this regard. [391]

Moreover, these findings are in line with Akiyama et al. [392], Cevikbas et al. [393], and Carstens et al. [394] indicating the role of spinal neurotransmitter receptors in itching and chronic diseases such as Dermatitis.
In a recent study, Koga et al. (2020) established the potential mechanisms underlying the spinal alterations and itching in mice with Dermatitis. [395]

5.1.1 Cervical spine

In a study by Kira et al. the correlation between cervical spine disfunction in patient with Dermatitis has been reviewed. They indicated that "the preferential involvement of the cervical cord and Dermatitis appears to be closely related." [396]
Ito et al. also, indicated that there is a correlation between spinal alteration and disc degeneration in the cervical spine and dermatitis. In their study, they observed that 67% of the patients with Dermatitis, had cervical spine disfunctions and suggested that more research be done on the topic. [397]
Our study results indicated a strong correlation (r=0.81) between EASI level and cervical spine severity score.
Other studies indicated the same correlation between neurogenic inflammation of the skin and cervical spine abnormalities such as anterolisthesis of cervical spine, retrolisthesis of cervical spine, and abnormal sagittal balance of the cervical spine.
For instance, Liu et al. recently studied the impact of cervical spine on neurogenic inflammation.). In their study, they examined expression of various markers in the cervical spinal cord and indicated that the disfunction of cervical spine may result to the release of CGRP from histamine independent neurons and lead to chronic itching and dermatitis of the skin. They suggest that, by targeting CGRP dermatitis–associated

chronic pruritus, dermatitis–associated chronic pruritus can be effectively treated. [398]

Moreover, in a study by Kira et al. (370) the correlation between disfunction in cervical spine in patient with Dermatitis has been reviewed. They indicated that "the preferential involvement of the cervical cord and Dermatitis appears to be closely related.They suggested that more research be done on this topic. ." [399]

Our results demonstrate severe facial dermatitis in patients showing high SBA at the AT-AX level and in the upper cervical spine. This fact has been observed by other studies. [400–407]

For instance, a study by Park et al. demonstrated the impact of upper cervical spine on the dermatitis of the face. [408] They suggested that mechanical manipulation of the spine would be helpful in treatment of Dermatitis.

In addition, Wiles et al. highlighted the importance of AT-AX in manifestation of dermatitis in the face.[409]

(i) Upper Cervical region: Atlas– Axis (AT-AX)

By dividing the cervical spine into its subsections, we found a meaningful correlation (r=0.82) between the SBA in the upper cervical spine C1-C2 (AT- AX) and the EASI level.

Biomechanical alterations on AT-AX may result in chronic inflammations leading to chronic disease such as dermatitis. [406]

In addition, as already mentioned, association of C1 and C2 with trigeminal nerves are indicated in various studies. [230–239]

For example, in 1975, at John Hopkins University, Knox et al. [410] reported that the pressure on the greater occipital nerves may stimulate tenderness

and mimic increased pain in eye and its surrounding skin, and can lead to chronic inflammation. They also suggested that the therapy should be applied directly on posterior neck tension to decrease painful stimuli of the irritated

. Additionally, the correlation between dermatitis in scalp area and AT-AX is reported in many studies. [298,411,412]

In line with these findings, a recent study by Muehlberger T. and Rodi T. [413] indicated that the tensions in Atlas (C1), Axis (C2) and C3, affect both frontal and occipital afferents resulting to neurogenic inflammation in neck, scalp, and face.

In addition, as mentioned above, alteration of the spine in the cervical area can cause inflammation of the skin of the face.

A recent study by Sugimoto et al. they stated that "*In patients with atopic dermatitis, not only skin but also intestinal and cervical spine disorders have been recognized in many cases*."[414]

Orme et al. from New York University of Medicine, presented an interesting case report from a 48-year-old woman with carcinoma tumour of the rectum. They explained that after the patient underwent surgery to correct her cervical disc disease (due to the tumour), she began to face inflammatory and chronic diseases, including dermatitis of the face. [415]

There are many other references that report similar correlations between the cervical spine and Dermatitis of the face. [416–420]

Consistent with these findings, in our study, approximately 92% of the patients with alteration of the cervical spine were diagnosed with facial dermatitis.

In addition, recently some scientists reported the manifestation of alteration of the cervical spine in patients with ear dermatitis. [421–423]

A study by Memar et al., published in 2019, indicates that the external posterior wall of the ear canal and the auricle receive sensory innervation through branches of the C2 and C3 spinal nerves that arise between the first two vertebrae, the atlas, and the axis (AT-AX).
They suggest more studies on correlation of ear dermatitis and neurogenic inflammation. [423]

(ii) Cervical Segments C3- C8

In this study, results indicated a meaningful correlation (r= 0.81) between the EASI levels and of SBA scores in the cervical spine (C3-C8).
A similar finding was described in a recent experimental study by Liu et al. [424] They examined the peripheral and spinal pathway of itching in a mouse model and reported a higher severity of dermatitis in mice with severe cervical spine alteration. Furthermore, in 2013, Converse et al., reported the case of a 61-year-old woman suffering from a hidden cervical spinal tumour and manifestation of dermatitis on her arms. [425] Netter´s dermatome map indicates that nervous fibres from C3-C8, may directly affect the situation of epithelial cell on the chest, shoulders, arms, and hands (Figure 28).
In line with this, in our study, patients with manifestation of dermatitis in the arms and hands, demonstrated a higher SBA in C3-C8 section.

5.1.2 EASI level and Sagittal Balance of the Spine (SBS)

Treatment of abnormal sagittal balance of the spine remains a challenge for orthopaedic surgeons, neurosurgeons, and paediatrics.[426] In an abnormal SBS patient, the impact of tensions received by spine may result in chronic inflammation. [427]

In 2014, Marcos Antonio Tebet, a Brazilian scientist, studied the secondary impacts of abnormal sagittal balance of spine on other pathologies. [378] His study demonstrated that the SBS is correlated with neurogenic claudication and inflammation.

Also, recently, Lovegreen et al.[428] established that biomechanical alteration in the lower limbs may affect sagittal balance in patients. They added that this fact may affect the patient's skin in the form of allergic dermatitis, acroangiodermatitis, skin infections and malignancies. [428,429]

The results of our study are in line with their findings.

When analysing the X-ray data collected from the sagittal balance of the spine, we found a significant correlation (r = 0.88) between the SBS severity score and the EASI level.

5.1.2 Thoracic Spine

Although our results cannot clearly demonstrate a meaningful correlation between total SBA in the thoracic spine and EASI, we ~~indicate a~~ found a meaningful correlation (r = 0.87) between the level of SBA in thoracic 10 (T10) and the level of EASI.

Other researchers have contemplated the impact of the chronic inflammatory process of dermatitis on the spine. [430–433]

In 2009, Haeck et al. [430] studied 125 adult patients with moderate to severe atopic dermatitis (AD) to see if there was any correlation between the chronic inflammatory process of dermatitis and low bone mineral density. (BMD) They found a high prevalence of spine and hip osteopenia in this population sample. Because no correlation was found between long-term use of corticosteroids and the low BMD they could not exclude that chronic

skin inflammation was a potential causative factor for low BMD in the spine.

Kido-Nakahara et al. [433] studied the process of itching in dermatitis. In this study, they stated that cutaneous sensory nerve fibres originating form the thoracic spine, has a direct impact on itching, and consequently, on the inflammatory process of dermatitis. Likewise, in a study published in 2017, by Elmariah et al.[431] investigated pruritus in dermatitis and its relationship with the dorsal roots of the thoracic spinal nerves.

Moreover, in 2019 Pail et al. .[434] in a study on the role of kinin receptors B1 and B2 in the mouse model with Dermatitis, found that the immunopositivity for either kinin receptor is affected by the alteration of the thoracic spine and results in increased mouse skin dermatitis. Closer to our line of thought, in a clinical case by Hird et al.[435], a dysfunction was observed in the tenth thoracic vertebra (T10) of a patient with dermatitis. Although they could not relate T10 dysfunction and dermatitis, due to the need for more information, our study reinforces their findings.

5.1.3 Lumbar Spine

In our study, analysing the data obtained from the lumbar spine examination demonstrated a significant difference ($P<0.0001$) between the severity of lumbar spine alteration in patients with mild Dermatitis and patients with Severe Dermatitis.

Although numerous studies indicated the role of lumbar spine´s alteration in generating neurogenic inflammation and chronic disease, in our study, a clear correlation between lumbar severity scores and EASI levels was not found. The calculated r square ($r= 0.697$) was very close to the

significant area (r= 0.70), however, scientifically we cannot consider it as correlated. Therefore, we suggest further studies on the correlation of biomechanical alteration of the lumbar spine and dermatitis.

However, analysing the data of lumbar spine, separately, presented a significant correlation between the level of L1 and L2 severity scores and EASI levels. This correlation was meaningful for L1 -L2 severity scores and the plasma CGRP levels.

In 2019, US Chiropractic Directory reported the cervical and lumbar spine injuries as the most injured areas. [435]

The lumbar spine tolerates the most pressure when holding and pushing and that may be the reason for more damage and injury. [207,208,211,436]

There are various studies indicating the correlation between lumbar spine and inflammatory diseases such as itching, asthma, and dermatitis. [437–440]

For instance, in 2011, Akiyama et al. [441] investigated the neurotransmitters and pathways of spinal itch- signalling neurons. In their study, they demonstrate that the lumbar spine manifests a high level of spontaneous firing in pruriceptive dorsal horn neurons to epithelial parts of the skin, generating itching sensation. In addition, Shiratori-Hayashi et al. [442] reported that in patients with Dermatitis skin astroglia activation in the lumbar and posterior horns generate the localized atopic dermatitis skin and amplifies a chronic itch sensation in mice. Moreover, Yamasaki et al. [443] investigated the allergic inflammation and its relationship with neuropathic pain. In their study, they also indicated a microglial activation in thoracic and lumbar spine of mice with dermatitis. In addition, dermatitis of the legs and feet is a common dermatitis that most of the time prevents patients from carrying out their daily activities.

So far, there are not many studies that have investigated foot and leg dermatitis and its correlation with the biomechanical alteration of the spine.

Although Lazzarini et al.[444], stated that it is clinically difficult to establish the reason of non-allergic dermatitis on the legs and feet, Carstens et al.[445] presented a case report of a 38-year-old man with low back pain. After the first diagnostic observations, they indicated signs of dermatitis on his legs.

5.1.4 Sacrum

According to Netter's dermatome map, nerve fibers from 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.

Back in 1964, Allende et al. [446] reported a rare case having Dermatitis herpetiformis and vitiligo on the sacral area. In this study they could not find an explanation and they suggested more studies are required to investigate this fact. Nowadays, understanding the process of neurogenic inflammation, provides us the knowledge to explain such chronic diseases.

In 1999, Eldred et al. [447] presented a study investigating a patient with dermatitis in lower part of the trunk. In that study, they stated that the sacral region has a correlation with dermatitis in lower part of the trunk. However, they suggested more research on the topic, with better sample population and more complete methodology.

Moreover, in 2018, Gray et al. [448] studied 5342 patients with incontinence-associated Dermatitis (IAD) and pressure in the sacral area. Their objective was to see if there is any relevant association between dermatitis and sacral pressure. In their study, one third of the patients had either urine or stool

incontinence, or both. Their analysis concluded that dermatitis may be as risk factor for sacral pressure.

In 1997, Fox et al. reported the case of a 41-year-old woman with cervical and sacrum SBA and genital itching and repeated episodes of vulvovaginitis. [449]. This report attracted the attention of scientists to study the correlation of spinal alterations and genital disorders.

In addition, studies indicating a correlation between spinal cord injuries in cervical and sacrum sections and dermatitis in penis area (Penile inflammation). In 2014, Iranian researchers lead by K. Rastegar, [450] presented the case study of a 20-year-old male with a 10-month history of cervical and sacroiliac pain. Their study indicated a manifestation of cervical and sacral spine alteration in dermatitis of the glans penis. In the same year, Lee et al. (2014) indicated a 55% correlation of thoracic spine with penile dermatitis.[451] Similar to SBA of the sacrum, biomechanical alterations in the cervical spine have also has reported to correlate with inflammatory disease the genital area. [452–461]

In our study, although results did not indicate a good correlation between EASI score and Total Lumbar/ Sacral severity score, patients with dermatitis in sacral- related parts of the body indicated a great improvement after chiropractic treatment. Therefore, we suggest more studies on the correlation of SBA in sacral part of the spine and dermatitis of genital area.

5.2 CGRP and Dermatitis

The role of CGRP in neurogenic inflammation has been indicated in various studies. A list of the most important findings about the role of

CGRP in neurogenic inflammation of skin and Dermatitis are provided in Table 87 .

Author/s (Year)	Key Finding	Model	Ref.
Zhang et al. (2021)	CGRP expressing nerve fibres also increased in Dermatitis lesions, the number of CGRP expressing nerve fibres also increased in AD skin lesions, CGRP may mediate itching and other pathological processes in AD patients, CGRP can regulate keratinocyte, mast cell and antigen-presenting cell functions.	Human	[462]
Javed et al. (2021)	CGRP has chemotactic characteristics to neutrophils and lymphocytes	Human	[463]
Sato et al. (2021)	CGRP is considered to mediate sensory nerve-immune cell interactions in the skin and mucous membrane	Mice	[464]
Amalia et al. (2021)	CGRP are suggested to have a role in the pathogenesis of Dermatitis	Human	[465]
Legat et al. (2021)	The induction of neurogenic inflammation, resulting in the release of CGRP in Dermatitis	Human	[466]
Trilisnawati et al. (2021)	CGRP initiate inflammation, including erythema, oedema permeability and vasodilation and attract cytokines from keratinocytes to continue the inflammatory response	Human	[467]
Kahremany et al. (2020)	Neurons lacking expression of CGRP resulted in reduced capsaicin/heat associated itch response in mice	Mice	[468]

Ebbinghaus et al. (2020)	CGRP was implicated in injury and neurogenic inflammation	Mice	[469]
Yosipovitch et al. (2020)	CGRP represents potential new therapeutic targets to address the neuroimmune pathophysiology of itch in Dermatitis	Human	[470]
Gupta et a. (2018)	CGRP sensory nerves and mast cells have an interactive role in skin inflammatory process	Human	[104]
Kubanov et al. (2015)	CGRP promote the development of inflammatory process in the skin and itch	Human	[12]
Granstein et al. (2015)	CGRP promotes Th2-mediated inflammation damage in Dermatitis	Human	[471]
Rogoz et al. (2014)	Pharmacological blockade of the CGRP pathway leads to a drastically attenuated itch in Dermatitis.	Mice	[472]
Kwak et al. (2014)	CGRP seem to affect scarring via sensory neurotransmission, it has a regulatory role for pain and itching sensation in hypertrophic scars.	Human	[473]
Russll et al. (2014)	CGRP was implicated in neurogenic inflammation	Mice	[79]
Akiyama et al. (2014)	CGRP may contribute to the spinal transmission of pain as well as itch	Human	[441]
McCoy et al. (2013)	Genetic ablation of CGRPα-expressing sensory neurons reduced sensitivity to noxious heat, capsaicin, and itch.	Mice	[474]

Sutherland et al. (2013)	CGRP is a mediator of neurogenic inflammation and the most powerful vasodilating neuropeptide	Human	[475]
McCoy et al. (2012)	CGRP may contribute to the spinal transmission of pain as well as itch	Mice	[476]
Mey et al. (2008)	CGRP has a strong vasomotor effect	Human	[477]
Salomon et al. (2008)	High CGRP level is found in patients with Dermatitis	Human	[100]
Jarvikallio (2003)	CGRP expressing nerve fibres also increased in Dermatitis skin lesions	Human	[110]
Greaves et al. (1996)	CGRP is found in the cutaneous free-nerve endings of unmyelinated nociceptor neurones which generate the sensations of pain and itch.	Human	[478]
Gillardon et al. (1995)	CGRP can regulate keratinocyte, mast cell and antigen-presenting cell functions and causes inflammation in skin	Human	[479]
Ostlere et al. (1995)	Subcutaneous injection of CGRP causes vasodilation and flare reaction	Human	[43]
Sung et al. (1992)	CGRP include promoting vasodilation and tissue oedema	Human	[480]

Table 87 - The most important findings about the role of CGRP in neurogenic inflammation of skin

CGRP is one of the inflammatory neuropeptides, produced by the sensory nerves in the dermis, which induces mast cells to release vasoactive amines, resulting in cutaneous inflammation.

A summary of CGRP roles and mechanism of actions in Dermatitis are presented in Table 88.

Source	Mechanisms	Connection with Dermatitis	Ref.
Nervous system, cardiovascular system, and lung tissues	Promotes CCL17/22, IL-4 production, Vasodilation, Mast cell degranulation, Inhibits CCL9/10, IFN-γ secretion	Promotes CCL17/22, IL-4 production, vasodilation, mast cell degranulation; Inhibits CCL9/10, IFN-γ secretion.	[462]

Table 88- CGRP roles and mechanism of actions in Dermatitis

The involvement of CGRP in the transmission of nociceptive information and pain sensitization in the periphery and spinal cord has already proven by several studies. [475,481–485]

Granstein et al. recognized that the level of CGRP increases in the Dermatitis patient's plasma. They also found that the amount of CGRP expressed by the nerve fibres was increased in dermatitis skin lesions. [486]

In addition, numerous findings have indicated that itching in dermatitis patients can be enriched by thermal stimulus and thus, using CGRP antagonists potentially downgrade itching [332–342]. For instance, most recently, Zhang et al. (2021) reviewed the role of neuropeptides in dermatitis and indicated the fact that CGRP may play a crucial role in itching and other pathological processes in dermatitis patients. [487] Ding et al. (2008) established that by enhancing Th2 cellular immunity and inhibiting Th1 cellular immunity, CGRP hypothetically promotes Th2-mediated cutaneous inflammation. (Figure 160) [488]

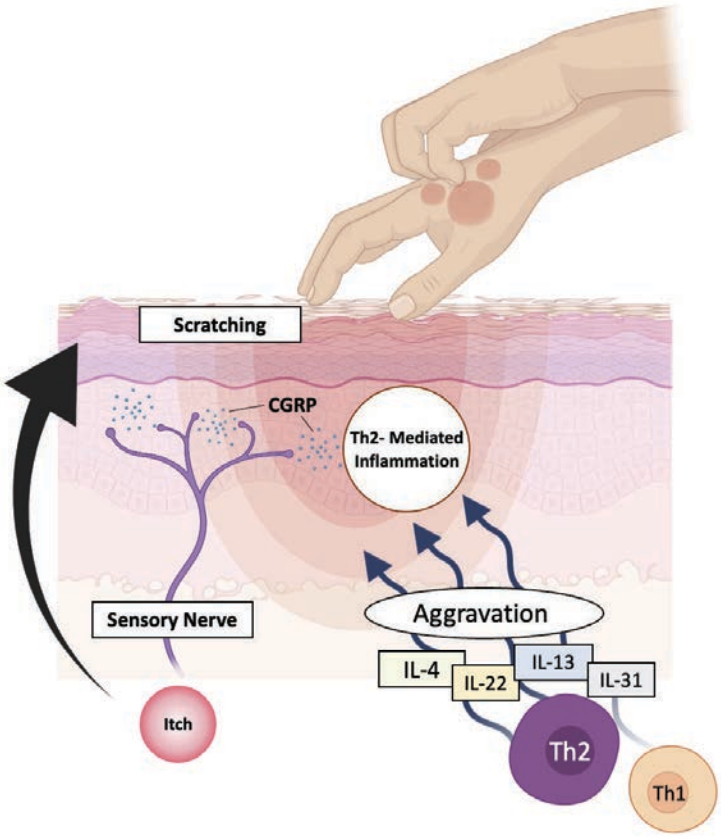


Figure 160- Th2-mediated inflammation: CGRP by enhancing Th2 cellular immunity and inhibiting Th1 cellular immunity, hypothetically promotes Th2-mediated inflammations and causes itching sensation. Reprinted and modified with permission from.[489]

In a study published in 2020, by Matsui et al., established that CGRP can increase the antigen presentation of Langerhans cells to Th2 cells and reduce its antigen presentation to Th1 cells. Therefore, CGRP contributes to the pathogenesis of dermatitis by stimulating the itching production and the chemotaxis of Th2 cells. [490]

In order to determine if there is a correlation between the level of CGRP and the quantification of dermatitis lesions, our findings present a significant difference ($p<0.001$) between the level of CGRP in patients with severe Dermatitis (EASI ≥ 7) and patients with mild Dermatitis

(EASI<7). In addition, analysis of the plasma CGRP levels and EASI scores showed a strong correlation between the level of CGRP in the plasma of patients with severe level of EASI (r=0.83). (See Figure 141)

According to numerous studies, CGRP has chemotactic characteristics to neutrophils and lymphocytes [13,491–493] and infiltration of the cells in the skin is one of the essential factors of inflammation. [13,492] Besides, neuropeptides control the release of cytokines and effect on the activity of immunological cells. [13,491,494–496] These properties can be both restraining or stimulating. Consequently, the severity of Dermatitis is influenced by the actions of neuropeptides. [494,495]

A study by Salomon et al. [497] reported that CGRP may play a crucial role in pathogenesis of Dermatitis by reducing the activity of Langerhans cells, decreasing proliferation of lymphocyte by mitogens stimulations, or reducing lymphocytes, particularly natural killer cells.

Moreover, Stander et al.[498] studied the expression and circulation of micro-opioid receptors in peripheral nervous system. Their results indicate that receptors in nerve fibres contained CGRP. The role of opioids in experience of itch is proved by many studies [498–500], therefore the observation of micro-opioid receptors containing CGRP in nerve fibres can illuminate the role of CGRP fibres in modulation of pruritus of dermatitis.

5.3 CGRP and Spine Severity Score

To determine if there is a correlation between the level of CGRP and the quantification of the spinal biomechanical alterations (SBA), our results also demonstrate a meaningful correlation (r = 0.70) between the level of CGRP and the spine severity score. (See Figure 142)

In other words, the higher SBA level, the higher CGRP level in plasma, and consequently, the more severity of EASI level.

This finding is in line with various studies. In 1997, Christensen et al. [501] investigated the spinal cord injuries and its relationship with the level of CGRP in the dorsal horn in rat model. They concluded that changes in the severity of spinal cord injuries will manipulate the level of CGRP in the rat model. Furthermore, Sang et al. [502] studied the level of CGRP and its effect on the neurological heterotopic ossification following spinal cord injuries. They concluded that CGRP accelerate the pathogenesis of neurological heterotopic ossification resulted from spinal cord injuries. Moreover, and the most similarly, Ackery et al. [503], studied the changes of CGRP level in patients with spinal cord injuries. They compared the level of CGRP to see if there is any difference in the level of CGRP between patients with normal spinal cord and patients with injured human spinal cord or not. In their semiquantitative analysis, they showed a significant enhancement ($p<0.001$) in the level of CGRP of patients with chronic spinal cord injuries. In addition, they reported that in their study some of the patients were suffering from dermatitis. Most recently, Xu et al. [504] reported that alteration in spinal would enhance the release of CGRP from the afferent terminals in spinal cord. Similarly, Loken et al. [505] reported that spinal alterations and injuries increase the level of CGRP in patients' plasma.

At present, no study reviewed the correlation of SBA level in different parts of the spine and CGRP level. However, our results presente a meaningful correlation between the alteration in plasma CGRP level in patients with Dermatitis and their SBA level in AT-AX section (see Figure 143), Cervical Spine section (see Figure 144), Thoracic 10 (see Figure

147), Lumbar 1 (see Figure 148), and Lumbar 2 (see Figure 149). In addition, our result established a significant correlation between alteration of CGRP levels and the SBA level obtained from sagittal balance of the spine (see Figure 146), and antero/retrolisthesis of the spine (see Figure 145).

B. Control Group

The current treatment for dermatitis consists of either a commercialized cream or a compound cream designed and patented by the dermatologist.[506]

However, Dermatitis as a complex disease triggered by neurogenic inflammation requires to be cured in a more effective way. Topical treatment, in the form of a compound cream, can temporarily relieve skin symptoms but when tensions return, symptoms tend to reappear. Understanding the mechanism and causative factors of neurogenic inflammation may allow us to find more effective treatments.

For this reason, the two main objectives of our study were to find a possible correlation between spinal biomechanical alterations (SBA), in part due to poor postural habits, and neurogenic inflammation and, to determine the effect of chiropractic SMT in normalizing the level of plasma CGRP and improving dermatitis lesions.

By analysing the data gathered from the control group (who did not undertake chiropractic treatment), we found that there was no significant change ($p= 0.53$) (See Figure 153) in the level of CGRP before and after using the compound cream. On the other hand, CGRP level in the treatment group, treated with both the cream and chiropractic SMT, has significantly decreased ($p<0.0001$) (See Figure 155).

These results indicate that Spinal Manipulation Therapy (SMT) may have a significant impact on the level of CGRP in patients with dermatitis.

Now, does SMT have any impact on the severity level of dermatitis (EASI level)?
Our result revealed that although the use of the cream in the control group decreased the EASI level after approximately 2 weeks, however, in a longer period, 3 months, the EASI level would rise again and cause the patients to return. to the dermatologist or they will use the cream constantly.
(See Figure 154).
However, our treatment group patients (who also underwent chiropractic SMT) after manual correction of vertebral alignment presented lower plasma CGRP level and decreased the EASI score. In addition, they maintained a lower CGRP level for a longer period (at least 3 months after participating in this study) (See Figure 155).

Our results agree with those of Muchizuki et al. [507] They examined the development of itching in dermatitis in relation with the effectiveness of non-invasive interventions for itch relief by correcting the spinal functions. Similar findings have been reported by Park et al. [508]

In summary, there is a need to find new, more effective, and non-invasive therapeutic modalities for the treatment of dermatitis, focusing on the causative factors of neurogenic inflammation.

CHAPTER 6:
CONCLUSION

1- Our study suggests that the quantification of the spinal biomechanical alterations (SBA) may correlate with the quantification of the dermatitis lesions (EASI).

2- Our study suggests that there may be a correlation between the plasma CGRP level and the SBA quantification.

3- It seems that there is a correlation between the plasma CGRP level and the quantification of dermatitis lesions (EASI) in the study patients.

4- The results obtained from the comparison between the treatment group and the control group of this study indicate that chiropractic SMT may affect the plasma CGRP level.

5- The results obtained by comparing the treatment group and the control group of this study indicate that chiropractic SMT may improve the outcome of dermatitis lesions.

However, considering that our conclusions are based on a relatively small number of patients, we think that more reasearch is needed, with a bigger population sample and a more refined methodology.

CHAPTER 7: BIBLIOGRAPHIC REFERENCES

1. Langan, S. M., Irvine, A. D. & Weidinger, S. Atopic dermatitis. *The Lancet* vol. 396 345–360 (2020).
2. Badloe, F. M. S. *et al.* IgE autoantibodies and autoreactive T cells and their role in children and adults with atopic dermatitis. *Clinical and translational allergy* **10**, 1–15 (2020).
3. Berger, W. E. Allergic rhinitis in children: diagnosis and management strategies. *Pediatric Drugs* **6**, 233–251 (2004).
4. Narla, S. & Silverberg, J. I. Association between atopic dermatitis and serious cutaneous, multiorgan and systemic infections in US adults. *Annals of Allergy, Asthma & Immunology* **120**, 66–72 (2018).
5. Brunner, P. M. *et al.* Increasing comorbidities suggest that atopic dermatitis is a systemic disorder. *Journal of Investigative Dermatology* **137**, 18–25 (2017).
6. Dieris-Hirche, J., Gieler, U., Kupfer, J. P. & Milch, W. E. Suizidgedanken, Angst und Depression bei erwachsenen Neurodermitikern. *Der Hautarzt* **60**, 641–646 (2009).
7. Deckert, S., Kopkow, C. & Schmitt, J. Nonallergic comorbidities of atopic eczema: an overview of systematic reviews. *Allergy* **69**, 37–45 (2014).
8. Kader, H. A. *et al.* Current Insights into Immunology and Novel Therapeutics of Atopic Dermatitis. *Cells* **10**, 1392 (2021).
9. Tokura, Y. & Hayano, S. Subtypes of atopic dermatitis: From phenotype to endotype. *Allergology International* (2021).
10. Nakashima, C., Ishida, Y., Kitoh, A., Otsuka, A. & Kabashima, K. Interaction of peripheral nerves and mast cells, eosinophils, and basophils in the development of pruritus. *Experimental Dermatology* vol. 28 1405–1411 (2019).
11. Dines, K. C. & Powell, H. C. Mast cells interactions with the nervous system: Relationship to mechanisms of disease. *Journal of neuropathology and experimental neurology* **56**, 627 (1997).
12. Kubanov, A., Katunina, O. R. & Chikin, V. v. Expression of neuropeptides, neurotrophins, and neurotransmitters in the skin of

patients with atopic dermatitis and psoriasis. *Bulletin of experimental biology and medicine* **159**, 318–322 (2015).
13. Lotti, T., Hautmann, G. & Panconesi, E. Neuropeptides in skin. *Journal of the American Academy of Dermatology* **33**, 482–496 (1995).
14. Wollenberg, A. *et al.* Consensus-based European guidelines for treatment of atopic eczema (atopic dermatitis) in adults and children: part II. *Journal of the European Academy of Dermatology and Venereology* **32**, 850–878 (2018).
15. Balestrini, A. *et al.* A TRPA1 inhibitor suppresses neurogenic inflammation and airway contraction for asthma treatment. *Journal of Experimental Medicine* **218**, (2021).
16. Katoh, N. Emerging treatments for atopic dermatitis. *The Journal of Dermatology* **48**, 152–157 (2021).
17. Mandlik, D. S. & Mandlik, S. K. Atopic dermatitis: new insight into the etiology, pathogenesis, diagnosis and novel treatment strategies. *Immunopharmacology and Immunotoxicology* **43**, 105–125 (2021).
18. Ahn, J., Grinich, E. E., Choi, Y., Guttman-Yassky, E. & Simpson, E. L. Emerging Systemic Therapeutic Biologics and Small Molecules for Atopic Dermatitis: How to Decide Which Treatment Is Right for Your Patients. *The Journal of Allergy and Clinical Immunology: In Practice* **9**, 1449–1460 (2021).
19. Young, T. K. *et al.* Management of pediatric atopic dermatitis by primary care providers: A systematic review. *Academic Pediatrics* (2021).
20. Saini, S. & Pansare, M. New Insights and Treatments in Atopic Dermatitis. *Pediatric Clinics of North America* **66**, 1021–1033 (2019).
21. Vakharia, P. P. & Silverberg, J. I. New therapies for atopic dermatitis: additional treatment classes. *Journal of the American Academy of Dermatology* **78**, S76–S83 (2018).
22. Oakes, R. C., Cox, A. D. & Burgdorf, W. H. C. Atopic dermatitis: a review of diagnosis, pathogenesis, and management. *Clinical pediatrics* **22**, 467–475 (1983).

23. Zhang, Y. *et al.* Current views on neuropeptides in atopic dermatitis. *Experimental Dermatology* (2021).
24. Salomon, J. & Baran, E. The role of selected neuropeptides in pathogenesis of atopic dermatitis. *Journal of the European Academy of Dermatology and Venereology* **22**, 223–228 (2008).
25. Legat, F. J. Itch in Atopic Dermatitis–What Is New? *Frontiers in Medicine* **8**, 629 (2021).
26. Newsom, M., Bashyam, A. M., Balogh, E. A., Feldman, S. R. & Strowd, L. C. New and emerging systemic treatments for atopic dermatitis. *Drugs* **80**, 1041–1052 (2020).
27. Lee, C. *et al.* Mechanistic correlations between two itch biomarkers, cytokine interleukin-31 and neuropeptide β-endorphin, via STAT3/calcium axis in atopic dermatitis. *British Journal of Dermatology* **167**, 794–803 (2012).
28. Tominaga, M. & Takamori, K. Itch and nerve fibers with special reference to atopic dermatitis: therapeutic implications. *The Journal of dermatology* **41**, 205–212 (2014).
29. Wong, L.-S., Wu, T. & Lee, C.-H. Inflammatory and noninflammatory itch: implications in pathophysiology-directed treatments. *International journal of molecular sciences* **18**, 1485 (2017).
30. Salomon, J. & Baran, E. The role of selected neuropeptides in pathogenesis of atopic dermatitis. *Journal of the European Academy of Dermatology and Venereology* **22**, 223–228 (2008).
31. Chen, S. *et al.* A spinal neural circuitry for converting touch to itch sensation. *Nature communications* **11**, 1–14 (2020).
32. Mu, D. *et al.* A central neural circuit for itch sensation. *Science* **357**, 695–699 (2017).
33. Schmelz, M. A neural pathway for itch. *Nature neuroscience* **4**, 9–10 (2001).
34. Liu, X. *et al.* Spinal GRPR and NPRA contribute to chronic itch in a murine model of allergic contact dermatitis. *Journal of Investigative Dermatology* **140**, 1856–1866 (2020).

35. Najafi, P., Dufor, O., ben Salem, D., Misery, L. & Carré, J. Itch processing in the brain. *Journal of the European Academy of Dermatology and Venereology* **35**, 1058–1066 (2021).
36. Kim, H. S. & Yosipovitch, G. The Skin Microbiota and Itch: Is There a Link? *Journal of clinical medicine* **9**, 1190 (2020).
37. Sorkin, L. S., Eddinger, K. A., Woller, S. A. & Yaksh, T. L. Origins of antidromic activity in sensory afferent fibers and neurogenic inflammation. in *Seminars in immunopathology* vol. 40 237–247 (Springer, 2018).
38. Matsuda, M., Huh, Y. & Ji, R.-R. Roles of inflammation, neurogenic inflammation, and neuroinflammation in pain. *Journal of anesthesia* **33**, 131–139 (2019).
39. Sorkin, L. S., Eddinger, K. A., Woller, S. A. & Yaksh, T. L. Origins of antidromic activity in sensory afferent fibers and neurogenic inflammation. in *Seminars in immunopathology* vol. 40 237–247 (Springer, 2018).
40. Donnelly, C. R., Chen, O. & Ji, R.-R. How do sensory neurons sense danger signals? *Trends in Neurosciences* (2020).
41. Zhang, Y. *et al.* Current views on neuropeptides in atopic dermatitis. *Experimental Dermatology* (2021) doi:10.1111/exd.14382.
42. Tore, F. & Tuncel, N. Mast cells: target and source of neuropeptides. *Current pharmaceutical design* **15**, 3433–3445 (2009).
43. Ostlere, L. S., Cowen, T. & Rustin, M. H. A. Neuropeptides in the skin of patients with atopic dermatitis. *Clinical and experimental dermatology* **20**, 462–467 (1995).
44. Persoon, C. M. Neuropeptide secretion principles: Vesicle populations, characteristics and fusion mechanisms. (2021).
45. Wood, E. A. *et al.* Neuropeptide Localization in Lymnaea stagnalis: From the Central Nervous System to Subcellular Compartments. *Frontiers in Molecular Neuroscience* **14**, (2021).
46. Zhang, Y. *et al.* Current views on neuropeptides in atopic dermatitis. *Experimental Dermatology* (2021).
47. Matsuda, M., Huh, Y. & Ji, R.-R. Roles of inflammation, neurogenic inflammation, and neuroinflammation in pain. *Journal of anesthesia* **33**, 131–139 (2019).

48. Choi, J. E. & di Nardo, A. Skin neurogenic inflammation. in *Seminars in immunopathology* vol. 40 249–259 (Springer, 2018).
49. Hökfelt, T. *et al.* Neuropeptide and small transmitter coexistence: fundamental studies and relevance to mental illness. *Frontiers in Neural Circuits* **12**, 106 (2018).
50. Rodríguez, B. *et al.* Neuropeptides and oligopeptidases in schizophrenia. *Neuroscience & Biobehavioral Reviews* **108**, 679–693 (2020).
51. Nahvi, R. J. & Sabban, E. L. Sex Differences in the Neuropeptide Y System and Implications for Stress Related Disorders. *Biomolecules* **10**, 1248 (2020).
52. Spiegel, D. R., Sommese, K., Turenkov, A. & Naimon, N. A case of peripartum obsessive-compulsive disorder: The potential role of corticosteroids, gonadal steroids, and the neuropeptide oxytocin in its pathogenesis. *Innovations in clinical neuroscience* **16**, 41 (2019).
53. Pondeljak, N. & Lugović-Mihić, L. Stress-induced interaction of skin immune cells, hormones, and neurotransmitters. *Clinical therapeutics* **42**, 757–770 (2020).
54. Xu, H. *et al.* Neurotransmitter and neuropeptide regulation of mast cell function: A systematic review. *Journal of Neuroinflammation* **17**, 1–15 (2020).
55. Barber, R. P. *et al.* The origin, distribution and synaptic relationships of substance P axons in rat spinal cord. *Journal of Comparative Neurology* **184**, 331–351 (1979).
56. Fan, Y. *et al.* The role of substance P in acupuncture signal transduction and effects. *Brain, behavior, and immunity* **91**, 683–694 (2021).
57. González-Moles, M. Á., Ramos-García, P. & Esteban, F. Significance of the Overexpression of Substance P and Its Receptor NK-1R in Head and Neck Carcinogenesis: A Systematic Review and Meta-Analysis. *Cancers* **13**, 1349 (2021).
58. Sampath, K. K., Katare, R. & Tumilty, S. Stress axis and osteopathy: A dual hormone approach. *International Journal of Osteopathic Medicine* **33**, 24–30 (2019).

59. Hall, J. M. F., Podawiltz, A., Mummert, D. I., Jones, H. & Mummert, M. E. Psychological stress and the cutaneous immune response: roles of the HPA axis and the sympathetic nervous system in atopic dermatitis and psoriasis. *Dermatology research and practice* **2012**, (2012).
60. Mai, L., Liu, Q., Huang, F., He, H. & Fan, W. Involvement of Mast Cells in the Pathophysiology of Pain. *Frontiers in Cellular Neuroscience* (2021).
61. Vidal Yucha, S. E., Tamamoto, K. A. & Kaplan, D. L. The importance of the neuro-immuno-cutaneous system on human skin equivalent design. *Cell proliferation* **52**, e12677 (2019).
62. Richardson, J. D. & Vasko, M. R. Cellular mechanisms of neurogenic inflammation. *Journal of Pharmacology and Experimental Therapeutics* **302**, 839–845 (2002).
63. Amara, S. G., Jonas, V., Rosenfeld, M. G., Ong, E. S. & Evans, R. M. *Alternative RN A processing in calcitonin gene expression generates mRN As encoding different polypeptide products*. *Nature* vol. 298 (1982).
64. van Rossum, D., Hanisch, U.-K. & QUIRION, R. Neuroanatomical localization, pharmacological characterization and functions of CGRP, related peptides and their receptors. *Neuroscience & Biobehavioral Reviews* **21**, 649–678 (1997).
65. Tanaka, T. *et al.* Dermal macrophages set pain sensitivity by modulating tissue NGF levels through SNX25-Nrf2 signaling. *bioRxiv* (2021).
66. Fusco, M. *et al.* Neurogenic inflammation in primary headaches. *Neurological Sciences* **24**, s61–s64 (2003).
67. Seifert, O. & Baerwald, C. Interaction of pain and chronic inflammation. *Zeitschrift für Rheumatologie* **80**, 205–213 (2021).
68. Guo, R. *et al.* Nerve growth factor enhances tooth mechanical hyperalgesia through CC chemokine ligand 19 in rats. *Frontiers in neurology* **12**, (2021).
69. Indo, Y. Neurobiology of pain, interoception and emotional response: lessons from nerve growth factor-dependent neurons. *European Journal of Neuroscience* **39**, 375–391 (2014).

70. Salehi, A., Delcroix, J.-D. & Swaab, D. F. Alzheimer's disease and NGF signaling. *Journal of neural transmission* **111**, 323–345 (2004).
71. Olson, L. NGF and the treatment of Alzheimer's disease. *Experimental neurology* **124**, 5–15 (1993).
72. Hellweg, R. & Hartung, H. Endogenous levels of nerve growth factor (NGF) are altered in experimental diabetes mellitus: a possible role for NGF in the pathogenesis of diabetic neuropathy. *Journal of neuroscience research* **26**, 258–267 (1990).
73. Unger, J. W., Klitzsch, T., Pera, S. & Reiter, R. Nerve growth factor (NGF) and diabetic neuropathy in the rat: morphological investigations of the sural nerve, dorsal root ganglion, and spinal cord. *Experimental neurology* **153**, 23–34 (1998).
74. Hellweg, R., Raivich, G., Hartung, H.-D., Hock, C. & Kreutzberg, G. W. Axonal transport of endogenous nerve growth factor (NGF) and NGF receptor in experimental diabetic neuropathy. *Experimental neurology* **130**, 24–30 (1994).
75. Zhang, H. *et al.* NGF rescues hippocampal cholinergic neuronal markers, restores neurogenesis, and improves the spatial working memory in a mouse model of Huntington's Disease. *Journal of Huntington's disease* **2**, 69–82 (2013).
76. Tasset, I. *et al.* NGF and nitrosative stress in patients with Huntington's disease. *Journal of the neurological sciences* **315**, 133–136 (2012).
77. Aloe, L. & Calzà, L. *NGF and related molecules in health and disease*. (Elsevier, 2003).
78. Delgado, A. v, McManus, A. T. & Chambers, J. P. Exogenous administration of Substance P enhances wound healing in a novel skin-injury model. *Experimental biology and medicine* **230**, 271–280 (2005).
79. Russell, F. A., King, R., Smillie, S.-J., Kodji, X. & Brain, S. D. Calcitonin gene-related peptide: physiology and pathophysiology. *Physiological reviews* **94**, 1099–1142 (2014).

80. Sawynok, J. Topical analgesics for neuropathic pain: preclinical exploration, clinical validation, future development. *European journal of pain* **18**, 465–481 (2014).
81. Welsh, S. E. *et al.* Neurokinin-1 receptor antagonist tradipitant has mixed effects on itch in atopic dermatitis: results from EPIONE, a randomized clinical trial. *Journal of the European Academy of Dermatology and Venereology* **35**, e338 (2021).
82. Misery, L., Huet, F., Gouin, O., Ständer, S. & Deleuran, M. Current pharmaceutical developments in atopic dermatitis. *Current opinion in pharmacology* **46**, 7–13 (2019).
83. Welsh, S. E. *et al.* Neurokinin-1 receptor antagonist tradipitant improves itch associated with mild atopic dermatitis: Results from EPIONE a randomized clinical trial. *medRxiv* (2020).
84. Edvinsson, L. Role of CGRP in migraine. in *Calcitonin Gene-Related Peptide (CGRP) Mechanisms* 121–130 (Springer, 2019).
85. Tringali, G. & Navarra, P. Anti-CGRP and anti-CGRP receptor monoclonal antibodies as antimigraine agents. Potential differences in safety profile postulated on a pathophysiological basis. *Peptides* **116**, 16–21 (2019).
86. Edvinsson, L., Haanes, K. A., Warfvinge, K. & Krause, D. N. CGRP as the target of new migraine therapies—successful translation from bench to clinic. *Nature Reviews Neurology* **14**, 338–350 (2018).
87. Yuan, H., Lauritsen, C. G., Kaiser, E. A. & Silberstein, S. D. CGRP monoclonal antibodies for migraine: rationale and progress. *BioDrugs* **31**, 487–501 (2017).
88. Tso, A. R. & Goadsby, P. J. Anti-CGRP monoclonal antibodies: the next era of migraine prevention? *Current treatment options in neurology* **19**, 1–11 (2017).
89. Arndt, J., Smith, N. & Tausk, F. Stress and atopic dermatitis. *Current allergy and asthma reports* **8**, 312–317 (2008).
90. Lagomarsino, V. N., Kostic, A. D. & Chiu, I. M. Mechanisms of microbial-neuronal interactions in pain and nociception. *Neurobiology of Pain* 100056 (2020).

91. Belkaid, Y. & Tamoutounour, S. The influence of skin microorganisms on cutaneous immunity. *Nature Reviews Immunology* **16**, 353–366 (2016).
92. Chen, Y. E., Fischbach, M. A. & Belkaid, Y. Skin microbiota–host interactions. *Nature* **553**, 427–436 (2018).
93. Tamari, M., ver Heul, A. M. & Kim, B. S. Immunosensation: Neuroimmune Cross Talk in the Skin. *Annual Review of Immunology* **39**, 369–393 (2021).
94. Chiu, I. M., von Hehn, C. A. & Woolf, C. J. Neurogenic inflammation and the peripheral nervous system in host defense and immunopathology. *Nature neuroscience* **15**, 1063–1067 (2012).
95. Bessou, P. & Perl, E. R. Response of cutaneous sensory units with unmyelinated fibers to noxious stimuli. *Journal of neurophysiology* **32**, 1025–1043 (1969).
96. Metzler-Wilson, K., Wilson, T. E., Ausmus, S. M. & Sventeckis, A. M. Effect of sensory blockade and rate of sensory stimulation on local heating induced axon reflex response in facial skin. *Autonomic Neuroscience* **233**, 102809 (2021).
97. Plinta, A. *et al.* Influence of Migraine on Axon Reflex-Mediated and Endothelial-Dependent Vasodilatation in the Skin. in *Proceedings of the Latvian Academy of Sciences. Section B. Natural, Exact, and Applied Sciences.* vol. 75 194–199 (2021).
98. Misery, L. Atopic dermatitis and the nervous system. *Clinical reviews in allergy & immunology* **41**, 259–266 (2011).
99. Laageide, L., Verhave, B., Samkoff, L., Looney, R. & Beck, L. Relapsing-remitting multiple sclerosis arising in a patient with atopic dermatitis on dupilumab. *JAAD Case Reports* **15**, 33 (2021).
100. Salomon, J. & Baran, E. The role of selected neuropeptides in pathogenesis of atopic dermatitis. *Journal of the European Academy of Dermatology and Venereology* **22**, 223–228 (2008).
101. Fan, J. & Mishra, S. K. The emerging role of neuroimmune interactions in atopic dermatitis and itch. *The FEBS Journal* (2021).
102. Seneviratne, J. Pathogenesis of atopic dermatitis: Current concepts. *Journal of Skin and Sexually Transmitted Diseases* 1–5 (2021).

103. Zhang, Y. *et al.* Current views on neuropeptides in atopic dermatitis. *Experimental Dermatology* (2021).
104. Gupta, K. & Harvima, I. T. Mast cell-neural interactions contribute to pain and itch. *Immunological reviews* **282**, 168–187 (2018).
105. Harvima, I. T., Nilsson, G., Suttle, M.-M. & Naukkarinen, A. Is there a role for mast cells in psoriasis? *Archives of dermatological research* **300**, 461–478 (2008).
106. Kulka, M., Sheen, C. H., Tancowny, B. P., Grammer, L. C. & Schleimer, R. P. Neuropeptides activate human mast cell degranulation and chemokine production. *Immunology* **123**, 398–410 (2008).
107. Ayasse, M. T., Buddenkotte, J., Alam, M. & Steinhoff, M. Role of neuroimmune circuits and pruritus in psoriasis. *Experimental dermatology* **29**, 414–426 (2020).
108. Järvikallio, A., Harvima, I. T. & Naukkarinen, A. Mast cells, nerves and neuropeptides in atopic dermatitis and nummular eczema. *Archives of dermatological research* **295**, 2–7 (2003).
109. Papanikolaou, M. *et al.* Prevalence, pathophysiology and management of itch in epidermolysis bullosa. *British Journal of Dermatology* (2020).
110. Järvikallio, A., Harvima, I. T. & Naukkarinen, A. Mast cells, nerves and neuropeptides in atopic dermatitis and nummular eczema. *Archives of dermatological research* **295**, 2–7 (2003).
111. Urashima, R. & Mihara, M. Cutaneous nerves in atopic dermatitis. *Virchows Archiv* **432**, 363–370 (1998).
112. Zhang, Y. *et al.* Current views on neuropeptides in atopic dermatitis. *Experimental Dermatology* (2021).
113. Tobin, D. *et al.* Increased number of immunoreactive nerve fibers in atopic dermatitis. *Journal of allergy and clinical immunology* **90**, 613–622 (1992).
114. DeFelice, M. L. & Yousef, E. Evaluation of risk factors for the severity of atopic dermatitis (AD). *Journal of Allergy and Clinical Immunology* **121**, S38 (2008).
115. Suárez, A. L., Feramisco, J. D., Koo, J. & Steinhoff, M. Psychoneuroimmunology of psychological stress and atopic

dermatitis: pathophysiologic and therapeutic updates. *Acta dermato-venereologica* **92**, 7–18 (2012).
116. Kucukosmanoglu, E., Keskin, O., Karcin, M., Cekmen, M. & Balat, A. Plasma adrenomedullin levels in children with asthma: Any relation with atopic dermatitis? *Allergologia et immunopathologia* **40**, 215–219 (2012).
117. Lipman, Z. M., Labib, A. & Yosipovitch, G. Current Clinical Options for the Management of Itch in Atopic Dermatitis. *Clinical, Cosmetic and Investigational Dermatology* **14**, 959 (2021).
118. Dou, Y.-C., Hagströmer, L., Emtestam, L. & Johansson, O. Increased nerve growth factor and its receptors in atopic dermatitis: an immunohistochemical study. *Archives of dermatological research* **298**, 31–37 (2006).
119. Yamaguchi, J., Aihara, M., Kobayashi, Y., Kambara, T. & Ikezawa, Z. Quantitative analysis of nerve growth factor (NGF) in the atopic dermatitis and psoriasis horny layer and effect of treatment on NGF in atopic dermatitis. *Journal of dermatological science* **53**, 48–54 (2009).
120. Zhang, Y. *et al.* Current views on neuropeptides in atopic dermatitis. *Experimental Dermatology* (2021).
121. Langan, S. M., Irvine, A. D. & Weidinger, S. Atopic dermatitis. *The Lancet* **396**, 345–360 (2020).
122. Peters, E. M. J. *et al.* Nerve growth factor partially recovers inflamed skin from stress-induced worsening in allergic inflammation. *Journal of Investigative Dermatology* **131**, 735–743 (2011).
123. Dou, Y.-C., Hagströmer, L., Emtestam, L. & Johansson, O. Increased nerve growth factor and its receptors in atopic dermatitis: an immunohistochemical study. *Archives of dermatological research* **298**, 31–37 (2006).
124. Tanaka, A. & Matsuda, H. Expression of nerve growth factor in itchy skins of atopic NC/NgaTnd mice. *Journal of veterinary medical science* **67**, 915–919 (2005).

125. Coates, S. J., Lee, E. H. & Granstein, R. D. Cutaneous Neuroimmunology. in *Clinical and Basic Immunodermatology* 179–199 (Springer, 2017).
126. Mollanazar, N. K., Smith, P. K. & Yosipovitch, G. Mediators of chronic pruritus in atopic dermatitis: getting the itch out? *Clinical reviews in allergy & immunology* **51**, 263–292 (2016).
127. Liu, J., Ting, J. P., Al-Azzam, S., Ding, Y. & Afshar, S. Therapeutic Advances in Diabetes, Autoimmune, and Neurological Diseases. *International journal of molecular sciences* **22**, 2805 (2021).
128. Perner, C. *et al.* Substance P release by sensory neurons triggers dendritic cell migration and initiates the type-2 immune response to allergens. *Immunity* **53**, 1063–1077 (2020).
129. Feistritzer, C. *et al.* Natural killer cell functions mediated by the neuropeptide substance P. *Regulatory peptides* **116**, 119–126 (2003).
130. Mahadevan, V. Anatomy of the vertebral column. *Surgery (Oxford)* **36**, 327–332 (2018).
131. Kayalioglu, G. The vertebral column and spinal meninges. in *The Spinal Cord* 17–36 (Elsevier, 2009).
132. Bazira, P. J. Clinically applied anatomy of the vertebral column. *Surgery (Oxford)* (2021).
133. Kalamchi, L. & Valle, C. Embryology, Vertebral Column Development. *StatPearls [Internet]* (2020).
134. Kayalioglu, G. The vertebral column and spinal meninges. in *The Spinal Cord* 17–36 (Elsevier, 2009).
135. Haussler, K. K. Anatomy of the thoracolumbar vertebral region. *Veterinary clinics of North America: equine practice* **15**, 13–26 (1999).
136. Neumann, D. A. Kinesiology of the musculoskeletal system; Foundation for rehabilitation. *Mosby & Elsevier* (2010).
137. Dimeglio, A., Bonnel, F. & Canavese, F. The growing spine. in *Spinal Anatomy* 25–52 (Springer, 2020).
138. Kemppainen, J. & Yaszay, B. Normal Cervical Spine Biomechanics. *The Management of Disorders of the Child's Cervical Spine* 15 (2018).

139. Jia, P., Zhu, S. & Guo, L. The Clinical Value of CT Scans for the Early Diagnosis and Treatment of Spinal Fractures and Paraplegia. *Journal of Healthcare Engineering* **2021**, (2021).
140. Insko, E. K. *et al.* Utility of flexion and extension radiographs of the cervical spine in the acute evaluation of blunt trauma. *Journal of Trauma and Acute Care Surgery* **53**, 426–429 (2002).
141. Funabashi, M. *et al.* Characterization of thoracic spinal manipulation and mobilization forces in older adults. *Clinical Biomechanics* 105450 (2021).
142. El-Khoury, G. Y. & Whitten, C. G. Trauma to the upper thoracic spine: anatomy, biomechanics, and unique imaging features. *AJR. American journal of roentgenology* **160**, 95–102 (1993).
143. Carvey, P. M., Hendey, B. & Monahan, A. J. The blood–brain barrier in neurodegenerative disease: a rhetorical perspective. *Journal of neurochemistry* **111**, 291–314 (2009).
144. Grant, R. Influence of vertebral artery blood flow research outcomes on clinical judgment. *Australian Journal of Physiotherapy* **47**, 167 (2001).
145. Pike, C. *et al.* Direct and indirect costs of non-vertebral fracture patients with osteoporosis in the US. *Pharmacoeconomics* **28**, 395–409 (2010).
146. Corlett, E. N. Background to sitting at work: research-based requirements for the design of work seats. *Ergonomics* **49**, 1538–1546 (2006).
147. Iordache, C., Ancuţa, C., Ancuţa, E., Ţănculescu, O. & Surlari, Z. Posture and Vertebral Pathology Issues in Dental Practice. *Romanian Journal of Oral Rehabilitation* **4**, 74–96 (2012).
148. Burton, A. K. Back injury and work loss: biomechanical and psychosocial influences. *Spine* **22**, 2575–2580 (1997).
149. Hallberg, I., Bachrach-Lindström, M., Hammerby, S., Toss, G. & Ek, A.-C. Health-related quality of life after vertebral or hip fracture: a seven-year follow-up study. *BMC musculoskeletal disorders* **10**, 1–13 (2009).
150. Tonsbeek, A. M., Groen, J. L. & Vleggeert-Lankamp, C. L. A. M. Surgical interventions for cervical radiculopathy caused by a

vertebral artery loop: a case report and review of the literature. *World neurosurgery* **135**, 28–34 (2020).
151. Harty, J. A., Lenehan, B. & O'Rourke, S. K. Odontoid lateral mass asymmetry: Do we over-investigate? *Emergency Medicine Journal* **22**, 625–627 (2005).
152. Pang, D. Atlantoaxial rotatory fixation. *Neurosurgery* **66**, 161–183 (2010).
153. Pang, D. Atlantoaxial rotatory fixation. *Neurosurgery* **66**, A161–A183 (2010).
154. Yang, S. Y. *et al.* A review of the diagnosis and treatment of atlantoaxial dislocations. *Global spine journal* **4**, 197–210 (2014).
155. Henderson, F. C. *et al.* Atlanto-axial rotary instability (Fielding type 1): characteristic clinical and radiological findings, and treatment outcomes following alignment, fusion, and stabilization. *Neurosurgical Review* **44**, 1553–1568 (2021).
156. Nader-Sepahi, A., Casey, A. T. H., Hayward, R., Crockard, H. A. & Thompson, D. Symptomatic atlantoaxial instability in Down syndrome. *Journal of Neurosurgery: Pediatrics* **103**, 231–237 (2005).
157. Song, K.-C., Cho, K.-S. & Lee, S.-B. Congenital defect of the posterior arch of cervical spine: report of three cases and review of the current literature. *Journal of Korean Neurosurgical Society* **48**, 294 (2010).
158. McGill, S. *Low back disorders: evidence-based prevention and rehabilitation*. (Human Kinetics, 2015).
159. Gasibat, Q. *A New Rehabilitation Approach for Managing and Preventing Low Back Pain: A Step Away from Surgical and Drug-Based Treatments*. (Partridge Publishing Singapore, 2017).
160. Eloqayli, H. Clinical decision-making in chronic spine pain: dilemma of image-based diagnosis of degenerative spine and generation mechanisms for nociceptive, radicular, and referred pain. *BioMed research international* **2018**, (2018).
161. Lee, C. K. *et al.* Correlation between cervical spine sagittal alignment and clinical outcome after cervical laminoplasty for

ossification of the posterior longitudinal ligament. *Journal of Neurosurgery: Spine* **24**, 100–107 (2016).
162. Steilen, D., Hauser, R., Woldin, B. & Sawyer, S. Chronic neck pain: making the connection between capsular ligament laxity and cervical instability. *The open orthopaedics journal* **8**, 326 (2014).
163. Metzger, R. L. Evidence-based diagnosis and treatment of cervical spine disorders. *The Nurse Practitioner* **44**, 30–37 (2019).
164. Saita, K. *et al.* Exponential correlations among neuropathic components, pain intensity, and catastrophic thoughts in patients with musculoskeletal pain disorder. *Current Medical Research and Opinion* 1 (2021).
165. Saita, K. *et al.* Exponential correlations among neuropathic components, pain intensity, and catastrophic thoughts in patients with musculoskeletal pain disorder. *Current Medical Research and Opinion* 1 (2021).
166. Moustafa, I., Youssef, A. S. A., Ahbouch, A. & Harrison, D. Demonstration of Autonomic Nervous Function and Cervical Sensorimotor Control After Cervical Lordosis Rehabilitation: A Randomized Controlled Trial. *Journal of Athletic Training* **56**, 427–436 (2021).
167. Scheer, J. K. *et al.* Cervical spine alignment, sagittal deformity, and clinical implications: a review. *Journal of Neurosurgery: Spine* **19**, 141–159 (2013).
168. Alijani, B. & Rasoulian, J. The sagittal balance of the cervical spine: radiographic analysis of interdependence between the occipitocervical and spinopelvic alignment. *Asian spine journal* **14**, 287 (2020).
169. Beltsios, M. *et al.* Sagittal alignment of the cervical spine after neck injury. *European Journal of Orthopaedic Surgery and Traumatology* **23**, 47–51 (2013).
170. Chaoqun, L. *et al.* Sagittal imbalance of the spine is associated with poor sitting posture among primary and secondary school students in China: A cross-sectional study. (2021).
171. Ludwig, K. *et al.* Craniocervical abnormalities in osteogenesis imperfecta type V. *Osteoporosis International* 1–7 (2021).

172. Gao, K. *et al.* Correlation between cervical lordosis and cervical disc herniation in young patients with neck pain. *Medicine* **98**, (2019).
173. Gao, K. *et al.* Correlation between cervical lordosis and cervical disc herniation in young patients with neck pain. *Medicine* **98**, (2019).
174. Moustafa, I. M., Diab, A. A., Hegazy, F. & Harrison, D. E. Demonstration of central conduction time and neuroplastic changes after cervical lordosis rehabilitation in asymptomatic subjects: a randomized, placebo-controlled trial. *Scientific Reports* **11**, 1–13 (2021).
175. PERLMAN, R. & HAWES, L. E. Cervical spondylolisthesis. *JBJS* **33**, 1012–1013 (1951).
176. Woo, J.-H. & Choi, H.-J. Spondylolytic Spondylolisthesis of Cervical Spine. *Korean Journal of Neurotrauma* **17**, 75 (2021).
177. Jiang, S.-D., Jiang, L.-S. & Dai, L.-Y. Degenerative cervical spondylolisthesis: a systematic review. *International orthopaedics* **35**, 869–875 (2011).
178. Fedorchuk, C. *et al.* Prevalence of Cervical Spondylolisthesis in the Sagittal Plane Using Radiographic Imaging in a Pediatric Population: A Cross Sectional Analysis of Vertebral Subluxation. *Journal of Radiology Case Reports* **15**, 1–18 (2021).
179. Wang, Z. *et al.* Spino Cranial Angle and Degenerative Cervical Spondylolisthesis. *World Neurosurgery* (2021).
180. Kawasaki, M., Tani, T., Ushida, T. & Ishida, K. Anterolisthesis and retrolisthesis of the cervical spine in cervical spondylotic myelopathy in the elderly. *Journal of Orthopaedic Science* **12**, 207 (2007).
181. Matsuda, M., Huh, Y. & Ji, R.-R. Roles of inflammation, neurogenic inflammation, and neuroinflammation in pain. *Journal of anesthesia* **33**, 131–139 (2019).
182. Segura-Trepichio, M., Pérez-Maciá, M. V., Candela-Zaplana, D. & Nolasco, A. Lumbar disc herniation surgery: Is it worth adding interspinous spacer or instrumented fusion with regard to disc

excision alone? *Journal of Clinical Neuroscience* **86**, 193–201 (2021).
183. Amin, R. M., Andrade, N. S. & Neuman, B. J. Lumbar disc herniation. *Current reviews in musculoskeletal medicine* **10**, 507–516 (2017).
184. Yeung, J. T., Johnson, J. I. & Karim, A. S. Cervical disc herniation presenting with neck pain and contralateral symptoms: a case report. *Journal of medical case reports* **6**, 1–4 (2012).
185. Kushchayev, S. v *et al.* ABCs of the degenerative spine. *Insights into imaging* **9**, 253–274 (2018).
186. Mazanec, D. & Reddy, A. Medical management of cervical spondylosis. *Neurosurgery* **60**, S1-43 (2007).
187. Perale, G. & Rossi, F. *Spinal Cord Injury (SCI) Repair Strategies*. (Woodhead Publishing, 2019).
188. Khan, A. N. *et al.* Inflammatory biomarkers of low back pain and disc degeneration: a review. *Annals of the new york academy of sciences* **1410**, 68–84 (2017).
189. Fujii, K. *et al.* Discogenic back pain: literature review of definition, diagnosis, and treatment. *JBMR plus* **3**, e10180 (2019).
190. Lyu, F.-J. *et al.* Painful intervertebral disc degeneration and inflammation: from laboratory evidence to clinical interventions. *Bone Research* **9**, 1–14 (2021).
191. Myers, R. R., Campana, W. M. & Shubayev, V. I. The role of neuroinflammation in neuropathic pain: mechanisms and therapeutic targets. *Drug discovery today* **11**, 8–20 (2006).
192. Hadjipavlou, A. G., Tzermiadianos, M. N., Bogduk, N. & Zindrick, M. R. The pathophysiology of disc degeneration: a critical review. *The Journal of bone and joint surgery. British volume* **90**, 1261–1270 (2008).
193. Lyu, F.-J. *et al.* Painful intervertebral disc degeneration and inflammation: from laboratory evidence to clinical interventions. *Bone Research* **9**, 1–14 (2021).
194. Li, J., Qin, S., Li, Y. & Shen, Y. Modic changes of the cervical spine: T1 slope and its impact on axial neck pain. *Journal of pain research* **10**, 2041 (2017).

195. Purmessur, D., Freemont, A. J. & Hoyland, J. A. Expression and regulation of neurotrophins in the nondegenerate and degenerate human intervertebral disc. *Arthritis research & therapy* **10**, 1–9 (2008).
196. Dallos, A. *et al.* Effects of the neuropeptides substance P, calcitonin gene-related peptide, vasoactive intestinal polypeptide and galanin on the production of nerve growth factor and inflammatory cytokines in cultured human keratinocytes. *Neuropeptides* **40**, 251–263 (2006).
197. Zhang, S. *et al.* The role of structure and function changes of sensory nervous system in intervertebral disc-related low back pain. *Osteoarthritis and Cartilage* (2020).
198. Peng, B. & DePalma, M. J. Cervical disc degeneration and neck pain. *Journal of pain research* **11**, 2853 (2018).
199. Gellhorn, A. C., Katz, J. N. & Suri, P. Osteoarthritis of the spine: the facet joints. *Nature Reviews Rheumatology* **9**, 216–224 (2013).
200. Fritz, J. M. Lumbar Spinal Stenosis. *Orthopaedic Physical Therapy Secrets* 461–467 (2006) doi:10.1016/B978-156053708-3.50058-1.
201. Boyle, J. J. W., Milne, N. & Singer, K. P. Influence of age on cervicothoracic spinal curvature: an ex vivo radiographic survey. *Clinical biomechanics* **17**, 361–367 (2002).
202. le Huec, J. C., Thompson, W., Mohsinaly, Y., Barrey, C. & Faundez, A. Sagittal balance of the spine. *European spine journal* **28**, 1889–1905 (2019).
203. Azimi, P., Yazdanian, T., Benzel, E. C. & Montazeri, A. Global sagittal balance of spine in asymptomatic controls: A systematic review and meta-analysis. *World Neurosurgery* (2021).
204. Yeung, K. H. *et al.* Implication of head position on global sagittal alignment of Adolescent Idiopathic Scoliosis with and without thoracic hypokyphosis after posterior spinal fusion. *Studies in health technology and informatics* **280**, 285 (2021).
205. Ling, F. P., Chevillotte, T., Thompson, W., Bouthors, C. & le Huec, J.-C. Which parameters are relevant in sagittal balance analysis of the cervical spine? A literature review. *European spine journal* **27**, 8–15 (2018).

206. le Huec, J. C., Thompson, W., Mohsinaly, Y., Barrey, C. & Faundez, A. Sagittal balance of the spine. *European spine journal* **28**, 1889–1905 (2019).
207. Leone, A., Cianfoni, A., Cerase, A., Magarelli, N. & Bonomo, L. Lumbar spondylolysis: a review. *Skeletal radiology* **40**, 683–700 (2011).
208. Morita, T., Ikata, T., Katoh, S. & Miyake, R. Lumbar spondylolysis in children and adolescents. *The Journal of bone and joint surgery. British volume* **77**, 620–625 (1995).
209. Sonne-Holm, S., Jacobsen, S., Rovsing, H. C., Monrad, H. & Gebuhr, P. Lumbar spondylolysis: a life long dynamic condition? A cross sectional survey of 4.151 adults. *European Spine Journal* **16**, 821–828 (2007).
210. Brooks, B. K., Southam, S. L., Mlady, G. W., Logan, J. & Rosett, M. 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. *Skeletal radiology* **39**, 669–673 (2010).
211. Brooks, B. K., Southam, S. L., Mlady, G. W., Logan, J. & Rosett, M. 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. *Skeletal radiology* **39**, 669–673 (2010).
212. Kim, D., Lee, U., Park, S., Kwak, D. & Han, S. Identification using frontal sinus by three-dimensional reconstruction from computed tomography. *Journal of forensic sciences* **58**, 5–12 (2013).
213. Dickie, A. M. *et al.* Comparison of ultrasonography, radiography and a single computed tomography slice for the identification of fluid within the canine tympanic bulla. *Research in veterinary science* **75**, 209–216 (2003).
214. Andreas, G.-W. J. & Johanssons, E. Observational methods for assessing ergonomic risks for work-related musculoskeletal disorders. A scoping review. *Revista Ciencias de la Salud* **16**, 8–38 (2018).

215. Sundaresan, N., Boriani, S. & Okuno, S. State of the art management in spine oncology: a worldwide perspective on its evolution, current state, and future. *Spine* **34**, S7–S20 (2009).
216. Nógrádi, A. & Vrbová, G. Anatomy and physiology of the spinal cord. in *Transplantation of neural tissue into the spinal cord* 1–23 (Springer, 2006).
217. Kirshblum, S. & Lin, V. W. *Spinal cord medicine*. (Springer Publishing Company, 2018).
218. Tsuchiya, K., Fujikawa, A., Honya, K., Nitatori, T. & Suzuki, Y. Diffusion tensor tractography of the lower spinal cord. *Neuroradiology* **50**, 221–225 (2008).
219. Dolma, S. & Kumar, H. Neutrophil, Extracellular Matrix Components, and Their Interlinked Action in Promoting Secondary Pathogenesis After Spinal Cord Injury. *Molecular Neurobiology* 1–14 (2021).
220. Parvin, S., Williams, C. R., Jarrett, S. A. & Garraway, S. M. Spinal Cord Injury Increases Pro-inflammatory Cytokine Expression in Kidney at Acute and Sub-chronic Stages. *Inflammation* 1–16 (2021).
221. Gomes, T. S. C. Sistema nervioso autónomo. *Consultado el* **15**,.
222. Richter, M. & Wright, R. A. Autonomic Nervous System (ANS). *Encyclopedia of Behavioral Medicine/Gellman MD, Turner JR (eds).-Springer, New York, NY* 165 (2013).
223. McCorry, L. K. Physiology of the autonomic nervous system. *American journal of pharmaceutical education* **71**, (2007).
224. Gomes, T. S. C. Sistema nervioso autónomo. *Consultado el* **15**,.
225. Gibbons, C. H. Basics of autonomic nervous system function. *Handbook of clinical neurology* **160**, 407–418 (2019).
226. Aalkjaer, C., Nilsson, H. & de Mey, J. G. R. Sympathetic and sensory-motor nerves in peripheral small arteries. *Physiological Reviews* **101**, 495–544 (2021).
227. Suer, M. Anatomy of the Trigeminal Nerve. in *Trigeminal Nerve Pain* 5–16 (Springer, 2021).
228. Kastoer, C., Leach, R. & Vanderveken, O. Face and neck: airway and sensorial capacities. *B-ENT/Royal Belgian Society for Ear,*

Nose, Throat, Head and Neck Surgery [Leuven]-Leuven, 2005, currens **12**, 11–19 (2016).
229. Ogata, H. *et al.* Optic, trigeminal, and facial neuropathy related to anti-neurofascin 155 antibody. *Annals of Clinical and Translational Neurology* **7**, 2297–2309 (2020).
230. Panjabi, M. M., Crisco III, J. J., Lydon, C. & Dvorak, J. The mechanical properties of human alar and transverse ligaments at slow and fast extension rates. *Clinical Biomechanics* **13**, 112–120 (1998).
231. Schofferman, J., Bogduk, N. & Slosar, P. Chronic whiplash and whiplash-associated disorders: an evidence-based approach. *JAAOS-Journal of the American Academy of Orthopaedic Surgeons* **15**, 596–606 (2007).
232. Ono, K., Kaneoka, K., Wittek, A. & Kajzer, J. Cervical injury mechanism based on the analysis of human cervical vertebral motion and head-neck-torso kinematics during low speed rear impacts. *SAE transactions* 3859–3876 (1997).
233. Panjabi, M. M. Cervical spine models for biomechanical research. *Spine* **23**, 2684–2699 (1998).
234. Aprill, C. & Bogduk, N. The prevalence of cervical zygapophyseal joint pain. A first approximation. *Spine* **17**, 744–747 (1992).
235. Bogduk, N. & Marsland, A. The cervical zygapophysial joints as a source of neck pain. *Spine* **13**, 610–617 (1988).
236. Silberstein, S. D., Lipton, R. B. & Dalessio, D. J. *Wolff's headache and other head pain*. (Oxford University Press, 2001).
237. Bogduk, N. & Aprill, C. On the nature of neck pain, discography and cervical zygapophysial joint blocks. *Pain* **54**, 213–217 (1993).
238. Lord, S. M., Barnsley, L., Wallis, B. J. & Bogduk, N. Third occipital nerve headache: a prevalence study. *Journal of Neurology, Neurosurgery & Psychiatry* **57**, 1187–1190 (1994).
239. Kerr, F. W. L. Structural relation of the trigeminal spinal tract to upper cervical roots and the solitary nucleus in the cat. *Experimental neurology* **4**, 134–148 (1961).
240. Trigeminal neuralgia _ MS Trust.

241. Cochard, L. R. *Netter's Atlas of Human Embryology E-Book: Updated Edition*. (Elsevier Health Sciences, 2012).
242. Stecco, C. *et al.* Dermatome and fasciatome. *Clinical Anatomy* **32**, 896–902 (2019).
243. Herringham, W. P. The minute anatomy of the brachial plexus. *Proceedings of the Royal Society of London* **41**, 423–441 (1887).
244. Head, H. On disturbances of sensation with especial reference to the pain of visceral disease. *Brain* **16**, 1–133 (1893).
245. Sherrington, C. S. Experiments in examination of the peripheral distribution of the fibres of the posterior roots of some spinal nerves. Part II. *Philosophical Transactions of the Royal Society of London. Series B, Containing Papers of a Biological Character* **190**, 45–186 (1898).
246. Foerster, O. The dermatomes in man. *Brain* **56**, 1–39 (1933).
247. Keegan, J. J. & Garrett, F. D. The segmental distribution of the cutaneous nerves in the limbs of man. *The Anatomical Record* **102**, 409–437 (1948).
248. Denny-Brown, D. & Kirk, E. Hyperesthesia from spinal and root lesions. *Transactions of the American Neurological Association* **93**, 116–120 (1968).
249. Kirk, E. J. & Denny-Brown, D. Functional variation in dermatomes in the macaque monkey following dorsal root lesions. *Journal of Comparative Neurology* **139**, 307–320 (1970).
250. Lee, M. W. L., McPhee, R. W. & Stringer, M. D. An evidence-based approach to human dermatomes. *Clinical Anatomy: The Official Journal of the American Association of Clinical Anatomists and the British Association of Clinical Anatomists* **21**, 363–373 (2008).
251. Herzog, W. The biomechanics of spinal manipulation. *Journal of bodywork and movement therapies* **14**, 280–286 (2010).
252. Fuhr, A. W. & Menke, J. M. Activator methods chiropractic technique. *Topics in Clinical Chiropractic* **9**, 30–44 (2002).
253. Kim Christensen, D. C. & DACRB, C. Postural Stability: Its Role in Chiropractic Care.

254. Schalow, P. R. Chiropractic Management of Performance Related Musculoskeletal Disorder in a Career Violist. *The American Journal of Case Reports* **21**, e923943-1 (2020).
255. Haas, M., Groupp, E. & Kraemer, D. F. Dose-response for chiropractic care of chronic low back pain. *The Spine Journal* **4**, 574–583 (2004).
256. Iben, A., Lise, H. & Charlotte, L.-Y. Chiropractic maintenance care-what's new? A systematic review of the literature. *Chiropractic & manual therapies* **27**, (2019).
257. Singh, A. *Athletic Care and Rehabilitation*. (Friends Publications (India), 2021).
258. Davis, M., Yakusheva, O., Liu, H., Anderson, B. & Bynum, J. The Effect of Reduced Access to Chiropractic Care on Medical Service Use for Spine Conditions Among Older Adults. *Journal of Manipulative and Physiological Therapeutics* (2021).
259. Bezdjian, S., Whedon, J. M., Russell, R. & Coulter, I. Patient Characteristics Associated With Self-Reported Adherence to Chiropractic Treatment Recommendations: A Feasibility Study. *Journal of Manipulative and Physiological Therapeutics* (2021).
260. Tvedskov, J. F., Tfelt-Hansen, P., Petersen, K. A., Jensen, L. T. & Olesen, J. CGRP receptor antagonist olcegepant (BIBN4096BS) does not prevent glyceryl trinitrate-induced migraine. *Cephalalgia* **30**, 1346–1353 (2010).
261. Aikawa, J. *et al.* Expression of calcitonin gene-related peptide in the infrapatellar fat pad in knee osteoarthritis patients. *Journal of orthopaedic surgery and research* **12**, 1–6 (2017).
262. Altman, D. G. Practical statistics for medical research Chapman and Hall. *London and New York* (1991).
263. Faul, F., Erdfelder, E., Lang, A.-G. & Buchner, A. G* Power 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behavior research methods* **39**, 175–191 (2007).
264. Faul, F., Erdfelder, E., Buchner, A. & Lang, A.-G. Statistical power analyses using G* Power 3.1: Tests for correlation and regression analyses. *Behavior research methods* **41**, 1149–1160 (2009).

265. Leshem, Y. A., Hajar, T., Hanifin, J. M. & Simpson, E. L. What the Eczema Area and Severity Index score tells us about the severity of atopic dermatitis: an interpretability study. *British Journal of Dermatology* **172**, 1353–1357 (2015).
266. Hanifin, J. M. *et al.* The eczema area and severity index (EASI): assessment of reliability in atopic dermatitis. *Experimental dermatology* **10**, 11–18 (2001).
267. Silverberg, J. I. *et al.* What are the best endpoints for Eczema Area and Severity Index and Scoring Atopic Dermatitis in clinical practice? A prospective observational study. *British Journal of Dermatology* **184**, 888–895 (2021).
268. Chansky, P. B., Mittal, L. & Werth, V. P. Dermatological evaluation in patients with skin of colour: the effect of erythema on outcome measures in atopic dermatitis. *The British journal of dermatology* **176**, 853 (2017).
269. Holm, E. A., Wulf, H. C., Thomassen, L. & Jemec, G. B. E. Instrumental assessment of atopic eczema: validation of transepidermal water loss, stratum corneum hydration, erythema, scaling, and edema. *Journal of the American Academy of Dermatology* **55**, 772–780 (2006).
270. Hanifin, J. M. *et al.* The eczema area and severity index (EASI): assessment of reliability in atopic dermatitis. *Experimental dermatology* **10**, 11–18 (2001).
271. Wolf, R. & Wolf, D. Abnormal epidermal barrier in the pathogenesis of atopic dermatitis. *Clinics in dermatology* **30**, 329–334 (2012).
272. Suárez-Fariñas, M. *et al.* Nonlesional atopic dermatitis skin is characterized by broad terminal differentiation defects and variable immune abnormalities. *Journal of allergy and clinical immunology* **127**, 954–964 (2011).
273. Das, A. & Sarkar, R. Signs and symptoms of skin disease. in *Concise Dermatology* 9–18 (CRC Press, 2021).
274. Deleuran, M., Olesen, A. B. & Thestrup-Pedersen, K. Clinical Symptoms of Atopic Eczema. in *Handbook of Atopic Eczema* 37–44 (Springer, 2006).

275. Ahire, P. & Udare, S. Clinical Manifestations of Atopic Dermatitis. *Atopic Dermatitis* 24 (2018).
276. Tsutsumi, M. *et al.* Abnormal morphology of blood vessels in erythematous skin from atopic dermatitis patients. *The American Journal of Dermatopathology* **38**, 363–364 (2016).
277. Leung, D. Y. M. Atopic dermatitis: new insights and opportunities for therapeutic intervention. *Journal of Allergy and Clinical Immunology* **105**, 860–876 (2000).
278. Harrop, J. S. *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: Invited submission from the joint section meeting on disorders of the spine and peripheral nerves, March 2005. *Journal of Neurosurgery: Spine* **4**, 118–122 (2006).
279. Lee, J. Y. *et al.* Thoracolumbar injury classification and severity score: a new paradigm for the treatment of thoracolumbar spine trauma. *Journal of Orthopaedic Science* **10**, 671–675 (2005).
280. Kotil, K., Alan, M. S. & Bilge, T. Medical management of Pott disease in the thoracic and lumbar spine: a prospective clinical study. *Journal of Neurosurgery: Spine* **6**, 222–228 (2007).
281. Kaale, B. R., Krakenes, J., Albrektsen, G. & Wester, K. Whiplash-associated disorders impairment rating: neck disability index score according to severity of MRI findings of ligaments and membranes in the upper cervical spine. *Journal of neurotrauma* **22**, 466–475 (2005).
282. Hasegawa, K., Kitahara, K., Shimoda, H. & Hara, T. Facet joint opening in lumbar degenerative diseases indicating segmental instability. *Journal of Neurosurgery: Spine* **12**, 687–693 (2010).
283. Lotz, J. C. *et al.* New treatments and imaging strategies in degenerative disease of the intervertebral disks. *Radiology* **264**, 6–19 (2012).
284. Garg, A. & Kapellusch, J. M. Applications of biomechanics for prevention of work-related musculoskeletal disorders. *Ergonomics* **52**, 36–59 (2009).

285. Anderson, P. A. *et al.* Cervical spine injury severity score: assessment of reliability. *JBJS* **89**, 1057–1065 (2007).
286. Zabjek, K. F. & Zeller, R. Emerging technology and analytical techniques for the clinical assessment of scoliosis. in *Book: Recent Advances in Scoliosis* 145–164 (2012).
287. Kumar, R., Aggarwal, A., Krishnan, V., Gopinathan, N. & Chakraborty, S. Femoroacetabular impingement and comparison of radiological indexes: a study on 50 cases. *Musculoskeletal surgery* **97**, 153–158 (2013).
288. Quek, J., Pua, Y.-H., Clark, R. A. & Bryant, A. L. Effects of thoracic kyphosis and forward head posture on cervical range of motion in older adults. *Manual therapy* **18**, 65–71 (2013).
289. Koslosky, E. & Gendelberg, D. Classification in Brief: The Meyerding classification system of spondylolisthesis. *Clinical orthopaedics and related research* **478**, 1125 (2020).
290. Hennenhoefer, K. & Schmidt, D. Toward a theory of the mechanism of high-velocity, low-amplitude technique: a literature review. *Journal of Osteopathic Medicine* **119**, 688–695 (2019).
291. Hawk, C., Rupert, R. L., Colonvega, M., Boyd, J. & Hall, S. Comparison of bioenergetic synchronization technique and customary chiropractic care for older adults with chronic musculoskeletal pain. *Journal of manipulative and physiological therapeutics* **29**, 540–549 (2006).
292. Cooperstein, R. Gonstead chiropractic technique (GCT). *Journal of chiropractic medicine* **2**, 16–24 (2003).
293. Shin, C., Kim, M. & Park, G. D. Impact of post-manipulation corrective core exercises on the spinal deformation and lumbar strength in golfers: a case study. *Journal of physical therapy science* **27**, 3027–3030 (2015).
294. Gleberzon, B. J. Chiropractic "name techniques": a review of the literature. *The Journal of the Canadian Chiropractic Association* **45**, 86 (2001).
295. Shankland, W. E. The trigeminal nerve. Part II: the ophthalmic division. *CRANIO®* **19**, 8–12 (2001).

296. Suer, M. Anatomy of the Trigeminal Nerve. in *Trigeminal Nerve Pain* 5–16 (Springer, 2021).
297. Terrier, L. *et al.* The trigeminal system: The meningovascular complex—A review. *Journal of Anatomy* (2021).
298. Goh, C. L. Eczema of the face, scalp and neck: an epidemiological comparison by site. *The Journal of dermatology* **16**, 223–226 (1989).
299. Amalia, S. N. *et al.* Suppression of neuropeptide by botulinum toxin improves imiquimod-induced psoriasis-like dermatitis via the regulation of neuroimmune system. *Journal of Dermatological Science* **101**, 58–68 (2021).
300. Zhang, Y. *et al.* Current views on neuropeptides in atopic dermatitis. *Experimental Dermatology* (2021).
301. Legat, F. J. Itch in Atopic Dermatitis–What Is New? *Frontiers in Medicine* **8**, 629 (2021).
302. Vink, R. Blocking neurogenic inflammation for the treatment of acute disorders of the central nervous system. (2013).
303. Choi, J. E. & di Nardo, A. Skin neurogenic inflammation. in *Seminars in immunopathology* vol. 40 249–259 (Springer, 2018).
304. Schmelz, M. & Petersen, L. J. Neurogenic inflammation in human and rodent skin. *Physiology* **16**, 33–37 (2001).
305. Geppetti, P., Nassini, R., Materazzi, S. & Benemei, S. The concept of neurogenic inflammation. *BJU international* **101**, 2–6 (2008).
306. Zegarska, B., Leliñska, A. & Tyrakowski, T. Clinical and experimental aspects of cutaneous neurogenic inflammation. *Pharmacological reports* **58**, 13 (2006).
307. Bandyopadhyay, M. *et al.* Skin delivery of hapten and neurokinin-1 receptor antagonists by microneedle arrays targets neurogenic inflammation and prevents contact dermatitis. (2021).
308. Cupini, L. M., Corbelli, I. & Sarchelli, P. Menstrual migraine: what it is and does it matter? *Journal of neurology* **268**, 2355–2363 (2021).
309. Marichal-Cancino, B. A., González-Hernández, A., Guerrero-Alba, R., Medina Santillán, R. & Villalón, C. M. A critical review of the neurovascular nature of migraine and the main mechanisms of

action of prophylactic antimigraine medications. *Expert Review of Neurotherapeutics* (2021).
310. Moisset, X., Giraud, P. & Dallel, R. Migraine in multiple sclerosis and other chronic inflammatory diseases. *Revue Neurologique* (2021).
311. Williamson, D. J. & Hargreaves, R. J. Neurogenic inflammation in the context of migraine. *Microscopy research and technique* **53**, 167–178 (2001).
312. Ramachandran, R. Neurogenic inflammation and its role in migraine. in *Seminars in immunopathology* vol. 40 301–314 (Springer, 2018).
313. Geppetti, P. *et al.* CGRP and migraine: neurogenic inflammation revisited. *The journal of headache and pain* **6**, 61–70 (2005).
314. Shreberk-Hassidim, R. *et al.* Atopic dermatitis in Israeli Adolescents from 1998 to 2013: trends in time and association with migraine. *Pediatric dermatology* **34**, 247–252 (2017).
315. Salas-Callo, C. I., Tosti, A., Stohmann, D., Contarini, P. & Pirmez, R. Eyelash involvement in frontal fibrosing alopecia: a prospective study. *Journal of the American Academy of Dermatology* (2021) doi:10.1016/j.jaad.2021.07.063.
316. cervical spine-eye-.
317. Toriyama, Y. *et al.* Pathophysiological function of endogenous calcitonin gene-related peptide in ocular vascular diseases. *American Journal of Pathology* **185**, 1783–1794 (2015).
318. Nagineni, C. N., Kommineni, V. K., William, A., Detrick, B. & Hooks, J. J. Regulation of VEGF expression in human retinal cells by cytokines: Implications for the role of inflammation in age-related macular degeneration. *Journal of Cellular Physiology* **227**, 116–126 (2012).
319. Sabatino, F., di Zazzo, A., de Simone, L. & Bonini, S. The Intriguing Role of Neuropeptides at the Ocular Surface. *Ocular Surface* vol. 15 2–14 (2017).
320. Sánchez-González, M. C. *et al.* Visual system disorders and musculoskeletal neck complaints: a systematic review and meta-

analysis. *Annals of the New York Academy of Sciences* vol. 1457 26–40 (2019).
321. di Zazzo, A. *et al.* Ocular surface diabetic disease: A neurogenic condition? *The Ocular Surface* **19**, 218–223 (2021).
322. Wahlestedt, C. *et al.* Calcitonin gene-related peptide in the eye: release by sensory nerve stimulation and effects associated with neurogenic inflammation. *Regulatory peptides* **16**, 107–115 (1986).
323. Jancsó, N., JANCSÓ-GÁBOR, A. & Szolcsanyi, J. The role of sensory nerve endings in neurogenic inflammation induced in human skin and in the eye and paw of the rat. *British journal of pharmacology and chemotherapy* **33**, 32–41 (1968).
324. Loh, B. K. & Wong, D. Myopic pre-foveoschisis: an earlier stage of myopic foveoschisis documented by optical coherence tomography. *Eye* vol. 24 1107–1109 (2010).
325. Dumitrache, M.-D. *et al.* Comparative effects of capsaicin in chronic obstructive pulmonary disease and asthma. *Experimental and therapeutic medicine* **22**, 1–12 (2021).
326. Barnes, P. J. Neurogenic inflammation and asthma. *Journal of Asthma* **29**, 165–180 (1992).
327. Butler, C. A. & Heaney, L. G. Neurogenic inflammation and asthma. *Inflammation & Allergy-Drug Targets (Formerly Current Drug Targets-Inflammation & Allergy)(Discontinued)* **6**, 127–132 (2007).
328. Barnes, P. J. Neurogenic inflammation in the airways. *Respiration physiology* **125**, 145–154 (2001).
329. Groneberg, D. A., Quarcoo, D., Frossard, N. & Fischer, A. Neurogenic mechanisms in bronchial inflammatory diseases. *Allergy* **59**, 1139–1152 (2004).
330. Barnes, P. J. Neurogenic inflammation in airways. *International Archives of Allergy and Immunology* **94**, 303–309 (1991).
331. Meggs, W. J. Neurogenic inflammation and sensitivity to environmental chemicals. *Environmental health perspectives* **101**, 234–238 (1993).
332. Choi, J. E. & di Nardo, A. Skin neurogenic inflammation. in *Seminars in immunopathology* vol. 40 249–259 (Springer, 2018).

333. Schmelz, M. & Petersen, L. J. Neurogenic inflammation in human and rodent skin. *Physiology* **16**, 33–37 (2001).
334. Wang, H. *et al.* Ethnic differences in pain, itch and thermal detection in response to topical capsaicin: African Americans display a notably limited hyperalgesia and neurogenic inflammation. *British Journal of Dermatology* **162**, 1023–1029 (2010).
335. Siiskonen, H. & Harvima, I. Mast cells and sensory nerves contribute to neurogenic inflammation and pruritus in chronic skin inflammation. *Frontiers in cellular neuroscience* **13**, 422 (2019).
336. Aubdool, A. A. & Brain, S. D. Neurovascular aspects of skin neurogenic inflammation. in *Journal of Investigative Dermatology Symposium Proceedings* vol. 15 33–39 (Elsevier, 2011).
337. Arck, P. & Paus, R. From the brain-skin connection: the neuroendocrine-immune misalliance of stress and itch. *Neuroimmunomodulation* **13**, 347–356 (2006).
338. Yosipovitch, G., Greaves, M. W. & Schmelz, M. Itch. *The Lancet* **361**, 690–694 (2003).
339. Misery, L. *et al.* CHRONIC ITCH: EMERGING TREATMENTS FOLLOWING NEW RESEARCH CONCEPTS. *British Journal of Pharmacology* (2021).
340. Wyckmans, M. M. Hell's itch could be caused by neurogenic inflammation: proposed pathophysiology and treatment options. *Journal of Travel Medicine* **28**, taaa204 (2021).
341. Legat, F. J. Itch in Atopic Dermatitis–What Is New? *Frontiers in Medicine* **8**, 629 (2021).
342. Umehara, Y. *et al.* Intractable Itch in Atopic Dermatitis: Causes and Treatments. *Biomedicines* **9**, 229 (2021).
343. Reyes, J. L. *et al.* Innate and Adaptive Cell Populations Driving Inflammation in Dry Eye Disease. *Mediators of Inflammation* vol. 2018 (2018).
344. Lee, J. J., Morillo-Hernandez, C., Agarwal, V., Standaert, C. J. & English, J. C. Cervical Spine Imaging and Treatment Outcomes in Scalp Dysesthesia: A Retrospective Cohort Study. *Journal of the American Academy of Dermatology* (2020) doi:10.1016/j.jaad.2020.08.010.

345. Trebst, C. *et al.* Longitudinal extensive transverse myelitis-it's not all neuromyelitis optica. *Nature Reviews Neurology* vol. 7 688–698 (2011).
346. ojos secos-cartton-.
347. ojos secos-.
348. Sasegbon, A. & Hamdy, S. The anatomy and physiology of normal and abnormal swallowing in oropharyngeal dysphagia. *Neurogastroenterology and Motility* vol. 29 (2017).
349. Barabino, S. *et al.* The role of systemic and topical fatty acids for dry eye treatment. *Progress in Retinal and Eye Research* vol. 61 23–34 (2017).
350. dry-eye3-.
351. Lin, C. C. & Chiu, M. J. Teaching neuro image: Cervical cord atrophy with dorsal root ganglionopathy in sjögren syndrome. *Neurology* vol. 70 e27 (2008).
352. Narváez, J., Nolla, J. M. & Valverde, J. No serological evidence that fibromyalgia is linked with exposure to human parvovirus B19 [2]. *Joint Bone Spine* vol. 72 592–594 (2005).
353. dry-eye1-.
354. Priola, A. M., Gned, D., Veltri, A. & Priola, S. M. Case 261. *Radiology* **288**, 898–900 (2018).
355. Sène, D. Small fiber neuropathy: Diagnosis, causes, and treatment. *Joint Bone Spine* vol. 85 553–559 (2018).
356. Giannaccare, G. *et al.* Dry eye disease in strabismus patients: Does eye deviation harm ocular surface? *Medical Hypotheses* **111**, 15–18 (2018).
357. Milin, M. *et al.* Sicca symptoms are associated with similar fatigue, anxiety, depression, and quality-of-life impairments in patients with and without primary Sjögren's syndrome. *Joint Bone Spine* **83**, 681–685 (2016).
358. Mrugacz, M. *et al.* Pro-inflammatory cytokines associated with clinical severity of dry eye disease of patients with depression. *Advances in Medical Sciences* **62**, 338–344 (2017).

359. Lambiase, A. *et al. Alterations of Tear Neuromediators in Dry Eye Disease*. *Arch Ophthalmol* vol. 129 https://jamanetwork.com/ (2011).
360. cgrp-eye-.
361. Milling, S. & Edgar, J. M. How T'reg-ulate healing of the injured spinal cord? *Immunology* vol. 158 253–254 (2019).
362. Szepietowski, J. C. & Reich, A. Pruritus in psoriasis: An update. *European Journal of Pain* **20**, 41–46 (2016).
363. Choi, J. E. & di Nardo, A. Skin neurogenic inflammation. in *Seminars in immunopathology* vol. 40 249–259 (Springer, 2018).
364. Glinski, W., Glinska-Ferenz, M. & Pierozynska-Dubowska, M. Neurogenic inflammation induced by capsaicin in patients with psoriasis. *Acta dermato-venereologica* **71**, 51–54 (1991).
365. Raychaudhuri, S. P. & Raychaudhuri, S. K. Role of NGF and neurogenic inflammation in the pathogenesis of psoriasis. *Progress in brain research* **146**, 433–437 (2004).
366. Wang, X. *et al.* Dysregulation of the gut-brain-skin axis and key overlapping inflammatory and immune mechanisms of psoriasis and depression. *Biomedicine & Pharmacotherapy* **137**, 111065 (2021).
367. Naukkarinen, A., Harvima, I. T., AALTO, M. & Horsmanheimo, M. Mast cell tryptase and chymase are potential regulators of neurogenic inflammation in psoriatic skin. *International journal of dermatology* **33**, 361–366 (1994).
368. Saraceno, R., Kleyn, C. E., Terenghi, G. & Griffiths, C. E. M. The role of neuropeptides in psoriasis. *British Journal of Dermatology* **155**, 876–882 (2006).
369. Zegarska, B., Leliñska, A. & Tyrakowski, T. Clinical and experimental aspects of cutaneous neurogenic inflammation. *Pharmacological reports* **58**, 13 (2006).
370. Steinhoff, M. *et al.* Clinical, cellular, and molecular aspects in the pathophysiology of rosacea. in *Journal of Investigative Dermatology Symposium Proceedings* vol. 15 2–11 (Elsevier, 2011).

371. Choi, J. E. & di Nardo, A. Skin neurogenic inflammation. in *Seminars in immunopathology* vol. 40 249–259 (Springer, 2018).
372. Buddenkotte, J. & Steinhoff, M. Recent advances in understanding and managing rosacea. *F1000Research* **7**, (2018).
373. Weiss, E. & Katta, R. Diet and rosacea: the role of dietary change in the management of rosacea. *Dermatology practical & conceptual* **7**, 31 (2017).
374. Sulk, M. *et al.* Distribution and expression of non-neuronal transient receptor potential (TRPV) ion channels in rosacea. *Journal of investigative dermatology* **132**, 1253–1262 (2012).
375. Kim, H. O. *et al.* Neurogenic rosacea in Korea. *The Journal of Dermatology* **48**, 49–55 (2021).
376. Deng, Z. *et al.* The association between rosacea and the condition of low tolerance to skincare of the facial skin: a case-control study in China. *Journal of Cosmetic Dermatology* (2021).
377. Rodrigues-Braz, D. *et al.* Cutaneous and ocular rosacea: Common and specific physiopathogenic mechanisms and study models. *Molecular Vision* **27**, 323 (2021).
378. Tebet, M. A. Current concepts on the sagittal balance and classification of spondylolysis and spondylolisthesis. *Revista Brasileira de Ortopedia (English Edition)* **49**, 3–12 (2014).
379. Mikkelsen, D. Chiropractic treatment of cystitis: a possible mechanism. *The British Journal of Chiropractic* **1**, 16–17 (1998).
380. Seaman, D. R. Toxins, toxicity, and endotoxemia: a historical and clinical perspective for chiropractors. *Journal of chiropractic humanities* **23**, 68–76 (2016).
381. Cashley, M. A. P. & Cashley, M. A. Chiropractic care of interstitial cystitis/painful bladder syndrome associated with pelvic lumbar spine dysfunction: a case series. *Journal of chiropractic medicine* **11**, 260–266 (2012).
382. Pang, X. *et al.* Increased number of substance P positive nerve fibres in interstitial cystitis. *British journal of urology* **75**, 744–750 (1995).
383. Rist, P. M. *et al.* Multimodal chiropractic care for migraine: A pilot randomized controlled trial. *Cephalalgia* **41**, 318–328 (2021).

384. Urits, I. *et al.* A comprehensive review of alternative therapies for the management of chronic pain patients: acupuncture, tai chi, osteopathic manipulative medicine, and chiropractic care. *Advances in Therapy* **38**, 76–89 (2021).
385. Connor, J. P. *et al.* Perceptions of chiropractic care among women with migraine: A qualitative substudy using a grounded-theory framework. *Journal of Manipulative and Physiological Therapeutics* **44**, 154–163 (2021).
386. Moore, C., Adams, J., Leaver, A., Lauche, R. & Sibbritt, D. The treatment of migraine patients within chiropractic: analysis of a nationally representative survey of 1869 chiropractors. *BMC complementary and alternative medicine* **17**, 1–10 (2017).
387. Tuchin, P. J., Pollard, H. & Bonello, R. A randomized controlled trial of chiropractic spinal manipulative therapy for migraine. *Journal of manipulative and physiological therapeutics* **23**, 91–95 (2000).
388. Chaibi, A., Tuchin, P. J. & Russell, M. B. Manual therapies for migraine: a systematic review. *The journal of headache and pain* **12**, 127–133 (2011).
389. Eldred, D. C. & Tuchin, P. J. TREATMENT OF ACUTE ATOPIC ECZEMA BY CHIROPRACTIC CARE: A Case Study. *Australasian Chiropractic & Osteopathy* **8**, 96 (1999).
390. Takeda, Y. & Arai, S. Relationship Between Vertebral Deformities And Allergic Diseases The Internet Journal of Orthopedic Surgery 2004; Volume 2; Number. *The Internet Journal of Orthopedic Surgery* **2**, (2004).
391. Han, Z.-A., Choi, J. Y. & Ko, Y. J. Dermatological problems following spinal cord injury in Korean patients. *The journal of spinal cord medicine* **38**, 63–67 (2015).
392. Akiyama, T., Iodi Carstens, M. & Carstens, E. Transmitters and pathways mediating inhibition of spinal itch-signaling neurons by scratching and other counterstimuli. *PloS one* **6**, e22665 (2011).
393. Cevikbas, F., Steinhoff, M. & Ikoma, A. Role of spinal neurotransmitter receptors in itch: new insights into therapies and

drug development. *CNS neuroscience & therapeutics* **17**, 742–749 (2011).
394. Carstens, E., Carstens, M. I., Akiyama, T., Davoodi, A. & Nagamine, M. Opposing effects of cervical spinal cold block on spinal itch and pain transmission. *Itch (Philadelphia, Pa.)* **3**, (2018).
395. Koga, K. *et al.* Sensitization of spinal itch transmission neurons in a mouse model of chronic itch requires an astrocytic factor. *Journal of Allergy and Clinical Immunology* **145**, 183–191 (2020).
396. Kira, J. *et al.* Clinical, immunological and MRI features of myelitis with atopic dermatitis (atopic myelitis). *Journal of the neurological sciences* **162**, 56–61 (1999).
397. Ito, S., Hattori, T., Fukutake, T. & Sugimoto, K. Is atopic dermatitis a risk factor for intervertebral disc degeneration? A preliminary clinical and MRI study. *Journal of the neurological sciences* **206**, 39–42 (2003).
398. Liu, M. *et al.* Inhibition of stress corrosion cracking in 304 stainless steel through titanium ion implantation. *Materials Science and Technology* **36**, 284–292 (2020).
399. Kira, J. & Ochi, H. Juvenile muscular atrophy of the distal upper limb (Hirayama disease) associated with atopy. *Journal of Neurology, Neurosurgery & Psychiatry* **70**, 798–801 (2001).
400. Dogru, M., Nakagawa, N., Tetsumoto, K., Katakami, C. & Yamamoto, M. Ocular surface disease in atopic dermatitis. *Japanese journal of ophthalmology* **43**, 53–57 (1999).
401. Nakano, E., Iwasaki, T., Osanai, T., Yamamoto, K. & Miyauchi, M. Ocular complications of atopic dermatitis. *Nippon Ganka Gakkai Zasshi* **101**, 64–68 (1997).
402. Park, Y. H., Koo, H. M., Chung, S. K. & Lee, J. Y. Ocular complications in patients with atopic dermatitis. *Journal of the Korean Ophthalmological Society* **40**, 3422–3428 (1999).
403. Hwang, S. W., Park, S. W., Wang, H. Y. & Yoon, I. H. Characteristics of atopic dermatitis related to ocular complications. *Korean Journal of Dermatology* **39**, 542–547 (2001).

404. Golan, S., Rabina, G., Kurtz, S. & Leibovitch, I. The prevalence of glaucoma in patients undergoing surgery for eyelid entropion or ectropion. *Clinical interventions in aging* **11**, 1429 (2016).
405. Rozas-Muñoz, E. & Game, D. Allergic Contact Dermatitis of the Face: a Review of the Common Agents Involved and Differential Diagnosis. *Current Treatment Options in Allergy* **7**, 233–247 (2020).
406. Belden, K. A., Mascarenhas, T. R., Hendricks, T., Merkow, D. & Chen, A. F. Skin Disease and Musculoskeletal Infection. *Infectious Diseases in Clinical Practice* **28**, 71–77 (2020).
407. Kira, J. *et al.* Clinical, immunological and MRI features of myelitis with atopic dermatitis (atopic myelitis). *Journal of the neurological sciences* **162**, 56–61 (1999).
408. Park, S.-K. & Cho, I.-Y. Suggestions of Utilizing Manipulative Therapy to Atopic Dermatitis. *The Journal of the Korea Contents Association* **8**, 171–181 (2008).
409. Wiles, M., Williams, J. & Ahmad, K. *Essentials of dermatology for chiropractors*. (Jones & Bartlett Learning, 2010).
410. Knox, D. L. & Mustonen, E. Greater occipital neuralgia: an ocular pain syndrome with multiple etiologies. *Transactions of the American Academy of Ophthalmology and Otolaryngology* **79**, OP513–OP519 (1975).
411. Waersted, A. & Hjorth, N. Pityrosporum orbiculare--a pathogenic factor in atopic dermatitis of the face, scalp and neck? *Acta dermato-venereologica. Supplementum* **114**, 146–148 (1985).
412. Devos, S. A. & van der Valk, P. G. M. The relevance of skin prick tests for Pityrosporum ovale in patients with head and neck dermatitis. *Allergy* **55**, 1056–1058 (2000).
413. Muehlberger, T. & Rodi, T. Anatomy of the Greater Occipital Nerve Compression Site in Migraine Surgery. in *Atlas of Surgical Therapy for Migraine and Tension-Type Headache* 31–38 (Springer, 2020).
414. Sugimoto, K., Hattori, T. & Kitukawa, Y. Antiseptic Treatment of Povidone-Iodine Solution as a Countermeasure against Staphylococcus Aureus in Atopic Dermatitis. *Dermatol Res* **1**, 1–3 (2019).

415. Orme, C. M. *et al.* Possible photoactivated dermatitis with features of post-inflammatory pigmentary alteration (PIPA) and rosacea. *Dermatology online journal* **21**, (2015).
416. Kessler, L. A. Delayed, traumatic dislocation of the cervical spine. *JAMA* **224**, 124–125 (1973).
417. Ochani, T. D., Almirante, J., Siddiqui, A. & Kaplan, R. Allergic reaction to spinal cord stimulator. *The Clinical journal of pain* **16**, 178–180 (2000).
418. Ito, S., Hattori, T., Fukutake, T. & Sugimoto, K. Is atopic dermatitis a risk factor for intervertebral disc degeneration? A preliminary clinical and MRI study. *Journal of the neurological sciences* **206**, 39–42 (2003).
419. Phillips, R. E. Face. in *The Physical Exam* 73–96 (Springer, 2018).
420. Constantinescu, C. S., Thomas, M. & Zaman, A. G. Atopic optic neuritis. *Ocular immunology and inflammation* **14**, 125–127 (2006).
421. Williams, H. L., Montgomery, H. & Powell, W. N. Dermatitis of the Ear. *Journal of the American Medical Association* **113**, 641–646 (1939).
422. Cheng, A. T. L. & Young, N. M. Inflammatory diseases of the ear. *The Indian Journal of Pediatrics* **64**, 747–753 (1997).
423. Memar, O., Caughlin, B. & Djalilian, H. R. Symptoms, Solutions for Ear Itch. *The Hearing Journal* **72**, 44–46 (2019).
424. Liu, X. *et al.* Spinal GRPR and NPRA contribute to chronic itch in a murine model of allergic contact dermatitis. *Journal of Investigative Dermatology* **140**, 1856–1866 (2020).
425. Convers, K. D., Sturm, J. M. & Slavin, R. G. Chronic bilateral pruritic arm dermatitis in a 61-year-old woman. in *Allergy & Asthma Proceedings* vol. 34 (2013).
426. Wang, M. Y. Improvement of sagittal balance and lumbar lordosis following less invasive adult spinal deformity surgery with expandable cages and percutaneous instrumentation. *Journal of Neurosurgery: Spine* **18**, 4–12 (2013).
427. Diab, A. A. M. & Moustafa, I. M. The efficacy of lumbar extension traction for sagittal alignment in mechanical low back pain: a

randomized trial. *Journal of back and musculoskeletal rehabilitation* **26**, 213–220 (2013).
428. Lovegreen, W., Murphy, D. P., Stevens, P. M., Seo, Y. I. L. & Webster, J. B. Lower limb amputation and gait. in *Braddom's Physical Medicine and Rehabilitation* 174–208 (Elsevier, 2021).
429. Munoz, C. A., Gaspari, A. & Goldner, R. Contact dermatitis from a prosthesis. *Dermatitis* **19**, 109–111 (2008).
430. Haeck, I. M. *et al.* Low bone mineral density in adult patients with moderate to severe atopic dermatitis. *British Journal of Dermatology* **161**, 1248–1254 (2009).
431. Elmariah, S. B. Adjunctive management of itch in atopic dermatitis. *Dermatologic clinics* **35**, 373–394 (2017).
432. Seike, M., Ikeda, M., Kodama, H., Terui, T. & Ohtsu, H. Inhibition of scratching behaviour caused by contact dermatitis in histidine decarboxylase gene knockout mice. *Experimental dermatology* **14**, 169–175 (2005).
433. Kido-Nakahara, M., Furue, M., Ulzii, D. & Nakahara, T. Itch in atopic dermatitis. *Immunology and Allergy Clinics* **37**, 113–122 (2017).
434. Pail, P. B. *et al.* The role of kinin B1 and B2 receptors in the mouse model of oxazolone-induced atopic dermatitis. *International immunopharmacology* **72**, 62–73 (2019).
435. Mark Studin, D. C. Efficacy of Chiropractic Care on Cervical Herniated Discs with Degenerative Changes in the Spine.
436. Liyew, W. A. Clinical presentations of lumbar disc degeneration and lumbosacral nerve lesions. *International Journal of Rheumatology* **2020**, (2020).
437. Worrill, N. Asthma: a descriptive case study. *The British Journal of Chiropractic* **2**, 4–5 (1998).
438. Balon, J. W. & Mior, S. A. Chiropractic care in asthma and allergy. *Annals of Allergy, Asthma & Immunology* **93**, S55–S60 (2004).
439. Yamasaki, R. *et al.* Allergic inflammation leads to neuropathic pain via glial cell activation. *Journal of Neuroscience* **36**, 11929–11945 (2016).

440. Barnes, P. J. Neurogenic inflammation in the airways. *Respiration physiology* **125**, 145–154 (2001).
441. Akiyama, T., Nagamine, M., Carstens, M. I. & Carstens, E. Behavioral model of itch, alloknesis, pain and allodynia in the lower hindlimb and correlative responses of lumbar dorsal horn neurons in the mouse. *Neuroscience* **266**, 38–46 (2014).
442. Shiratori-Hayashi, M. *et al.* STAT3-dependent reactive astrogliosis in the spinal dorsal horn underlies chronic itch. *Nature medicine* **21**, 927–931 (2015).
443. Yamasaki, R. *et al.* Allergic inflammation leads to neuropathic pain via glial cell activation. *Journal of Neuroscience* **36**, 11929–11945 (2016).
444. Lazzarini, R., Mendonça, R. & Hafner, M. Allergic contact dermatitis to shoes: contribution of a specific series to the diagnosis. *Anais brasileiros de dermatologia* **93**, 696–700 (2018).
445. Carstens, G. J., Horowitz, M. B., Purdy, P. D. & Pandya, A. G. Radiation dermatitis after spinal arteriovenous malformation embolization: case report. *Neuroradiology* **38**, S160–S164 (1996).
446. ALLENDE, M. F. & REED, E. Dermatitis herpetiformis and vitiligo. *Archives of dermatology* **89**, 156 (1964).
447. Eldred, D. C. & Tuchin, P. J. TREATMENT OF ACUTE ATOPIC ECZEMA BY CHIROPRACTIC CARE: A Case Study. *Australasian Chiropractic & Osteopathy* **8**, 96 (1999).
448. Gray, M. & Giuliano, K. K. Incontinence-associated dermatitis, characteristics and relationship to pressure injury: a multisite epidemiologic analysis. *Journal of Wound, Ostomy, and Continence Nursing* **45**, 63 (2018).
449. Fox, B., Sahuquillo, J., Poca, M. A., Huguet, P. & Lience, E. *REACTIVE ARTHRITIS WITH A SEVERE LESION OF THE CERVICAL SPINE*. *British Journal of Rheumatology* vol. 36 (1997).
450. Rastegar, K. *et al. Send Orders for Reprints to reprints@benthamscience.net Cervical Spine Involvement: A Rare Manifestation of Reiter's Syndrome*. *The Open Rheumatology Journal* vol. 8 (2014).

451. Lee, M. H. *et al.* Penile herpes zoster. *Korean Journal of Dermatology* **52**, 911–912 (2014).
452. Calixte, N., Brahmbhatt, J. & Parekattil, S. Genital pain: algorithm for management. *Translational andrology and urology* **6**, 252 (2017).
453. Graziottin, A., Gambini, D. & Bertolasi, L. Genital and sexual pain in women. *Handbook of clinical neurology* **130**, 395–412 (2015).
454. Wesselmann, U. Neurogenic inflammation and chronic pelvic pain. *World journal of urology* **19**, 180–185 (2001).
455. Lev-Sagie, A. Female Genital Pain and Penetration Disorders. in *The Overactive Pelvic Floor* 43–56 (Springer, 2016).
456. Das, M. C. Pelvic Inflammatory Disease. *Gynaecology For Postgraduate And Practitioners* 385 (2007).
457. Golpanian, R. S., Smith, P. & Yosipovitch, G. Itch in organs beyond the skin. *Current Allergy and Asthma Reports* **20**, 1–10 (2020).
458. Stoffel, J. T., van der Aa, F., Wittmann, D., Yande, S. & Elliott, S. Fertility and sexuality in the spinal cord injury patient. *World journal of urology* **36**, 1577–1585 (2018).
459. Fox, B., Sahuquillo, J., Poca, M. A., Huguet, P. & Lience, E. Reactive arthritis with a severe lesion of the cervical spine. *British journal of rheumatology* **36**, 126–129 (1997).
460. Fugl-Meyer, K. S. *et al.* Standard operating procedures for female genital sexual pain. *The journal of sexual medicine* **10**, 83–93 (2013).
461. Basson, R. Recent advances in women's sexual function and dysfunction. *Menopause* **11**, 714–725 (2004).
462. Zhang, Y. *et al.* Current views on neuropeptides in atopic dermatitis. *Experimental Dermatology* (2021).
463. Javed, H. *et al.* Co-localisation of nociceptive markers in the lumbar dorsal root ganglion and spinal cord of dromedary camel. *Journal of Comparative Neurology* (2021).
464. Sato, T. *et al.* Distribution of alpha-synuclein in the rat cranial sensory ganglia, and oro-cervical regions. *Annals of Anatomy-Anatomischer Anzeiger* 151776 (2021).

465. Amalia, S. N. *et al.* Suppression of neuropeptide by botulinum toxin improves imiquimod-induced psoriasis-like dermatitis via the regulation of neuroimmune system. *Journal of Dermatological Science* **101**, 58–68 (2021).
466. Legat, F. J. Itch in Atopic Dermatitis–What Is New? *Frontiers in Medicine* **8**, 629 (2021).
467. Trilisnawati, D., Yahya, Y. F., Devi, M. & Toruan, T. L. Prevention of Irritant Contact Dermatitis Due to Hand Hygiene in The Era of COVID 19 Pandemic. *Bioscientia Medicina: Journal of Biomedicine and Translational Research* **4**, 29–44 (2020).
468. Kahremany, S., Hofmann, L., Gruzman, A. & Cohen, G. Advances in understanding the initial steps of pruritoceptive itch: how the itch hits the switch. *International Journal of Molecular Sciences* **21**, 4883 (2020).
469. Ebbinghaus, M. *et al.* Gain-of-function mutation in SCN11A causes itch and affects neurogenic inflammation and muscle function in Scn11a+/L799P mice. *PloS one* **15**, e0237101 (2020).
470. Yosipovitch, G., Berger, T. & Fassett, M. S. Neuroimmune interactions in chronic itch of atopic dermatitis. *Journal of the European Academy of Dermatology and Venereology* **34**, 239–250 (2020).
471. Granstein, R. D., Wagner, J. A., Stohl, L. L. & Ding, W. Calcitonin gene-related peptide: key regulator of cutaneous immunity. *Acta physiologica* **213**, 586–594 (2015).
472. Rogoz, K., Andersen, H. H., Lagerström, M. C. & Kullander, K. Multimodal use of calcitonin gene-related peptide and substance P in itch and acute pain uncovered by the elimination of vesicular glutamate transporter 2 from transient receptor potential cation channel subfamily V member 1 neurons. *Journal of Neuroscience* **34**, 14055–14068 (2014).
473. Kwak, I. S., Choi, Y. H., Jang, Y. C. & Lee, Y. K. Immunohistochemical analysis of neuropeptides (protein gene product 9.5, substance P and calcitonin gene-related peptide) in hypertrophic burn scar with pain and itching. *Burns* **40**, 1661–1667 (2014).

474. McCoy, E. S. *et al.* Peptidergic CGRPα primary sensory neurons encode heat and itch and tonically suppress sensitivity to cold. *Neuron* **78**, 138–151 (2013).
475. Sutherland, H. G. *et al.* Association study of the calcitonin gene-related polypeptide-alpha (CALCA) and the receptor activity modifying 1 (RAMP1) genes with migraine. *Gene* **515**, 187–192 (2013).
476. McCoy, E. S., Taylor-Blake, B. & Zylka, M. J. CGRPα-expressing sensory neurons respond to stimuli that evoke sensations of pain and itch. *PloS one* **7**, e36355 (2012).
477. de Mey, J. G. R., Megens, R. & Fazzi, G. E. Functional antagonism between endogenous neuropeptide Y and calcitonin gene-related peptide in mesenteric resistance arteries. *Journal of Pharmacology and Experimental Therapeutics* **324**, 930–937 (2008).
478. Greaves, M. W. & Wall, P. D. Pathophysiology of itching. *The Lancet* **348**, 938–940 (1996).
479. Gillardon, F. *et al.* Calcitonin gene-related peptide and nitric oxide are involved in ultraviolet radiation-induced immunosuppression. *European Journal of Pharmacology: Environmental Toxicology and Pharmacology* **293**, 395–400 (1995).
480. Sung, C.-P. *et al.* CGRP stimulates the adhesion of leukocytes to vascular endothelial cells. *Peptides* **13**, 429–434 (1992).
481. Javed, H. *et al.* Co-localisation of nociceptive markers in the lumbar dorsal root ganglion and spinal cord of dromedary camel. *Journal of Comparative Neurology* (2021).
482. Sato, T. *et al.* Distribution of alpha-synuclein in the rat cranial sensory ganglia, and oro-cervical regions. *Annals of Anatomy-Anatomischer Anzeiger* 151776 (2021).
483. Durham, P. L. & Vause, C. v. Calcitonin gene-related peptide (CGRP) receptor antagonists in the treatment of migraine. *CNS drugs* **24**, 539–548 (2010).
484. Traub, R. J., Solodkin, A. & Ruda, M. A. Calcitonin gene-related peptide immunoreactivity in the cat lumbosacral spinal cord and the effects of multiple dorsal rhizotomies. *Journal of Comparative Neurology* **287**, 225–237 (1989).

485. Bird, G. C. *et al.* Pain-related synaptic plasticity in spinal dorsal horn neurons: role of CGRP. *Molecular pain* **2**, 1744–8069 (2006).
486. Granstein, R. D., Wagner, J. A., Stohl, L. L. & Ding, W. Calcitonin gene-related peptide: key regulator of cutaneous immunity. *Acta physiologica* **213**, 586–594 (2015).
487. Zhang, Y. *et al.* Current views on neuropeptides in atopic dermatitis. *Experimental Dermatology* (2021).
488. Ding, W., Stohl, L. L., Wagner, J. A. & Granstein, R. D. Calcitonin gene-related peptide biases Langerhans cells toward Th2-type immunity. *The Journal of Immunology* **181**, 6020–6026 (2008).
489. Furue, K. *et al.* The IL-13–OVOL 1–FLG axis in atopic dermatitis. *Immunology* **158**, 281–286 (2019).
490. Matsui, K., Shi, X., Komori, S. & Higuchi, A. Effects of anti-allergy drugs on Th1 cell and Th2 cell development mediated by Langerhans cells. *Journal of Pharmacy & Pharmaceutical Sciences* **23**, (2020).
491. Piotrowski, W. & Foreman, J. C. Some effects of calcitonin gene-related peptide in human skin and on histamine release. *British Journal of Dermatology* **114**, 37–46 (1986).
492. Pincelli, C., Fantini, F. & Giannetti, A. Neuropeptides and skin inflammation. *Dermatology* **187**, 153–158 (1993).
493. Piotrowski, W. & Foreman, J. C. Some effects of calcitonin gene-related peptide in human skin and on histamine release. *British Journal of Dermatology* **114**, 37–46 (1986).
494. Gordon, D. J., Ostlere, L. S. & Holden, C. A. Neuropeptide modulation of Th1 and Th2 cytokines in peripheral blood mononuclear leucocytes in atopic dermatitis and non-atopic controls. *British Journal of Dermatology* **137**, 921–927 (1997).
495. Kang, H., Byun, D.-G. & Kim, J.-W. Effects of substance P and vasoactive intestinal peptide on interferon-gamma and interleukin-4 production in severe atopic dermatitis. *Annals of Allergy, Asthma & Immunology* **85**, 227–232 (2000).
496. Calvo, C.-F., Chavanel, G. & Senik, A. Substance P enhances IL-2 expression in activated human T cells. *The Journal of Immunology* **148**, 3498–3504 (1992).

497. Salomon, J. & Baran, E. The role of selected neuropeptides in pathogenesis of atopic dermatitis. *Journal of the European Academy of Dermatology and Venereology* **22**, 223–228 (2008).
498. Ständer, S., Gunzer, M., Metze, D., Luger, T. & Steinhoff, M. Localization of μ-opioid receptor 1A on sensory nerve fibers in human skin. *Regulatory Peptides* **1**, 75–83 (2002).
499. Melo, H. *et al.* Itch induced by peripheral mu opioid receptors is dependent on TRPV1-expressing neurons and alleviated by channel activation. *Scientific reports* **8**, 1–9 (2018).
500. Carstens, E. & Akiyama, T. Itch: Mechanisms and treatment. (2014).
501. Christensen, M. D. & Hulsebosch, C. E. Spinal cord injury and anti-NGF treatment results in changes in CGRP density and distribution in the dorsal horn in the rat. *Experimental neurology* **147**, 463–475 (1997).
502. Sang, X., Wang, Z., Shi, P., Li, Y. & Cheng, L. CGRP accelerates the pathogenesis of neurological heterotopic ossification following spinal cord injury. *Artificial cells, nanomedicine, and biotechnology* **47**, 2569–2574 (2019).
503. Ackery, A. D., Norenberg, M. D. & Krassioukov, A. Calcitonin gene-related peptide immunoreactivity in chronic human spinal cord injury. *Spinal cord* **45**, 678–686 (2007).
504. Xu, H. *et al.* Governor Vessel electro-acupuncture promotes the intrinsic growth ability of spinal neurons through activating calcitonin gene-related peptide/α-calcium/calmodulin-dependent protein kinase/neurotrophin-3 pathway after spinal cord injury. *Journal of Neurotrauma* **38**, 734–745 (2021).
505. Löken, L. S. *et al.* Contribution of dorsal horn CGRP-expressing interneurons to mechanical sensitivity. *Elife* **10**, e59751 (2021).
506. Thomsen, S. F. Atopic dermatitis: natural history, diagnosis, and treatment. *International Scholarly Research Notices* **2014**, (2014).
507. Mochizuki, H., Schut, C., Nattkemper, L. A. & Yosipovitch, G. Brain mechanism of itch in atopic dermatitis and its possible alteration through non-invasive treatments. *Allergology International* **66**, 14–21 (2017).

508. Park, S.-K. & Cho, I.-Y. Suggestions of Utilizing Manipulative Therapy to Atopic Dermatitis. *The Journal of the Korea Contents Association* **8**, 171–181 (2008).