Universitat de Girona
Facultat de Medicina

FINAL DEGREE PROJECT

Homeostasis and Epidermal Barrier Analysis in Psoriatic Patients:

The Impact Of Emollients.

Author: Daniel Maroto Morales
Tutor: Salvador Arias Santiago
Methodological Tutor: Rafael Marcos Gragera

AKNOWLEDGMENTS

Primero, me gustaría dar mi más sincero agradecimiento a Salvador Arias; has sido el mejor tutor que poder desear. Gracias por tu atención, amabilidad, confianza, por darme tanta responsabilidad y creer en mí durante todos estos meses. Eres un ejemplo a seguir en la investigación médica y uno personal para mí mismo.

Me gustaría agradecer el gran apoyo y acogida que he recibido por parte de todo el equipo de Dermatología del Hospital Universitario Virgen de las Nieves; en especial a Trinidad Montero por enseñarme con tanta amabilidad y estar siempre dispuesta a ayudarme en todo lo que necesitaba y más.

También a Rafael Ramos por su constante apoyo y su gran guía metodológica durante todo el trabajo.

Por último; a mi familia, mis compañeros de piso (mi otra familia) y a mis amigos; por hacer de estos 6 años una experiencia que recordar con alegría y nostalgia; y por cambiar mi vida en este proceso de la mejor manera imaginable.

INDEX

ABBREVIATIONS

AMPs: antimicrobial peptides

AU: arbitrary units

BB-UVB: broadband ultraviolet B

BMI: body mass index

BSA: body surface area

cAMP: cyclic adenosine monophosphate

CD4: cluster of differentiation 4

CDK: cyclin-dependent kinase

CI: confidence interval

DLQI: dermatology life quality index

H3, H4, H3K27: Histone H3, Histone H4, Histone H3K27

HLA: human leukocyte antigen

IFN: interferon

IL: interleukin

MHC: major histocompatibility complex

MPA: multi probe adapter

NB-UVB: narrowband ultraviolet B

NF-kB: nuclear factor kappa B

OR: odds ratio

PASI: psoriasis area and severity index

PUVA: psoralen ultraviolet A photochemotherapy

QoL: quality of life

SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2

SCH: stratum corneum hydration

TEWL: Transepidermal water loss

Th17: lymphocyte T helper 17

TNFα: tumour necrosis factor alpha

UV: ultraviolet

VEGF: vascular endothelial growth factor

1. ABSTRACT

BACKGROUND: Skin diseases may modify epidermal barrier function. Psoriasis is a chronic multi-systemic inflammatory disease that may affects the epidermal barrier. Emollients are an option as a coadjutant therapy for psoriasis management, but little is known about how epidermal barrier function is modified by moisturizers administration in psoriatic patients.

HYPOTHESIS AND OBJECTIVES: The objective of this before-and-after study is to analyse skin homeostasis and epidermal barrier function differences between psoriatic plaque, non-affected skin in psoriatic patients and control skin; also, to evaluate the effect of two types of moisturizers on psoriatic and healthy participants.

METHODS: Thirty-one patients with plaque-type psoriasis and thirty-one gender and age-matched healthy controls were enrolled. Temperature, Transepidermal water loss (TEWL), stratum corneum hydration (SCH), pH, elasticity and erythema index were measured using non-invasive tools in the healthy control and involved and uninvolved psoriatic skin before and after the use of two determined moisturizers

RESULTS: Healthy controls had lower TEWL, temperature, and higher pH levels than psoriatic patients. SCH levels were found lower in psoriatic plaques than in uninvolved and healthy skin (13,44 vs 30,55 vs 30,90 Arbitrary Units (AU); $p<0,001$). TEWL was significantly higher in plaques than in psoriatic uninvolved skin (13,23 vs 8,54 g/h/m²; $p<0,001$)., which was also higher than in control healthy skin (8,54 vs 6,41 g/h/m²; $p=0,023$).

After emollients application on psoriatic plaques, SCH experimented a significant increment after the application of water-based formula (13,44 vs 22,89 AU; $p=0,003$). However, TEWL showed a decrease of 5,59 g/h/m² (5,68 SD, $p<0,001$) after use of Vaseline jelly; and the contrary effect after the water-formula application (increment of 3,60 g/h/m² (6,86 SD, $p=0,006$).

CONCLUSION: Uninvolved psoriatic skin showed epidermal barrier dysfunction compared to healthy controls; in addition, psoriatic plaques barrier impairment was significantly higher than not-affected skin. Use of emollients may improve epidermal barrier function in psoriatic patients. SCH and TEWL parameters were the most changed after moisturizers application.

KEYWORDS: Homeostasis, Moisturizers, Emollients, Psoriasis, Skin Physiology, Transepidermal Water Loss, Stratum Corneum Hydration, Skin Barrier.

2. INTRODUCTION

A) PSORIASIS

Psoriasis is a chronic, immune-mediated inflammatory disease. Their most common manifestations are typically scattered, erythematous, scaly papules and plaques. Nevertheless, this disease can involve lots of different skin patterns or even affect several joints and nails changes.

Its aetiology remains unclear even though numerous risk factors have been related to its predisposition or pathology; such us epigenetic alterations, obesity, alcohol consumption, smoking or stress (1). It is significant the psychosocial impact that causes this disease (2), in addition to the risk that supposes to develop many organic comorbidities (3).

EPIDEMIOLOGY

Psoriasis affects 1-3% of the world population (4). This corresponds to about 125 million psoriasis patients in all over the world. Prevalence rates show a worldwide geographic variation from 0,51% (USA) to 11,43% (Norway) (5). This probably reflects the fact that psoriasis is a complex disease influenced by genetic and environmental factors.

Variation in prevalence appeared to depend on the distance from the equator, with population located closer to the equator (Egypt, Sri Lanka, Taiwan) being less affected by psoriasis compared with the more distant ones (North Europe, Australia)

The estimated incidence for adults also varied from 78.9/100.000 person-years (USA) to 230/100.000 person-years (Italy). The incidence goes significantly lower in children, reaching about 40,8/100.000 person-years (6).

Data estimation from Spain reveals prevalence numbers from 1,4 to 2,7% in general adult population. Corresponding to a prevalence of 1,88% of the male sample; therefore, the prevalence in women is about 1,56%. Some epidemiological studies such

as *J.M.Fernánez-Armenteros et Al, 2019* establishes the male sex as a risk factor of psoriasis (OR=1.21, 95% IC:1.15-1.27).

Another Spanish study, selected dermatologist from multiple areas of the country collected all of the diagnosis reached during 2 specific periods of the year (6 days altogether). Psoriasis estimated diagnosis for these 6 days period reached the number of 10.344 (IC 95% 6.260-14.428). This digit would represent 3.872 cases of new diagnosis; leaving the rest 6.472 to revisions appointments (7).

The age of onset can be at any age even though it is very uncommon to appear under the age of 10 years. Studies reporting age-specific incidence rates stablish a dual peak of psoriasis onset around 30-39 years old and 50 to 69 years old (8). This corresponds to the believed that there are two clinical presentation of the disease; type I (early-onset) and type II (late-onset). Usually, the type I cases are related to typical HLA alterations and family history of psoriasis; unlike type II onset.

AETIOLOGY

Psoriasis aetiology is stablished as a multifactorial process where both extrinsic and intrinsic factors play and importance roll in the disease development (9).

GENETICS:

The genetic predisposition to psoriasis is been proven to be associated to over 424 genes loci single nucleotide polymorphism alongside copy number variations and epigenetic alterations (10).

MAJOR HISTOCOMPATIBILITY COMPLEX GENES

One of the most known intrinsic modifications has always been related to the histocompatibility antigens (HLA), situated on the Surface of cells and connected with the chromosomal region forming the histocompatibility complex (MHC). Specifically, the

presence of HLA-Cw6 antigen has being observed at the 90% of the early-onset psoriasis patients and at 50% of the late onset ones. However, this finding can be also be related to the 7% of the regular population; that discredit it to be a good early predictor (11). Only a 10% of HLA-Cw6 carriers develop psoriasis.

Another well-studied HLA component connected to psoriasis is HLA B27, that is particularly related to reactive arthritis or sacroiliitis forms of the disease. This factor can be seen in other rheumatic affections known as spondyloarthropathies.

NON-MAJOR HISTOCOMPATIBILITY COMPLEX GENES

Furthermore, there are over 15 chromosomal regions suspected of being connected with psoriasis, called PSORS1-15, where HLA-Cw6 is contained (10). Only 28% of the genetic heritability of psoriasis are explain, and MHC signals alone contribute 40% of this detectable heritability (12). Nevertheless, exists some discrepancy between studies, determine that PSORS1 could account for around 50% of psoriasis heritability (9).

There is strong evidence indicating that these genes are disproportionately involved in immunity and host defence, including functions like lymphocyte differentiation and regulation, type I interferon (IFN) and pattern recognition, and response to viruses and bacteria. Strongly recognising psoriasis as an immune-related disease, even though many of them remain to be formally identified (12).

Most of the non-MHC associations identified thus far, reveal several interconnected functional axes:

- IL-23-IL-17 (interleukine-23//17) pathway signalling
- Interferon signalling
- NF-kB (nuclear factor kappa B) signalling
- Dendritic cell and macrophage function
- Keratinocyte responses

EPIGENETICS

Currently, epigenetic alternations are becoming one of the main levels of study in psoriasis genetics. The most important alternations are DNA methylation, histone modifications and the role of microRNA.

Chen et al. Indicated in 2008 a potential role of the p16gene alternation in psoriasis. This study describes the methylation of p16INK4a gene promoter in the epidermis of 30% of psoriatic patients, being also correlated with higher Psoriasis Area and Severity Index (PASI) scores (13). This down regulation of the p16INK4a protein leads to higher levels of CDK4 and CDK6 which has been identified in many hyperproliferative skin diseases, including skin cancer.

Some other features of psoriatic DNA methylation would be the enrichment of many PSORS regions (that causes higher gene expression) or the increase global DNA methylation in peripheral blood mononuclear cells and skin lesion of psoriatic patients compared to healthy controls; still on an early research status (1).

About histone modifications, there are been described reduced levels of acetylated H3 and H4; as well as increased levels of H3K27 making a difference between responders and non-responders to the biological agent after three months of treatment (14).

The last significant epigenetic alternation being studied in psoriasis would be microRNA; reporting overexpression of many types of microRNA playing a triggering role; furthermore significantly increased levels of miRNA-210 in CD4+ T cells in psoriasis patients (15). Another microRNA that were shown significantly increased in psoriatic patients are miRNA-33 (16) and miRNA-155; this last one levels being also correlated with clinical severity and decreasing after treatment (17).

ENVIRONMENTAL FACTORS:

MICROBIOTA AND INFECTIONS

Microbiota is taking an important role in many different diseases, especially in autoimmune or immune-mediated conditions.

In healthy subjects, there is a mutual coexistence of different microorganisms within the skin, mucous membranes (upper airways, urogenital tract, intestines), which constitutes an immunological balance with immune system cells (18). Any disruption of this micro-environment may occur or provoke either an infection by the dominate microorganism, or the activation of the immune system; triggering an immune reaction.

Because of the similarity of many proteins and compounds of the bacterial wall to human substances, a reaction may occur leading to an auto-aggressive process. This reaction can take an innate or an adaptive pathway on the immune system response. In psoriasis, is very important the adaptive pathway, due to the high sensitization of T cells (especially Th17 cells) (1).

This balance between the microbiota and the immune system can be threatened by unhealthy lifestyle, such tobacco, alcohol intake or diet. Furthermore, streptococcal throat infection and guttate psoriasis has been repeatedly confirmed; as well as this infections have been demonstrated to exacerbate pre-existing chronic plaque psoriasis (12).

DIET AND OBESITY

Although obesity does not have a correlation in defining the onset of the disease; it has been demonstrated that obese individuals are more likely to present with severe psoriasis. Strongly related to the chronic inflammatory process that supposes obesity.

Obesity, increased body mass index and waist circumference which are significant risk factors for the development of psoriasis (19). In fact, the prevalence of psoriasis and metabolic syndrome is significantly higher in psoriatic patients than in the general population; estimating that around 50% of psoriatic patients are overweight or obese.

Metabolic syndrome diagnosis, carotid atheroma plaques, and many hallmarks such as mean values of insulin, aldosterone or acute phase parameters are significantly higher in psoriatic patients in comparison to control population (20). As well as protective parameters of metabolic disease like glycoprotein clusterin (apolipoprotein J) or 25-hydroxyvitamin D levels were found statistically lower (21).

In the same way, the benefits of reduction in body weight in psoriasis are significant in both the severity of disease and the response to treatment. Many diets like the traditional Mediterranean diet, are associated with reduced risk for chronic inflammatory diseases, mostly because of their anti-inflammatory and antioxidant properties (19).

SMOKING AND ALCOHOL INTAKE

Heavy smoking (>20 cigarettes daily) has been associated with more than a double increased risk of severe psoriasis. Moreover, the prevalence of smoking is significantly higher in the group of patients with psoriasis.

It is believed that the mechanisms correlated to smoking and the development of psoriasis have to do with smoking caused oxidative stress, increasing the free radicals exposure and triggering a cascade of systemic disorders; including developments of psoriasis (22).

The correlation between alcohol intake and risk of psoriasis is still nuclear with many conflicting conclusions. Some studies have shown that alcohol and acetone can stimulate keratinocyte proliferation; but still require further investigation and understanding the pathomechanism (1).

MEDICATIONS

It has been evidenced that some drugs may initiate psoriasis de novo, exacerbate pre-existing psoriasis lesions, and cause a treatment-resistant form of psoriasis.

Drugs that are proven to be related with the onset or exacerbation of psoriasis include beta-blockers, antivirals and antidepressants, synthetic antimalarials (chloroquine and hydroxychloroquine), lithium, non-steroidal anti-inflammatory drugs, interferons and terbinafine (23).

New drugs including monoclonal antibody and small-molecule-based targeted therapies have been also reported to induce or exacerbate symptoms of psoriasis; such as TNF-alfa antagonists, nivolumab, pembrolizumab, VEGF (vascular endothelial growth factor) antagonists and rituximab (24).

The mechanisms that causes drugs onset or exacerbations of the psoriasis remain largely unknown (12).

ULTRAVIOLET RADIATION

Even though UV exposure is most often beneficial in psoriasis, in some cases, aggravation of psoriasis has been observed.

The pathological mechanism of the worsening of the symptoms after UV exposure is not fully understood; being related to the Koebner reaction after sunburn (as skin trauma) or to the coexistence of others photosensitivity disorders (25).

There is a subset of patients with psoriasis in whom UV exposure can even trigger the diseases and induce lesions de novo. This finding has been described as photosensitive psoriasis.

PSICOLOGICAL FACTORS

The appearance of skin lesions in psoriasis could lead to mental disorders, due to the significant influence that this disease has on the quality of life. However, stress and depression may have a role in the onset and aggravation of its symptoms, which can lead to a vicious feedback of both pathologies.

Psychological stress is associated with alterations in the regulation of the immune system and activation of abnormal T cells; that could be a key point to its relation to psoriasis (26).

HISTOLOGY

The hallmark of psoriasis is a chronic inflammation that leads to uncontrolled keratinocyte proliferation and dysfunctional differentiation.

Histologically, the main findings that characterize this disease are an acanthosis (epidermal hyperplasia), that overlies inflammatory infiltrates (dendritic cells, macrophages, T cells and neutrophils. This inflammation usually guides to neovascularization). Some other typical discoveries are paraqueratosic hyperqueratosis, papillomatosis and dermic vasodilatation (27).

Squamous cells usually manifest enlarged extracellular spaces with only a few desmosome connections. This added to the hyperqueratosis that is caused by the increased number of mitoses of the basal layer leads to the typical epidermal desquamative lesion (12).

PATHOLOGY

Alterations in the innate and adaptive cutaneous immune responses are responsible for most of the pathology of psoriatic inflammation.

This immune response is caused by an activation of the innate immune system driven by endogenous cytokines and other danger signals (autoinflammatory perpetuation); or taken place through T cell autoimmune reactions. Both autoimmune and inflammatory mechanisms can overlap and even potentiate on another (28).

These reactions entail the main clinical finding in psoriasis, which is the excessive dysfunctional keratinocytes production. However, the psoriatic plaque in not only

caused by inflammation in the epidermal layer; interaction of keratinocytes with many different cell types perpetuate this process (29).

The pathogenesis can be conceptualized in two different phases: an initiation phase triggered by the different environmental already explain; and a maintenance phase characterized by a chronic clinical progression.

It is well known that dendritic cells play a main role in the initial stages of psoriasis. This are antigen-presenting cells that are activated by a not entirely clear mechanism. One of the most trust mechanism would involve the recognition of antimicrobial peptides (AMPs) secreted by keratinocytes in response to injury. AMPs are characteristically overexpressed in psoriatic skin, some of these peptides are LL37 or S100 proteins (30).

This AMPs would activate plasmacytoid dendritic cells, starting the development of the psoriatic plaque by the production of type I IFN. This last one factor, is in charge of the myeloid dendritic cells' maturation (on the lymph node); provoking an extensive inflammatory chain which would finally cause the proliferation of lymphocytes Th17 (as well as many other lymphocytes). The most important and recognized Th17 activation pathway is through TNFα-IL23 mediators

The maintenance phase of the psoriatic inflammation is leaded by this adaptive immune response via different T cells. Th17 cells activate keratinocyte proliferation in the epidermis, by secretion of many important cytokines named IL-17, IL-21 and IL-22. Pro-inflammatory signals would also have an important implication in neovascular formation, itself chronification and extracellular processes (27,31).

It is important to understand that this complex entwined immunopathology is nowadays being researched. The mechanisms exposed are the currently most accepted hypothesis.

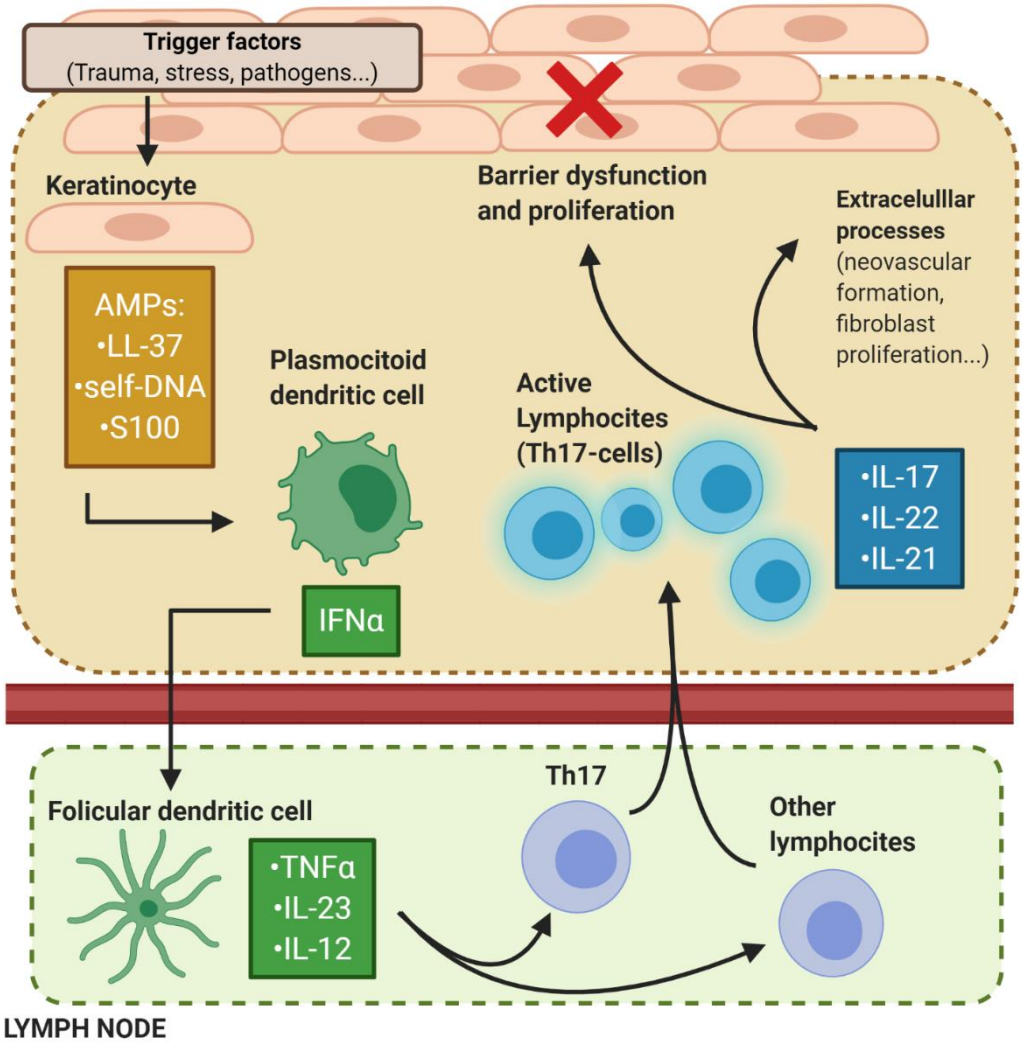

Figure 1. Psoriasis physiopathology main pathway. AMPs: antimicrobial peptides; IFNα: alpha interferon; TNFα: tumour necrosis factor alpha; IL: interleukin; TH17: lymphocyte T helper 17.

CLINICAL FEATURES

There have been reported many different dermatological patrons of this condition. This clinical presentation is usually grouped in five classical variants in psoriasis:

1- Plaque psoriasis or Psoriasis Vulgaris:

It represents approximately 80% to 90% of all clinical manifestations of psoriasis (32). This presentation is characterized by well demarcated, erythematous, scaly patches or plaques.

These plaques can appear anywhere on the body; however, they commonly affect areas including the scalp, trunk, gluteal fold, and extensor surfaces; especially elbows and knees. Scalp affectation occurs in 75% to 90% of patients with psoriasis and it is usually the reason of non-scarring alopecia. The size of the lesions can range from small erythematous papules (less than 1 centimetre) to large thick plaques than can cover a whole limb (33).

These areas are often affected symmetrically and they are usually well-demarcated. Lesions can characteristically appear by the Koebner phenomenon (trauma such from scratching, cuts or pressure can develop this new lesions) and when the scale is lifted from the plaque (known as the Brocq scraping technique), it appears the typical Auspitz sign (punctate bleeding spots when the psoriasis scales are scraped off).

Patients can also experiment pruritus at this affected regions, but it appears classically with moderate to severe psoriasis or during exacerbations (32).

Nail psoriasis appears in about 50% of patients in the moment of the diagnosis rising up to 90% in patients with psoriatic arthritis; with a global lifetime incidence of 80-90%. The common classical signs of nail psoriasis are nail plate pitting, subungual hyperqueratosis, discolouration in the form of yellow or Brown patches underneath the nail plate and onycholysis. It is important to differentiate nail psoriasis affection with other entities like onychomycosis (34).

2- Inverse psoriasis:

Also named flexural psoriasis; this variant affects flexural and intertriginous locations also clinically characterized by slightly erosive erythematous plaques. Some authors include the inverse psoriasis as an uncommon localization inside plaque psoriasis.

Represents a sometimes difficult to diagnose clinical variant of psoriasis, due to its clinical similarity with other skin disorders that involve skin folds (mechanical intertrigo, fungal and bacterial infections, contact dermatitis, etc) (35).

3- Guttate psoriasis:

This distinct variant comprises about 2% of psoriasis cases and is characterized by multiple 3-to 5-mm erythematous plaques. Approximately 66% of new-onset guttate psoriasis is triggered by streptococcal infection (pharyngitis or perianal). It is more common in children and adolescents and most of these cases resolve spontaneously in weeks to months (extraordinary cases can chronify) (32,36).

4- Pustular psoriasis:

Further subdivided into generalized pustular psoriasis and localized pustular psoriasis. Pustular psoriasis is a very rare condition with prevalence ranging from 7,46 cases/million in Asian populations (Japan) to 1,76 cases/million in Caucasian populations (France) (37).

Both variants have similar presentations, involving eruption of superficial sterile pustules typically with an erythematous base or studded on a background of erythema. Localized pustular psoriasis includes two specific entities: palmoplantar psoriasis and acrodermatitis continua of Hallopeau, both of them affecting hands and feet (37,38).

5- Erythrodermic psoriasis:

Corresponds to 1% to 3% of psoriasis cases, it is the more dangerous variant treated as a dermatological emergency because can provoke extended desquamation accompanied of life-threatening electrolyte disturbances.

This presentation involves a generalized inflammatory erythema affecting at least 75% of the body surface area. Patients usually presents systemic symptoms like fever, tachycardia, fatigue, malaise, chills, dehydration, etc (39).

COMORBIDITIES

Comorbidities classically associated with psoriasis are psoriatic arthritis, inflammatory bowel diseases (mostly Crohn disease), psychological/psychiatric disorders and uveitis.

Recently, both metabolic syndrome and its individual components have been associated with psoriasis; including as psoriatic comorbidities cardiovascular risk, non-alcoholic fatty liver disease, celiac disease and erectile dysfunction (3).

- Approximately 33% of psoriasis patients develop psoriatic arthritis during their lifetime. Arthritis is characterized by stiffness, pain and swelling of joints that can progress to joint destruction (32). This type of arthritis is typically presented with dactylitis and enthesitis in oligoarticular or polyarticular patterns; also very well correlated with nail psoriasis (up to 80% of patients with psoriatic arthritis present nail manifestations) (40).

  It is important to distinguish this arthritis form from other joint diseases in a psoriasis framework, due to only 56% of patients with psoriasis and joint symptoms have psoriatic arthritis (32). It is important to mention the thin correlation between antigen HLA-B27 positivity and psoriatic arthritis development, as well as acute anterior uveitis.

- Patients diagnosed with psoriasis have a 2.9-times higher risk of developing Crohn Disease, when compared with the general population (3). Several genetic

susceptibility loci are found shared by both entities, most of them located on chromosome 16q (41).

- Psychological and psychiatric disorders are probably the most life-quality affecting comorbidity; the emotional and social impact of this disease cannot be underestimate. Psoriasis is strongly related to an increase of the risk to develop depression (odds ratio [OR], 1.57 [95% CI, 1.40-1.76]), anxiety disorder (OR, 2.91 [95% CI, 2.01-4.21]) and suicidal ideation (OR, 2.05 [95% CI, 1.54-2.74]).(42,43) Of course, life quality measures are significantly correlated with the degree of psoriasis (2).

  Is important to notice that this psychological condition not only make an impact to the patients, but to their psychosocial environment. Studies show that life quality index of psoriasis' cohabitants are as well impaired, with anxiety and depression levels significantly higher than control population (44).

DIAGNOSIS

As many other dermatological entities, psoriasis diagnosis is mainly based on the typical clinical findings that were already expose. However, skin biopsy may be required in case of not typical presentations, although is very unusual on the clinical practice.

The diagnostic workup for this pathology must include familiar and personal antecedents of skin inflammatory disease, possible triggers and a comprehensive skin and nail examination; including the evaluation of morphology and distribution of psoriasis lesions. Screening of common comorbidities such us psoriatic arthritis are essential to make a good prevention of future complications (32).

Considerable different scores are often used in psoriasis in order to classify diagnosis depending on the severity of the symptoms or the life quality aggrievance. The most validated and clinical used index are PASI (Psoriasis Area and Severity Index), BSA (Body Surface Area) and DLQI (Dermatology Life Quality Index); PASI and BSA consist on the

assess of psoriatic lesions extension and severity signs, while DLQI is a questionary about the quality of life impact of the disease in several common situations; they will be widely explained on the variable paragraph.

This variables have demonstrated a strong connection with each other (normally, higher index of severity correlate with a life quality decline), as well as a relation to comorbidities development (45,46). Depending on this index, we can classify psoriasis according to its severity in mild, moderate or severe psoriasis:

SEVERITY	MEASURES
Mild	•<3% BSA* •Minimal effect on the patient's QoL**; acceptable level of symptomatic control by skin care measures and topical treatment.
Morderate	•3% - 10% BSA •Routine skin care measures cannot, or would not be expected to control symptoms; or substantially affects the patient's QoL, either due to its extension, physical disconfort or localization.
Severe	•>10% BSA •Topical therapy cannot, or would not be expected to satisfactorily control the symptoms; or the disease causes severe degratacion of patient's QoL

*BSA = body surface area; **QoL = quality of life

Figure 2. Psoriasis classification depending on the severity of the symptoms.

Many other pathologies have some skin lesions that might not be easy to differentiate from psoriatic finding. The most common differential diagnoses include tinea capitis,

tinea corporis, seborrheic dermatitis, atopic dermatitis, lichen planus, pityriasis rosea and even cutaneous lymphoma like mycosis fungoides (33,47).

TREATMENT

Even though there is no cure for psoriasis, there are multiple effective treatment options that can grant patients a mostly asymptomatic state. The treatment would be chosen according to the severity of the clinical findings, comorbidities, and access to health care; as well as the previous treatment response.

TOPICAL THERAPY

Emollients or moisturizers are an important adjuvant therapy, never recommended as monotherapy. Their use can correct scaling skin conditions, ameliorate symptoms and assist the penetration of other topical treatments. The effects of emollients on psoriasis would be explained on paragraph 1.C. “EMOLLIENTS”.

Topical therapy might always be the first encounter on a mild psoriasis case. There is a plenty topical therapeutic spectrum, in which corticosteroids and vitamin D3 analogues have taken the outstanding role. Some other options less relevant are, for example, topical calcineurin inhibitors or topical keratolytics (47).

- Topical corticosteroids: used due to their anti-inflammatory, antiproliferative and locally vasoconstrictive effects; are considered the cornerstone of topical treatment, this is a very often well tolerated and effective therapy for patients with mild psoriasis. The choice of potency and vehicle of topical corticosteroids must be based on body location of the lesion, to minimize adverse effects and maximize adherence.

  It is preferred to use high or mid-potency topical corticosteroids for the trunk and extremities or in case of highly thick lesions. On the contrary, for facial,

axillary, inframammary, and groin areas; low-potency corticosteroids are mostly preferred (32).

The stablish application regimen for topical corticosteroids recommends a twice a day application during the acute phase of active psoriasis. Once the lesions are shown quiescent; the application can be switch to twice per week. Applying topical therapy on the maintenance phase, when lesions are quiescent, is also known as proactive management; and it has been proved that it reduces the risk of recurrence (48).

Although it is uncommon, long-term use of corticosteroid even in topical administration could provoke side effects to take in count; such as local skin changes, tachyphylaxis or hypothalamic-pituitary-adrenal axis suppression (specially to be avoided on children) (47).

- Topical vitamin D3 analogues: their mechanism consist on binding to vitamin D receptors on T cells and keratinocytes, blocking keratinocyte proliferation and boosting keratinocyte differentiation (32).

  Vitamin D analogues prove efficacy (quite inferior to corticosteroids) as well as a safety profile, making them a good option for monotherapy in mild to moderate psoriasis. The primary adverse effect to be controlled is burning and local irritation, normally controlled over time (32,47).

- Combination products: two different combinations have shown higher efficacy than the last monotherapy topical treatments. This are corticosteroids in conjunction with topical vitamin D analogues (betamethasone and calcipotriol is the most used combination) or corticosteroids combined with keratolytic agents (specially used to break down thick scales and letting corticosteroids reach the skin). Combinations are also very well tolerated within a time of application once daily (49).

PHOTOTHERAPY

Phototherapy consist on emission of specific wavelengths of light acting as a beneficial effect in psoriasis lesions; these wavelengths of light affects by the inhibition of epidermal hyperproliferation and causing and immunomodulatory effect (50).

There are several types of phototherapy: narrowband ultraviolet B (NB-UVB); broadband ultraviolet B (BB-UVB); and psoralen ultraviolet A photochemotherapy (oral or bath PUVA), NB-UVB being the most used for psoriasis (51).

Phototherapy can be applied on mild localised psoriasis as targeted phototherapy, as well as on more extensive lesions by full-body-surround phototherapy sessions. It is a mainstay treatment from mild to severe psoriasis but inconvenient reside in its limited availability of phototherapy centres and the limitation that suppose for patients to assist to frequent continued sessions.

SYSTEMIC THERAPY

Systemic treatments for psoriasis can be separated in two main groups of drugs; oral medications and biological therapy. Both of them indicated for a first encounter on moderate to severe psoriasis.

Oral medication or classical systemic therapy: this type of medication has been the only and best indication for moderate to severe psoriasis for many years; however, since the biological treatment apparition, it has been mostly replaced. Classical therapy can be considered in cases of limited access to biologics and for patients who prefer noninjectable medications. In this group the most relevant drugs are: (27,47,52)

- **Methotrexate:** is a folic acid analogue that inhibits DNA by blocking thymidine and purine biosynthesis. The most commonly secondary effects include teratotoxicity, nausea, leukopenia, and liver analytic alterations (requires liver function monitoring and full blood count).

- **Cyclosporin:** is a T cell-inhibiting immunosuppressant in the group of calcineurin inhibitors. Outstanding side effects are hypertension, renal toxicity and non-melanoma skin cancer.
- **Acitretin:** is part of the synthetic vitamin A-related molecules, also known as retinoids. It affects transcriptional processes through nuclear receptors inhibiting keratinocyte hyperproliferation. Cheilitis is the most common dose-dependent adverse effect. Less common secondary effects would include conjunctivitis, effluvium and hepatitis.
- **Aprelimast:** a phosphodiesterase-4 inhibitor, stops the hydrolyzation of the second messenger cAMP, reducing the expression of pro-inflammatory cytokines. The most common adverse effect are nausea and diarrhoea, as well as infections of the upper respiratory tract; all usually self-resolving over time.
- **Fumaric acid esters:** are thought to have immunomodulatory, anti-inflammatory, apoptotic and antiproliferative actions on activated T cells. Common adverse events include gastrointestinal complaints, lymphocytopenia, eosinophilia and proteinuria (requiring full blood count and urine sediment during therapy.

Biological therapy: the term “biologics” currently refers to complex engineered molecules such us monoclonal antibodies and receptor fusion proteins. Differently from classical therapies, these treatments can only be administrated subcutaneously (or intravenously in some cases). Biologics affects targeting directly on specific inflammatory pathways of the pathogenesis. Immunopathological mechanism review of psoriasis is very relevant in this point; as it was displayed on (-chapter PATHOLOGY-), this treatments act on different components of this inflammatory chain. The main biological therapy groups can be divided on: (32)

- **TNF-alfa inhibitors**: etanercept, infliximab, adalimumab and certolizumab.
- **IL- 12/23 inhibitors**: ustekinumab.
- **IL-17 inhibitors**: can target the IL-17 ligand or its receptor:
    - IL-17A ligand: secukinumab and ixekinumab.
    - IL-17A and IL-17F ligands: bimekizumab (not yet approved in Spain).

- IL-17 receptor: brodalumab.

- **IL-23 inhibitors:** guselkumab, tildrakizumab and risankizumab.

Biological therapy is taking a main roll in moderate to severe psoriasis, not only for its significant higher efficacy, but also for its great safety prolife (53). Some adverse effects that were shown slightly higher than placebo, and are common to all biologics include: injection site reaction, nasopharyngitis and upper respiratory tract infections.

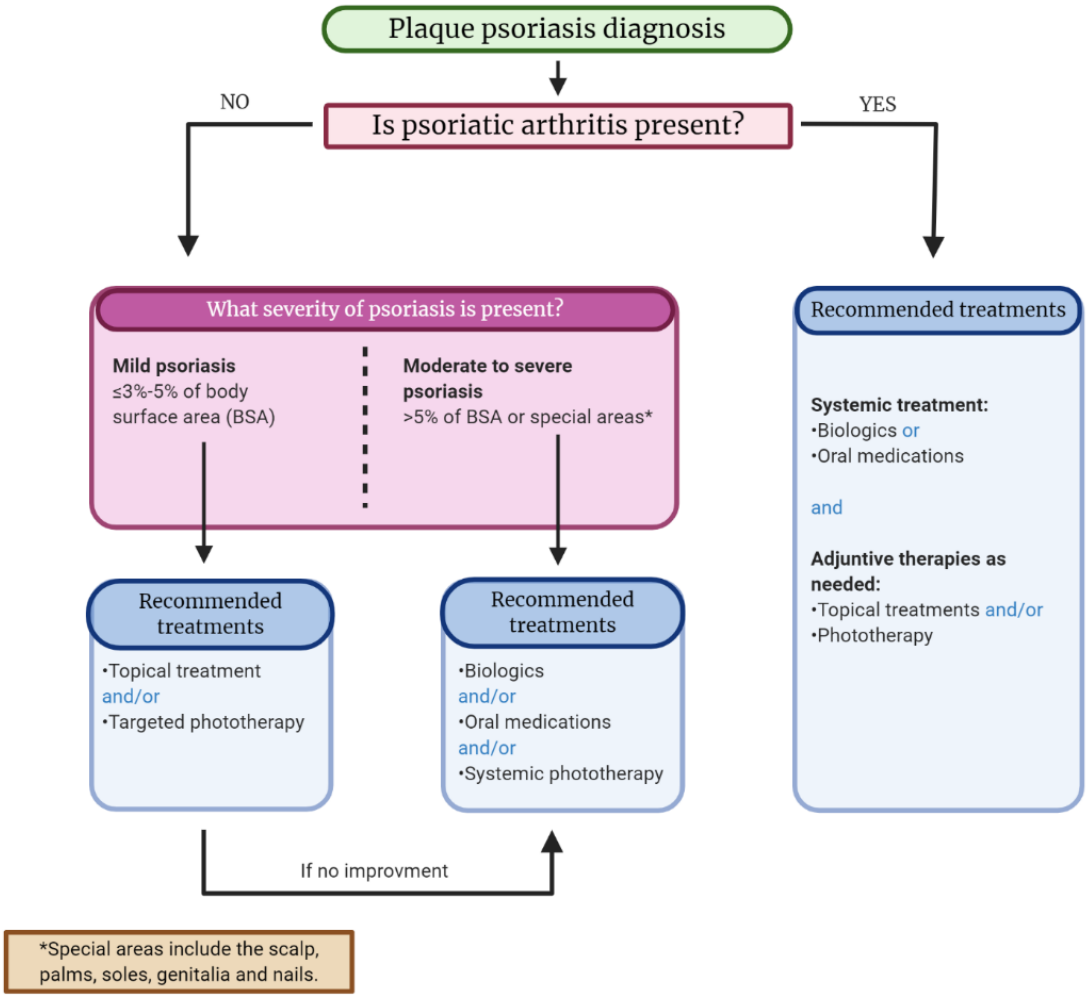

Figure 3. Plaque psoriasis therapy algorithm.

B) SKIN BARRIER AND HOMESTATIC PARAMETERS

Skin is the largest organ of the human body; it is the main barrier to all external factors and accomplished multiple defensive and regulatory functions. Skin is a continuous frequent target for allergic and immunologic responses. Loss of skin integrity because of injury or illness may result acutely in substantial physiologic imbalance and ultimately in disability or even death (54).

This skin barrier function resides in the epidermis and particularly in the stratum corneum. Epidermal barrier is important not only protecting the human body against many external stressors, but by maintaining skin homeostasis. Some of this significant functions of stratum corneum are acting as a permeability barrier, hydration, antimicrobial barrier, mechanical barrier, UV barrier, initiation of an inflammation process, psychosensory interface, etc.

Assessment of the epidermal barrier usually involves different measurements of homeostatic regulators, that are very useful to detect any skin alteration specially on early stages:

- Transepidermal Water Loss (TEWL): regarded as one of the most important parameters for measuring the integrity of the skin barrier. It is defined as the flux density of water, that diffuses from the epidermis and dermis through the stratum corneum in the skin surface. Increased TEWL levels seems to be associated with skin barrier impairments. TEWL results are highly skin area-dependent but symmetrically between right and left measuring sites (55).

- Stratum corneum hydration (SCH): levels of stratum corneum hydration can reflect both systemic and cutaneous condition. SCH values are found reduced in dermatology affections like atopic dermatitis or psoriasis, associated as wells with disease severity. Some systemic conditions like haemodialysis patients, postmenopausal women or growth hormone deficits shows reduced levels of SCH (56).

- Skin surface pH: the lipid skin coat contains a high concentration of hydrogen ions, constituting a barrier for positive electrolytes and protection against chemical and

microbial action. Acidic skin pH is intended to be a protection, making pH value a good predictor of skin barrier impairment (57).

- Other individual characteristics of the skin, that are used as good predictors in skin disease are elasticity, temperature erythema index; useful for analysis of skin test and management of skin diseases, these alterations would mostly depend on the skin lesion characteristics (58,59).

C) EMOLLIENTS

The role of moisturizers in skin barrier repair is not to be despised. Emollients improve the barrier function of the stratum corneum providing water and lipids. This lipid replacement therapy could reduce inflammation and restores epidermal function (60).

Their main composition are saturated and unsaturated hydrocarbons with variable length. Moisturizers contain occlusive ingredients, such us petrolatum or lanolin, that coat the skin surface with a water-repellent lipid layer; impeding the bidirectional movement of water (mostly reducing the skin water loss). This property can make these agents to temporally ameliorate the xerosis of many dermatological diseases, for example, psoriasis. Dry skin is the most common clinical manifestation of dermatologic diseases (61).

Many emollients can also contain certain substances like glycerine (useful to imbibe water from the surrounding atmosphere to the applicated skin), vegetable oils (do not provide scientifically proven benefits but contribute to the moisturizer texture) and ceramides (that can improve epidermal permeability and hydration at sufficient concentrations) (62).

Moisturizers can come in many different vehicles or preparations, such as creams, ointments, lotion, bath oil and soap substitutes. Creams and ointments are substantially more occlusive and greasier than lotions; and therefore, more effective.

One of the most common used emollients are petroleum jelly (Vaseline), liquid paraffin and mineral oils. They can be used liberally and frequently due to their safety profile; it does not exclude emollients from have some frequently-low side effects like irritant dermatitis, allergic contact dermatitis or fragrance allergy (63).

EMOLLIENTS AND PSORIASIS

Considering that the most common clinical representation of psoriasis is dry skin; emollients play a main role on this pathology therapy; but they have not yet been shown to provide stand-alone therapy for even mild cases of psoriasis.

Moisturizers help in normalizing hyperproliferation, differentiation and apoptosis; as well as having anti-inflammatory effects. This mechanism proved emollients to be helpful combating the characteristic psoriatic water loss and Koebner's phenomenon. Hence, emollients reduce scaling, improve itching, soften cracks and improve the penetration of other topical drugs (63,64).

Emollients have been shown to significantly improve skin conditions and quality of life for psoriasis patients. This products are useful as adjuvant treatments, actually, the use of corticosteroids and retinoids without concurrent moisturizers may exacerbate dry skin, preceding skin fissures and increasing the aggravation of psoriasis symptoms (65).

3. JUSTIFICATION

Psoriasis affects almost 3% of the population, not only in our media but all over the world. Even though the great progress psoriasis management and treatment over the years, it still has not a definitive cure. Making it a frequent disease that causes a long-life affection once it appears.

It has been proved the significant impact that this disease can cause in the psychosocial aspect and quality of life of their affected and their surrounding ones. The elevated increase of the suicidal ideation and emotional disturbance shown on psoriatic patients is preoccupying (42,43). Importance on investigating action measures to try to reduce the impact of the disease is primal to avoid patients' social distancing and improve their mental health status.

In psoriasis, homeostatic parameters have proved to be good predictors not only on skin barrier function, but in its clinical signs and symptoms (54). Analysing these parameters, we are able to prove the beneficial effect of many therapies in order to improve the management's quality.

There is scarce information about how epidermal barrier function is modified by emollients in psoriatic patients; they have been proved to be beneficial in adjuvant therapy but we do not really know their effect on individual homeostatic variables, and if it exists variance for not-impaired skin between psoriatic patients and general population. Emollients are recommended as adjuvant therapy on psoriatic patients; however, their significance is being underestimate due to absence of research and analysis.

Furthermore, no studies compare skin barrier modification between different composed emollients on psoriatic characteristically lesions.

The same way, few studies have stablished basal differences between skin barrier parameters on a psoriatic plaque. In this study we pretend to confirm this variance and to assess skin barrier in order to have a general information of the skin homeostatic function.

This study gives an opportunity to evaluate the impact of emollients in epidermal barrier function in patients with psoriasis. Giving the possibility to improve skin homeostasis could be the key on helping ameliorate the disease progress and its clinical symptoms; emollients are an accessible and safe approach that could easily reduce clinical and social impact on psoriasis disease.

4. HYPOTHESIS

Primary hypothesis

-The use of emollients may influence skin barrier function on psoriatic skin plaque in a short time period.

Secondary hypothesis

-Epidermal barrier function and skin homeostasis may differ between non-affected skin psoriatic skin and healthy controls.

-Epidermal barrier function and skin homeostasis may differ between affected and non-affected skin in psoriasis patients.

5. OBJECTIVES

Main objective

-To analyse skin homeostasis and epidermal barrier function differences between psoriatic plaque, non-affected skin in psoriasis patients and control skin; and to evaluate the effect of two types of moisturizers.

Secondary objectives

-To assess if it exists significant homeostasis difference between a psoriasis plaque before and after the application of emollients.

-To evaluate if there is any difference in the homeostatic patron of the psoriatic plaque depending on the emollient used (Vaseline or water-based cream).

-To assess any changes of the non-affected skin homeostasis because of the emollient's application.

6. SUBJECTS AND METHODS

STUDY DESIGN

A) A Before-and-after study on patients with psoriasis to assess changes in skin barrier function after the application of two different emollients.

B) A cross-sectional study to assess skin homeostasis differences between healthy skin, involved and uninvolved skin in psoriatic patients.

STUDY POPULATION

All participants were recruited from July, August and October 2020 in the Dermatology Service of the Hospital Universitario Virgen de las Nieves in Granada. Cases were patients that accomplished inclusion criteria.

Inclusion criteria:

- Age older than 18 years old.
- Plaque-psoriasis clinical type.
- Currently active skin lesions.
- Lesions large enough to not compromise the measure procedure.
- Not coexistence of another inflammatory skin disease.

Exclusion criteria:

- Patients who did not wished to participate.
- Once in the evaluation time, no active skin lesions were found.

Controls were healthy volunteers, gender-and-age-matched (±5 years) with cases. These volunteers were people who attended the Dermatology Service for different conditions no related to psoriasis or any inflammatory skin disease.

SAMPLE SIZE

Accepting an alpha risk of 0.05 and a beta risk of 0.2 in a two-sided test, 28 subjects are necessary to recognize as statistically significant a difference greater than or equal to 0.05 units. The standard deviation is assumed to be 15 g/h/m² in TEWL parameter (our main dependent variable), taking as reference preceding comparable studies that utilized the same principal variables (66). It has been anticipated a drop-out rate of 0%.

31 cases subjects were studied on this investigation, added to 31 controls, results on a total sample size of 62 subjects.

STUDY VARIABLES:

Independent variables:

This study dependent variable was the application of two different emollients:

- Pure Vaseline jelly: "Vaselina esterilizada pura Orravan pomada, 32g" was used for this study. 100% vaseline composition (mixture of semisolid hydrocarbons), without any excipients contained; in an ointment pharmacologic form.
- Water-based formula: formulated by Santamaría D-) pharmacy. It is composed with an emulsifier base NEO PCL O/W. Their practical relevancy leans on its low-fat content.

Dependent variables:

All variables were measured using a Multi Probe Adapter (MPA, Courage + Khazaka electronic GmbH, Germany). In order to avoid random error, every variable was measured ten times, except elasticity parameter that is automatically measured four times. The average of all data obtained was used for the statistical analysis.

- TEWL: measured in g/h/m² (water transported/ time/ surface) using Tewameter® TM 300. The procedure consists on the equilibration of the probe

on the skin for 10 to 15 seconds (the time it takes for 10 measures to be taken). This probe measures the density gradient of the water evaporation from the skin; these values are a reflection of skin barrier function. It generally reflects integrity of the stratum corneum.

- SCH: in arbitrary units, using Corneometer® CM 825. This probe system requires to apply pressure onto the skin to take an SCH value. Ten times were need to press on all studied surfaces in order to obtain the results. The measurement is based on capacitance measurement of a dielectric medium, here the stratum corneum, the uppermost layer of the skin. With increasing hydration, its dielectric properties change. The measurement can detect even slightest changes in the hydration level.
- Skin temperature: measured in in ºC, using Skin-Thermometer ST 500. Measure range from 22ºC to 40ºC, with a resolution of 0.1ºC. When activated, the probe sensor detects the relative infrared temperature. It takes one second for each temperature quantification.
- Skin pH: measured in pH units expressed with one decimal, using Skin-pH-Meter PH 905. Skin pH measurement is based on a high-quality combined electrode. It counts with an activation button that register one value each time is pressed.
- Erythema index: in arbitrary units, using Mexameter® MX 18. The measurement principle is based on absorption/reflection of specific emitted light wavelengths. The probe activation system is the same as Corneometer® CM 825; by pressure application.
- Skin elasticity: using R2 value (visco-elasticity parameter), measured in %, using Cutometer® Dual MPA 580). This probe applies negative pressure, measuring different elasticity parameters by the suction method; depending on the penetration depth.

All device technical data and measurement principles are completely explained on: https://www.courage-khazaka.de/en/16-wissenschaftliche-produkte/alle-produkte/182-mpa-e

Co-variables or clinical variables:

CASES AND CONTROLS COMMON CO-VARIABLES:

- Age: in years old.
- Sex: female or male.
- Smoking habit: analysed as a categorical dichotomous variable; yes or no. Any actual smoking consume was taking in count as a "yes".
- Alcohol intake: stablished as a categorical dichotomous variable; yes or no. More than three standard drink units per day were taken as a "yes".
- Daily hydration: stablished as a categorical dichotomous variable; yes or no. Skin hydration routine was asked to every case and control, accepting their testimony as a valid answer. In psoriatic cases, regularly use of emollients on affected areas was taken as affirmative.
- Anthropometric measures: weight (Kg), height (m) and abdominal perimeter (cm) were analysed in this study. Weight and height were asked to the subject, obtaining approximately data; while abdominal perimeter was measure by the analyst during the procedure. Body mass index (BMI) was calculated during the data analysis phase.

SPECIFIC CASES CO-VARIABLES

- Time evolution since age of onset: in years old, as an approximation by asking the patients during the procedure.
- Family history of psoriasis: analysed as a dichotomous variable (yes/no), asked directly to the subjects; only professionally diagnosis of psoriasis was accepted in this variable.
- Psoriatic arthropathy: analysed as a categorical dichotomous variable; yes or no. Only previous diagnosis of psoriatic arthritis was stablished as a "yes".
- Psoriasis severity: two different scores were analysed as severity markers:

- PASI: stablish severity in values from 0 (not illness) to 72 (maximum affection). In this score is taking in count 4 different areas of the body: head, arms, trunk and legs. This index is observer-dependent; the analyser sets to every skin area:
  - The extension in percentage of skin impaired (from 0% to 100%; divided in 7 possible intervals [0%; <10%; 10-29%; 30-49%; 50-69%; 70-89%; 90-100%]).
  - The severity of three clinical signs (erythema, induration and desquamation) on a scale from 0 to 4 (from none to maximum).

- BSA: estimates only the body surface area affection by using the handprint or palm method. Taking the patient palm for reference, estimate how many patient palms fit in the same 4 areas analysed for PASI score (head, arms, trunk and legs). Every palm correlate with an 1% of the body surface.

Licensed online calculators were used to estimate both scores; every case severity index was stablished by the same analyst, avoiding possible observer-related discrepancies.

- Quality of life index: Dermatology life quality index (DLQI) was used for this point. DLQI is an adult-designed questionnaire (ANNEX 1), that assess the implication of the dermatology disease at issue in different psychosocial situations. It is self-explanatory and can be simply handed to the patient who is asked to fill it in without the need for detailed explanation. It is usually completed in one or two minutes.

  DLQI is composed of ten questions with four possible answers (“not at all”, “a little”, “a lot”, “very much”). An extra answer is included if the patient considers the question is not relevant.

Answers are rated from 0 (“not at all”) to 3 points (“very much”); “not relevant” response is also rated as 0 points. Thus, possible results scores range from 0 (no effect at all on patient’s life) to 30 (extremely large effect on patient’s life).

- Current treatment: this variable was divided and analysed as four different accumulative variables. Treatments where grouped depending on their form of application, similar efficacy, safety profile and impact on patient’s life. The four-group assessed where: topical treatment, oral medications, phototherapy and biologics. Patients could be on concomitant therapies at the time; or in case of clinical regression, not even on one of them.

PROCEDURES

Data acquisition:

All data were collected on July, August and October months at Dermatology Service of the Hospital Universitario Virgen de las Nieves in Granada. Determinate days when it was stipulated a psoriasis clinic visit; patients that accomplished inclusion criteria, were called to the investigation unit and offered to participate in the study. Controls were selected also at the Dermatology Service, attempting the closest age and gender match respect to the cases.

Only one investigator was in charge of all the procedure explanation as well as the data collection. Location for data acquisition was determinate as the investigation unit at Dermatology Service; only the investigator and one subject at a time (and an accompanist in exceptional cases) where in the room during the procedure. The average ambient air temperature and humidity was determined 24±3ºC, and 42±2%; measured with the TFA® Lab Thermometer IP65 LT-101.

First of all, possible subjects were explained the purpose of the study, the procedure as well as the proper ethical considerations. If the subject under consideration agree with

all the terms and conditions, written informed consent (ANNEX 2) was signed and the data collection could be started.

For cases, lesion area was examined and assess to be suitable for the measurement process; then, not-impaired skin area was selected as well, preferably symmetrically to the lesion. Independent variables were taken in both areas with the different devices already exposed on the variables paragraph; the procedure is completely non-invasive; the measures are taken only by placing the dispositive onto the skin. Ten measurements were taken for each individual parameter expecting skin elasticity, that was taken four times; all results were displayed on a computer software connected to the Multi Probe Adapter. Only average results were collected on the proper recompilation data sheet (ANNEX 3).

Afterwards the first mensuration, both emollients (dependent variable) were applied onto two different locations in the same areas that were considered early. Moisturizers application was lesion-dependent, trying the most possible equality between both applied surfaces.

Next, an emollient absorption time was stablished so the next measurement could be valid. Waiting time lasted from four to six minutes in every case, that time was benefited to interrogate all of the co-variables.

Finally, the second measurement was taken, this time on each four localizations (two for each emollient on both plaque and healthy skin). The process of this measurement was equal to the first one. The whole procedure for psoriatic cases lasted from thirty to forty minutes for each patient.

In the case of controls, the procedure remained the same reducing the co-variables size and keeping from doing the impaired skin measurements. A specifically recompilation data sheet for controls were elaborated (ANNEX 4). Controls measurement procedure took around ten minutes for subject.

All safety measures were respected on the data acquisition operation due to SARS-CoV-2 situation. Either investigator and subject were appropriate masks during all procedure. Examiner took charge of all device disinfestation before and after any data collection, as well as handwashing and room ventilation.

Data analysis:

- Univariate results:

The results were expressed as percentages for categorical variables. For continuous variables, we used mean and standard deviation (if a normal distribution can be assumed) or median, first and third quartile (if a normal distribution cannot be assumed). The Shapiro-Wilk test was used to check the normality of data distribution; normal distribution could be assumed in all variables.

- Bivariate results:

Categorical variables were compared with Chi Square of Pearson test. For continuous variables, Student's t-test for independent variables was used. Specially, to compare homeostasis parameters before and after the emollient's application, Student's t-test for paired samples was used.

- Multivariate results:

In addition, multivariate logistic regression analysis was performed in order to add the covariates that could skew the main association.

P value <0.05 was considered statistically significance. Statistical Analyses were performed using the SPSS package (IBP SPSS Statistics, Version 25.0 for Windows, Chicago, IL, USA).

7. ETHICAL CONSIDERATIONS

All basic ethical principles were respected according the World Medical Association *Declaration of Helsinki – Ethical Principle for Medical Research Involving Human subjects (last amended at the 64th WMA General Assembly, Fortaleza, Brazil, October 2013).* Moreover, this study respected the criteria established by the Nuremberg Code, the Belmont Report and the Oviedo Convention.

Before the start of this study, the project was evaluated and accepted by the clinical research ethical committee of Hospital Universitario Virgen de las Nieves, in Granada (ANNEX 5).

Prior to the beginning of the data collection, every subject participating in the trial was properly informed about this study to the fullest extent using language and terms they were able to understand in order to allow a fully knowledgeable decision.

Following *Law 41/2002, of November 14th – "Básica reguladora de la autonomía del paciente y de derecho y obligaciones en materia de información y documentación clínica"*; every patient was properly informed of the aim, procedures, anticipated benefits and potencial negative consequences of the study. Subjects were given a study information sheet that contained all of this data. Information sheet was attached to the written informed consent (ANNEX 2), that was signed by every subject included in this study as well as by the informer investigator. In addition, it was explained to the participants their right to refuse entry into the study or withdraw from the study at any time without repercussion to their future medical care. All measures taken were non-invasive. A proper e-mail contact was given to all participants in case of need more information about the study in the future.

All data collected from each and every subject included in the study was treated and used anonymously, preserving the confidentiality of the patient according to the *Organic Law 3/2018, of December 5th – "Protección de Datos Personales y Garantía de los derecho digitales".* Subject's information was only used in purpose of research. Subjects will be identified by a numeric code instead of their names or recognizable data. Personal identity of the subjects as well as their personal medical information will be

maintained in privacy; being only available for the research team and pertinent health authorities. In any presentation of the results of this study at publications or conferences, the subject's identities will remain confidential.

Investigators declared no conflict of interest or commercial bias in any aspect of this study, subjects were not retributed for their participation.

8. RESULTS

General characteristics:

A total of 62 subjects, consisting of 31 psoriatic patients and 31 healthy controls were included in the study. TABLE 1 summarized the general characteristics of the sample.

Both study groups were formed by 14 females and 17 males. The mean age of psoriatic subjects were 53.23 years old, and 47.77 for the control group (range 18-81 years).

Significant differences between control and psoriatic groups were found in smoking habit, family history of psoriasis and anthropometric measures. Smoking habit was determined remarkably higher in psoriatic patients than controls, with numbers of 13 (41.9%) and 4 (12.9%) currently smokers, respectively. Family history of psoriasis is bibliography clearly related to psoriasis disease, which is notably remark in the difference of 14 (45.2%) occasions in the psoriatic group and 3 in the control subjects.

Regarding BMI significant differences were found (30.88 vs 24.01 kg/m², $p<0.001$ for patients and controls, respectively). Mean weight on controls resulted 69,10 kg (±11.73), contrasted with 89.15 kg (±17.84) on psoriatic patients ($p<0.001$). As well as abdominal perimeter (110.58 vs 90.42 cm, $p<0.001$, for patients and controls, respectively).

Table 1. Characteristics of the sample

	All participants (n=62)	Controls (n=31)	Psoriatic patients (n=31)	p*
Age (years)	50.50 (±15.82)	47.77 (±16.19)	53.23 (±15.21)	0.559
Sex (%)				1
- **Female**	28 (45.2%)	14 (45.2%)	14 (45.2%)	
- **Male**	34 (54.8%)	17 (54.8%)	17 (54.8%)	
Smoking habit				**0.010**
- **Non-smoker**	45 (72.6%)	27 (87.1%)	18 (58.1%)	
- **Smoker**	17 (27.4%)	4 (12.9%)	13 (41.9%)	
Alcohol intake (excessive)	4 (6.5%)	1 (3.2%)	3 (9.7%)	0.301
Family history of psoriasis (yes)	17 (27.4%)	3 (9.7%)	14 (45.2%)	**0.002**
Emollients use (yes)	27 (43.5%)	11 (35.5%)	16 (51.6%)	0.2
Weight (Kg)	79.13 (±18.06)	69.10 (±11.73)	89.15 (±17.84)	**<0.001**
Height (m)	1.70 (±0.11)	1.69 (±0.11)	1.70 (±0.11)	0.773
IMC (kg/m2)	27.48 (± 5.95)	24.013 (±2.83)	30.88 (±6.29)	**<0.001**
Abdominal perimeter (cm)	100.50 (±17.21)	90.42 (±12.04)	110.58 (±15.72)	**<0.001**
DLQI			5.81 (±4.82)	
PASI			5.23 (±3.78)	
BSA			6.41 (±4.91)	
Psoriatic arthritis (yes)			15 (48.4%)	
Current treatment				
- **Topical**			19 (61.3%)	
- **Oral medication**			6 (19.4%)	
- **Phototherapy**			5 (16.1%)	
- **Biologic drugs**			14 (45.5%)	

BMI = body mass index; DLQI = Dermatology Life Quality Index; PASI = Psoriasis Area and Severity Index; BSA = Body Surface Area.

*p value after using Student T test for independent samples or Welch's test when needed to compare continuous variables and the chi-square of Pearson test or Fisher's exact test, as appropriate, were applied to compare categoric data between controls and psoriatic patients.

Skin homeostasis analysis between psoriatic plaque, uninvolved psoriatic skin and healthy controls:

Skin barrier function parameters between healthy controls and involved and uninvolved skin in psoriatic patients before any application of emollients were compared (TABLE 2).

TEWL was significantly higher at psoriatic plaques than uninvolved psoriatic skin; in addition, TEWL values were also notably higher at not-impaired psoriatic skin than

healthy control skin (13.23 vs 8.54 vs 6.41 g/h/m²; p<0.05 in all comparisons). SCH was significantly lower at psoriatic plaques than both uninvolved psoriatic skin and healthy controls (13.44 vs 30.55 vs 30.90 AU, p<0.001 between unimpaired skin and psoriatic plaques).

Temperature was higher at psoriatic plaques and uninvolved psoriatic skin respect to control skin (30.68 vs 30.63 vs 29.71 °C, p<0.01 comparing control skin and psoriatic skin). pH results were significantly lower in psoriatic plaques and uninvolved psoriatic skin than healthy controls (6.26 vs 6.284 vs 6.60, p<0.01 between control skin and psoriatic skin). Erythema index was remarkably higher in psoriatic plaques than on control skin; as well as control skin was significantly higher than uninvolved psoriatic skin (380.40 vs 307.63 vs 262.41 AU, p<0.05 in all comparisons). No differences in elasticity were found.

Table 2. Homeostasis parameters at controls versus uninvolved psoriatic skin and psoriatic plaque before emollients' application.

	Control	Uninvolved psoriatic skin before emollient's application	Psoriatic plaque before emollient's application	p*	p**	p***
TEWL (g/h/m²)	6.41 (±4.41)	8.54 (±3.87)	13.23 (±7.85)	**0.022**	**0.021**	**<0.001**
SCH (AU)	30.90 (±12.22)	30.55 (±11.78)	13.44 (±14.17)	0.073	**<0.001**	**<0.001**
Temperature (°C)	29.71 (±1.19)	30.63 (±1.75)	30.68 (±2.11)	**0.007**	**0.010**	0.812
pH	6.60 (±0.36)	6.28 (±0.51)	6.26 (±0.51)	**0.002**	**0.002**	0.674
Elasticity (%)	0.6423 (±0.16)	0.6288 (±0.17)	0.6361 (±0.16)	0.904	0.838	0.853
Erythema (AU)	307.63 (±55.05)	262.41 (±55.23)	380.40 (±96.41)	**0.031**	**0.002**	**<0.001**

TEWL = Transepidermal Water Loss; SCH = Stratum Corneum Hydration; AU = arbitrary unit.

*p value after using a linear regression model adjusted by smoking habit and anthropometric measures to compare homeostasis parameters between control and uninvolved psoriatic skin before emollient's application.
**p value after using linear regression model adjusted by smoking habit and anthropometric measures to compare homeostasis parameters between control and psoriatic plaque before emollient's application.
*** p value after using Student's T test for paired samples to compare homeostasis parameters between uninvolved psoriatic skin and psoriatic plaque before emollient's application.

Skin homeostasis changes in patients with psoriasis after emollients application:

Homeostasis parameters changed after emollients' application. These parameters were compared depending on the repercussion in the different skin situations studied: uninvolved psoriatic skin (TABLE 3), psoriatic plaque (TABLE 4) and healthy control skin (TABLE 5).

-Uninvolved psoriatic skin:

TEWL was significantly higher after the application of the water-based formula (12.21 vs 8.542 g/h/m²; p=0.02). TEWL experience a descent of -1.43 g/h/m² (4.015 SD) after applying Vaseline jelly with almost significant results, p=0,056. Differences between both emollients on TEWL parameters were also significant (8.03 vs 12.21 g/h/m²; p<0.001). SCH was significantly higher after the application of the water-based formula (38.08 vs 30.55 AU; p=0.05). Vaseline jelly application showed not difference on SCH, however, SCH compared after both administrations differed significantly (38.08 vs 28.58 AU; p<0.001).

Temperature was significantly lower after the application of the water-based formula (30.31 vs 30.63 °C; p=0.03). Temperature did not show significant results after Vaseline jelly application. Differences between both emollients on temperature parameters were also significant (30.31 vs 30.66°C; p=0.012).

No differences in pH, erythema or elasticity were found after applying moisturizers.

Table 3. Homeostasis parameters at uninvolved psoriatic skin before and after application of different emollients.

	Uninvolved psoriatic skin before emollients' application	Uninvolved psoriatic skin after Vaseline jelly application	Uninvolved psoriatic skin after water-based formula application	Mean difference at uninvolved skin before and after Vaseline jelly application	Mean difference at uninvolved skin before and after water-based formula application	p*	p**	p***
TEWL (g/h/m²)	8.54 (±3.87)	8.03 (±3.60)	12.21 (±5.11)	-1.43 (SD 4.01)	2.75 (SD 4.58)	0.056	**0.020**	**<0.001**
SCH (AU)	30.55 (±11.78)	28.58 (±11.71)	38.08 (±10.73)	-1.96 (SD 11.39)	7.54 (SD 13.76)	0.345	**0.050**	**<0.001**
Temperature (°C)	30.63 (±1.75)	30.66 (±1.94)	30.30 (±1.90)	0.03 (SD 0.79)	-0.33 (SD 0.79)	0.823	**0.030**	**0.012**
pH	6.28 (±0.51)	6.42 (±0.40)	6.37 (±0.39)	0.13 (SD 0.50)	0.09 (SD 0.45)	0.138	0.290	0.358
Elasticity (%)	0.6288 (±0.17)	0.6656 (±0.17)	0.6508 (±0.16)	0.0367 (SD 0.17)	0.0219 (SD 0.15)	0.240	0.413	0.589
Erythema (AU)	262.41 (±55.23)	258.37 (±51.95)	249.90 (±61.10)	-4.04 (SD 25.92)	-12.51 (SD 34.32)	0.392	0.051	0.147

TEWL = Transepidermal Water Loss; SCH = Stratum Corneum Hydration; AU = arbitrary unit.

*p value after using Student's T test for paired samples to compare homeostasis parameters between uninvolved psoriatic skin before and after Vaseline jelly application
**p value after using Student's T test for paired samples to compare homeostasis parameters between uninvolved psoriatic skin before and after water-based formula application
***p value after using Student's T test for paired samples to compare homeostasis parameters between uninvolved psoriatic skin after both different emollients' application

-Psoriatic plaque:

TEWL decreased by 5.59 g/h/m² (5.68 SD) after Vaseline Jelly application, and experimented an increase of 3.60 g/h/m² (6.86 SD) after water-based formula application; both significant with p<0.001, and p=0.006, respectively. SCH increased significantly after applying the water-based formula (13.44 vs 22.89 AU; p=0.003). No significant effect was reported after the Vaseline jelly administration, but showed an increasing trend (p=0.264).

Temperature was lower after the water-based formula application; decreasing by 0.436°C (0.96 SD), p=0.017. No differences on temperature were observed after

Vaseline jelly application. Both erythema and melanin index showed significantly changes after the two emollients application. Erythema index increased by 59.33 AU (53.83 SD) and 58.16 AU (66.88 SD) after Vaseline jelly and water-based formula application respectively (both p<0.001). Non statistical differences were observed between post-application values (p=0.912 for erythema index)

No differences in pH or elasticity were found after emollients application.

Table 4. Homeostasis parameters at psoriatic plaque before and after application of different emollients

	Psoriatic plaque before emollients' application	Psoriatic plaque after Vaseline jelly application	Psoriatic plaque after water-based formula application	Mean difference at uninvolved skin before and after Vaseline jelly application	Mean difference at uninvolved skin before and after water-based formula application	p*	p**	p***
TEWL (g/h/m²)	13.23 (±7.85)	7.63 (±5.21)	16.83 (±6.86)	-5.59 (SD 5.68)	3.60 (SD 6.86)	**<0.001**	**0.006**	**<0.001**
SCH (AU)	13.44 (±14.17)	15.64 (±10.59)	22.89 (±14.66)	2.20 (SD 10.75)	9.44 (SD 16.23)	0.264	**0.003**	**<0.001**
Temperature (°C)	30.68 (±2.11)	30.72 (±1.87)	30.24 (±1.92)	0.04 (SD 0.90)	-0.44 (SD 0.96)	0.813	**0.017**	**<0.001**
pH	6.26 (±0.51)	6.35 (±0.35)	6.33 (±0.45)	0.09 (SD 0.40)	0.07 (SD 0.33)	0.229	0.277	0.685
Elasticity (%)	0.6361 (±0.16)	0.6350 (±0.18)	0.6461 (±0.13)	-0.0011 (SD 0.21)	0.0099 (SD 0.18)	0.977	0.762	0.664
Erythema (AU)	380.40 (±96.41)	439.73 (±90.14)	438.56 (±84.40)	59.33 (SD 53.83)	58.16 (SD 66.88)	**<0.001**	**<0.001**	0.912

TEWL = Transepidermal Water Loss; SCH = Stratum Corneum Hydration; AU = arbitrary unit.

*p value after using Student's T test for paired samples to compare homeostasis parameters between psoriatic plaque before and after Vaseline jelly application
**p value after using Student's T test for paired samples to compare homeostasis parameters between psoriatic plaque before and after water-based formula application
***p value after using Student's T test for paired samples to compare homeostasis parameters between psoriatic plaque after both different emollients' application

-Healthy control skin:

TEWL decreased by 0.99 g/h/m² (2.32 SD) after Vaseline Jelly application, and experimented an increase of 2.83 g/h/m² (4.07 SD) after water-based formula application; both significant with p=0.025, and p=0.010, respectively. SCH only increase by 7.33 AU (7.21 SD) after the water-based formula application (p<0.001). No effect was reported after applying the Vaseline jelly (p=0.817).

Temperature was decreased after the application of Vaseline jelly and the water-based formula by 0.49°C (0.81 SD) and 0,59°C (1.06 SD), respectively (p<0.001 for both comparisons). Erythema index significantly decreased by 16.62 AU (34.80 SD) after the water-based formula application (p=0.012). No erythema index difference was shown after applying Vaseline jelly (p=0.073).

No relevant changes were analysed for pH and elasticity parameters, even though they showed significant differences between both emollients results (p= 0.013 for pH, p=0.012 for elasticity).

Table 5. Homeostasis parameters at control skin before and after application of different emollients.

	Control skin before emollients' application	Control skin after Vaseline jelly application	Control skin after water-based formula application	Mean difference at uninvolved skin before and after Vaseline jelly application	Mean difference at uninvolved skin before and after water-based formula application	p*	p**	p***
TEWL (g/h/m²)	6.41 (±4.41)	5.42 (±4.36)	9.23 (±4.98)	-0.99 (SD 2.32)	2.83 (SD 4.07)	**0.025**	**0.010**	**<0.001**
SCH (AU)	30.90 (±12.22)	30.48 (±11.68)	38.23 (±12.42)	-0.42 (SD 10.02)	7.33 (SD 7.21)	0.817	**<0.001**	**<0.001**
Temperature (°C)	29.71 (±1.19)	29.22 (±1.22)	29.12 (±1.23)	-0.49 (SD 0.81)	-0.59 (SD 1.06)	**0.002**	**0.004**	0.523
pH	6.60 (±0.36)	6.73 (±0.25)	6.57 (±0.29)	0.13 (SD 0.42)	-0.02 (SD 0.37)	0.095	0.720	**0.013**
Elasticity (%)	0.6423 (±0.16)	0.6478 (±0,13)	0.5944 (±0.1433)	0.0054 (SD 0,16)	-0.4791 (SD 0.1399)	0.851	0.066	**0.012**
Erythema (AU)	307.63 (±55.05)	297.23 (±58.69)	291.01 (±53.15)	-10.40 (SD 31.14)	-16.62 (SD 34.80)	0.073	**0.012**	0.197

TEWL = Transepidermal Water Loss; SCH = Stratum Corneum Hydration; AU = arbitrary unit.

*p value after using Student's T test for paired samples to compare homeostasis parameters between control skin before and after Vaseline jelly application

**p value after using Student's T test for paired samples to compare homeostasis parameters between control skin before and after water-based formula application

***p value after using Student's T test for paired samples to compare homeostasis parameters between control skin after both different emollients' application

9. DISCUSSION

Skin homeostasis analysis showed differences between control skin, uninvolved skin and plaques in psoriasis patients. Psoriatic plaques showed higher TEWL and Erythema values, as well as lower SCH values than uninvolved skin and healthy controls. TEWL was also significantly higher in uninvolved psoriatic skin than on control skin, but with a lower value. In addition, psoriatic patients (plaque and uninvolved skin) seem to have relatively higher skin temperature levels, and lower values of skin pH and melanin index.

After the emollient's application, increased SCH and erythema levels at psoriatic plaques were observed. Another very important parameter was TEWL, that showed a decrease on psoriasis plaque only after the Vaseline jelly application; even though the water-based cream caused its increment. Differences on temperature may be strongly related to the moisturizer's nature (water-based formula always decreased temperature values).

The objective measurements have proven that the whole epidermal barrier is affected in psoriatic patients, not just at psoriatic plaques. Some homeostasis parameters have previously been evaluated in psoriatic patients, of which the most studied are TEWL and SCH.

Other research showed higher TEWL at psoriatic plaques than uninvolved psoriatic skin and healthy control (66,67). However, differences in TEWL between uninvolved psoriatic skin and healthy controls are controversial. With similar participants number, *Nikam et al.* found higher TEWL on psoriatic skin (66), in agreement with our results; while *Takahashi et al*. did not assess any differences (67).

On the other hand, other studies show lower SCH levels at psoriatic plaques than on not-impaired skin; showing no differences between psoriatic skin or control skin (67,68). This finding supports our SCH results.

Some authors explain the differences of TEWL and SCH values between psoriatic plaques and not-impaired skin in the same subject by a decrease in AQP3 expression showed in plaques and perilesional skin (69).

There have been reported controversial results for pH values in psoriatic patients. According to our results, *Cannavò et al.* founds lower pH values for psoriatic plaque and uninvolved skin.(68) However, *Delfino et al.* reported no difference on this parameter (70).

Changes in elasticity in psoriasis have been only evaluated by *Choi et al.* who shows lower values for psoriatic patients assessed by R7 parameter (71); this corresponds to the ratio of elastic recovery to total deformation. R7 is a less reliable parameter for measuring elasticity than the one used in this study (R2, overall elasticity)(72).

Temperature and erythema were also higher in psoriatic skin, which could be explained by its inflammatory pathogenesis (73).

There is scarce research on the role of emollients in epidermal barrier function in psoriasis, aside from TEWL and SCH valuation. Our results show improvement in epidermal barrier function on the psoriatic plaque, related to a significant SCH increment after the formula application, and TEWL reduction only after Vaseline jelly application. The TEWL increase due to the water-based formula is explained by its composition; only water composition is not occlusive enough to revert this parameter (61).

Stratum corneum hydration (SCH) may be the parameter most willingly improved by emollient therapy, probably due to the presence of effective humectants like glycerine in the water-based formula, that are not contained on Vaseline or petrolatum. In agreement with our results, several studies with similar subject samples achieved relatable results (74,75).

However, TEWL values shows controversy; while some researches showed no significant differences in this parameter after emollients' application (75,76); *Simpson et al.* reported a significant decrease of TEWL values after the application (77), and *Mohammed et al.* found all contrary results, a remarkable increment on this parameter (78). This inconsistency data on the effect of moisturizers on TEWL is probably explained by the different composition of the moisturizers used in each study, which do not exactly adjust between each other.

The reduction on temperature after the water-based formula application on psoriatic skin is explained by its opposite effect on the TEWL, as it rise the Transepidermal water loss, the temperature was slightly affected (79).

Erythema rises on psoriatic plaque after applications is explained by a physical effect. With the emollient administration, the dry scales that covered the lesion surface got hydrated or even dropped off; displaying a deep, more erythematous layer of the plaque. No other studies evaluate these parameters before and after emollients' application over skin.

Elasticity and pH values did not change after applying moisturizers. Only another study support pH findings with no significant affection by the use of emollients (76). No previous information was found about elasticity parameter to contrast these results.

The importance of these results on psoriasis lean on the potential that moisturizers have shown to improve skin barrier function through hydration parameters like TEWL and SCH. Correcting skin homeostasis by non-aggressive emollients could be the key to a simple and safe way to ameliorate this disease severity and its major impact on quality of life.

In this study only two different composed moisturizers have been proved and have shown significant variability between them. This stablish a precedent to experiment the homeostasis repercussion of contrasting emollients and encourage to study which components are more beneficial to repair skin barrier function, not only on psoriasis illness but in many others dry skin diseases. Finally, due to study limitations, only short-term alteration could be considered; it would be interesting to assess the possible homeostatic modification caused by a large use (days or weeks) of these moisturizers as well as its repercussion on clinical on a long-distance term.

There is a clear gap in data regarding which emollient to recommend to each patient, as well as amount and frequency of application. Evidence generated by this research should help design and potentiate future studies comparing moisturizers in different dry skin diseases to improve patient education and care.

10. STUDY LIMITATIONS

This study was subject to several limitations:

An important limitation considered is the strong variability effect of the homeostasis parameters depending on external conditions (air temperature, ambient humidity…). Nevertheless, in order to increase outcome reliability, all participants were measured in the same room and the ambient conditions were also measured.

Nevertheless, quantity of moisturizer application was not standardized or measured, each administration was executed by the same investigator; avoiding possible inter-examiner variability. This investigator was instructed to made the least possible variation between subjects, also adapting the application to every different skin lesion.

Even though we considered before the start of the study the minimum sample size necessary to assume normality, and we achieve it; with 31 psoriatic subjects and 31 matched controls; we are aware that the sample could be much more representative the more it was enlarged. Because of time limitation and SARS-CoV-2 situation, we could not reach the substantial sample size expected.

In addition, the control group matching did not achieve the greatest accurate conditions that we could have expected, assuming a selection bias. Again, due to time limitation, the matching only took gender and age criteria; abandoning any other important individual characteristic such us skin phototype, frequent use of emollients, anthropometric measures, other comorbidities etc.

We could be assuming another selection bias referred to the sample selection. Subjects were selected in clinical appointments if they accomplished including criteria; any randomized sampling process was performed.

As this was a research on real-life clinical practice, concomitant systemic and topic medication was allowed, giving the possibility of strong variability between subjects. The sample size in this subgroup was very low and we used paired samples to assess the effect of emollients' application; meaning that confounding factors regarding intra-

individual characteristics are controlled (each participant is compared with himself). In that way, concomitant treatments would not change the results.

All covariables were taken by subjects' testimony, for this reason, recall bias could be presupposed. Some questions were related to long-time events like the onset disease year; or difficult information such as currently treatment that in some patients could reach to three or four different therapies.

We assume a certain degree of observer/interviewer bias; only one investigator was in charge of the whole procedure, which can influence data recording and introduce error into the proper interview or the questionnaire included during the course of the research.

Even though, investigator receive an adequate formation in order to the data collection, it exist the possibility of an information bias by wrong acquisition of the information because of the inexperience of the examiner on the researching field.

11. CONCLUSIONS

This study shows to the role of non-invasive, objective and easily performed measurements to evaluate epidermal barrier function. Psoriatic patients have higher TEWL and lower SCH values, both at psoriasis plaques and uninvolved skin, than healthy control skin. Changes in epidermal barrier function after one application of two specifical and different composed emollients were analysed. SCH on psoriatic plaques improve significantly after a water-based moisturizer administration; TEWL parameters show variable results depending on the composition of the emollient. Other homeostatic parameters show no variance after the use of moisturizers or have not strong relevancy on the skin barrier function.

The analysis of the cutaneous homeostasis parameters might help us to understand the role of emollients in the improvement of psoriatic patients care, recommending determined composed moisturizers to improve skin barrier function and, therefore, to improve psoriatic skin symptoms and quality of life.

12. REFERENCES

1. Roszkiewicz M, Dopytalska K, Szymańska E, Jakimiuk A, Walecka I. Environmental risk factors and epigenetic alternations in psoriasis [Internet]. Vol. 27, Annals of Agricultural and Environmental Medicine. Institute of Agricultural Medicine; 2020 [cited 2020 Oct 7]. p. 335–42. Available from: http://www.aaem.pl/Environmental-risk-factors-and-epigenetic-alternations-in-psoriasis,112107,0,2.html

2. Kwan Z, Bong YB, Tan LL, Lim SX, Yong ASW, Ch'ng CC, et al. Determinants of quality of life and psychological status in adults with psoriasis. Arch Dermatol Res [Internet]. 2018 Jul 1 [cited 2020 Oct 7];310(5):443–51. Available from: https://link.springer.com/article/10.1007/s00403-018-1832-x

3. de Oliveira M de FSP, Rocha B de O, Duarte GV. Psoriasis: Classical and emerging comorbidities. An Bras Dermatol [Internet]. 2015 [cited 2020 Oct 7];90(1):09–20. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4323693/

4. Fernández-Armenteros JM, Gómez-Arbonés X, Buti-Solé M, Betriu-Bars A, Sanmartin-Novell V, Ortega-Bravo M, et al. Epidemiology of Psoriasis. A Population-Based Study. Actas Dermosifiliogr [Internet]. 2019 Jun 1 [cited 2020 Oct 7];110(5):385–92. Available from: https://www.actasdermo.org/en-epidemiology-psoriasis-a-population-based-study-articulo-S1578219019300186

5. Michalek IM, Loring B, John SM. A systematic review of worldwide epidemiology of psoriasis [Internet]. Vol. 31, Journal of the European Academy of Dermatology and Venereology. Blackwell Publishing Ltd; 2017 [cited 2020 Oct 6]. p. 205–12. Available from: https://onlinelibrary.wiley.com/doi/full/10.1111/jdv.13854

6. Parisi R, Symmons DPM, Griffiths CEM, Ashcroft DM. Global epidemiology of psoriasis: A systematic review of incidence and prevalence. J Invest Dermatol [Internet]. 2013 Feb 1 [cited 2020 Oct 7];133(2):377–85. Available from: https://www.jidonline.org/article/S0022-202X(15)36098-X/fulltext

7. Buendía-Eisman A, Arias-Santiago S, Molina-Leyva A, Gilaberte Y, Fernández-Crehuet P, Husein-ElAhmed H, et al. Análisis de los diagnósticos realizados en la actividad ambulatoria dermatológica en España: muestreo aleatorio nacional DIADERM. Actas Dermosifiliogr [Internet]. 2018 Jun [cited 2020 Oct 10];109(5):416–23. Available from: https://www.actasdermo.org/es-linkresolver-analisis-diagnosticos-realizados-actividad-ambulatoria-S0001731018300760

8. Icen M, Crowson CS, McEvoy MT, Dann FJ, Gabriel SE, Maradit Kremers H. Trends in incidence of adult-onset psoriasis over three decades: A population-based study. J Am Acad Dermatol [Internet]. 2009 Mar 1 [cited 2020 Oct 7];60(3):394–401. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3028518/

9. Boehncke WH. Etiology and Pathogenesis of Psoriasis [Internet]. Vol. 41, Rheumatic Disease Clinics of North America. W.B. Saunders; 2015 [cited 2020 Oct 7]. p. 665–75. Available from: https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(14)61909-7/fulltext

10. Singh S, Pradhan D, Puri P, Ramesh V, Aggarwal S, Nayek A, et al. Genomic alterations driving psoriasis pathogenesis [Internet]. Vol. 683, Gene. Elsevier B.V.; 2019 [cited 2020 Oct 7]. p. 61–71. Available from: www.sciencedirect.com/science/article/pii/S0378111918310060

11. Chen L, Tsai TF. HLA-Cw6 and psoriasis [Internet]. Vol. 178, British Journal of Dermatology. Blackwell Publishing Ltd; 2018 [cited 2020 Oct 7]. p. 854–62. Available from: https://onlinelibrary.wiley.com/doi/full/10.1111/bjd.16083

12. Gudjonsson JE, Elder JT. Fitzpatrick. In: Kang S, Amagai M, Bruckner AL, Enk AH, Margolis DJ, McMichael AJ, et al., editors. Fitzpatrick's Dermatology. 9th ed. New York: McGraw-Hill Education; 2019. p. 457–97.

13. Chen M, Chen ZQ, Cui PG, Yao X, Li YM, Li AS, et al. The methylation pattern of p16INK4a gene promoter in psoriatic epidermis and its clinical significance. Br J Dermatol [Internet]. 2008 May [cited 2020 Oct 7];158(5):987–93. Available from: https://onlinelibrary.wiley.com/doi/full/10.1111/j.1365-2133.2008.08505.x

14. Ovejero-Benito MC, Reolid A, Sánchez-Jiménez P, Saiz-Rodríguez M, Muñoz-Aceituno E, Llamas-Velasco M, et al. Histone modifications associated with biological drug response in moderate-to-severe psoriasis. Exp Dermatol [Internet]. 2018 Dec 1 [cited 2020 Oct 7];27(12):1361–71. Available from: https://onlinelibrary.wiley.com/doi/full/10.1111/exd.13790

15. Wu R, Zeng J, Yuan J, Deng X, Huang Y, Chen L, et al. MicroRNA-210 overexpression promotes psoriasis-like inflammation by inducing Th1 and Th17 cell differentiation. J Clin Invest [Internet]. 2018 Jun 1 [cited 2020 Oct 7];128(6):2551–68. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5983326/

16. García-Rodríguez S, Arias-Santiago S, Orgaz-Molina J, Magro-Checa C, Valenzuela I, Navarro P, et al. Alteraciones en los niveles de expresión del microARN-33 en plasma de pacientes con psoriasis. Actas Dermosifiliogr [Internet]. 2014 Jun [cited 2020 Oct 10];105(5):497–503. Available from: https://www.actasdermo.org/en-abnormal-levels-expression-plasma-microrna-33-articulo-S1578219014001097

17. García–Rodríguez S, Arias–Santiago S, Blasco-Morente G, Orgaz-Molina J, Rosal-Vela A, Navarro P, et al. Increased expression of microRNA-155 in peripheral blood mononuclear cells from psoriasis patients is related to disease activity. J Eur Acad Dermatology Venereol [Internet]. 2017 Feb 1 [cited 2020 Oct 10];31(2):312–22. Available from: https://onlinelibrary.wiley.com/doi/full/10.1111/jdv.13861

18. Prescott SL, Larcombe DL, Logan AC, West C, Burks W, Caraballo L, et al. The skin microbiome: Impact of modern environments on skin ecology, barrier integrity, and systemic immune programming [Internet]. Vol. 10, World Allergy Organization Journal. BioMed Central Ltd.; 2017 [cited 2020 Oct 8]. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5568566/

19. Barrea L, Nappi F, Di Somma C, Savanelli MC, Falco A, Balato A, et al. Environmental risk factors in psoriasis: The point of view of the nutritionist [Internet]. Vol. 13, International Journal of Environmental Research and Public Health. MDPI AG; 2016 [cited 2020 Oct 8]. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4962284/

20. Arias-Santiago S, Orgaz-Molina J, Castellote-Caballero L, Arrabal-Polo MÁ, Garcia-Rodrigueź S, Perandrés-López R, et al. Atheroma plaque, metabolic syndrome and inflammation in patients with psoriasis. Eur J Dermatology [Internet]. 2012 May [cited 2020 Oct 10];22(3):337–44. Available from: https://www.jle.com/fr/revues/ejd/e-docs/atheroma_plaque_metabolic_syndrome_and_inflammation_in_patients_with_psoriasis_293020/article.phtml?tab=texte

21. García-Rodríguez S, Arias-Santiago S, Perandrés-López R, Orgaz-Molina J, Castellote L, Buendía-Eisman A, et al. Disminución de los niveles plasmáticos de clusterina en pacientes con psoriasis. Actas Dermosifiliogr [Internet]. 2013 Jul [cited 2020 Oct 10];104(6):497–503. Available from: https://www.actasdermo.org/en-decreased-plasma-levels-clusterin-in-articulo-S1578219013001194

22. Zhu KJ, He SM, Sun LD, Hu DY, Cheng H, Zhang Z, et al. Smoking and psoriasis: A meta-analysis of case-control studies [Internet]. Vol. 63, Journal of Dermatological Science. J Dermatol Sci; 2011 [cited 2020 Oct 8]. p. 126–8. Available from: https://www.jdsjournal.com/article/S0923-1811(11)00146-0/fulltext

23. Awad VM, Sakhamuru S, Kambampati S, Wasim S, Malik BH. Mechanisms of Beta-Blocker Induced Psoriasis, and Psoriasis De Novo at the Cellular Level. Cureus [Internet]. 2020 Jul 2 [cited 2020 Oct 8];12(7):e8964. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7398737/

24. Balak D, Hajdarbegovic E. Drug-induced psoriasis: clinical perspectives. Psoriasis Targets Ther [Internet]. 2017 Dec [cited 2020 Oct 8];Volume 7:87–94. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5774610/

25. de Gruijl FR. For better or for worse, UV in psoriasis [Internet]. Vol. 25, Experimental Dermatology. Blackwell Publishing Ltd; 2016 [cited 2020 Oct 8]. p. 945–6. Available from: https://onlinelibrary.wiley.com/doi/full/10.1111/exd.13216

26. Ferreira BIRC, Da Costa Abreu JLP, Dos Reis JPG, Da Costa Figueiredo AM. Psoriasis and associated psychiatric disorders: A systematic review on etiopathogenesis and clinical correlation [Internet]. Vol. 9, Journal of Clinical and Aesthetic Dermatology. Matrix Medical Communications; 2016 [cited 2020 Oct

8]. p. 36–43. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4928455/

27. Rendon A, Schäkel K. Psoriasis pathogenesis and treatment [Internet]. Vol. 20, International Journal of Molecular Sciences. MDPI AG; 2019 [cited 2020 Oct 8]. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6471628/

28. Liang Y, Sarkar MK, Tsoi LC, Gudjonsson JE. Psoriasis: a mixed autoimmune and autoinflammatory disease [Internet]. Vol. 49, Current Opinion in Immunology. Elsevier Ltd; 2017 [cited 2020 Oct 9]. p. 1–8. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5705427/

29. Harden JL, Krueger JG, Bowcock AM. The immunogenetics of Psoriasis: A comprehensive review [Internet]. Vol. 64, Journal of Autoimmunity. Academic Press; 2015 [cited 2020 Oct 9]. p. 66–73. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4628849/

30. Morizane S, Gallo RL. Antimicrobial peptides in the pathogenesis of psoriasis. J Dermatol [Internet]. 2012 Mar [cited 2020 Oct 9];39(3):225–30. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3527011/

31. De Masson A, Bouaziz JD, Battistella M, Bagot M, Bensussan A. Immunopathologie du psoriasis From bench to bedside. Medecine/Sciences [Internet]. 2016 Mar 1 [cited 2020 Oct 9];32(3):253–9. Available from: https://www.medecinesciences.org/en/articles/medsci/full_html/2016/03/medsci20163203p253/medsci20163203p253.html

32. Armstrong AW, Read C. Pathophysiology, Clinical Presentation, and Treatment of Psoriasis: A Review [Internet]. Vol. 323, JAMA - Journal of the American Medical Association. American Medical Association; 2020 [cited 2020 Oct 9]. p. 1945–60. Available from: https://pubmed.ncbi.nlm.nih.gov/32427307/

33. Boehncke WH, Schön MP. Psoriasis [Internet]. Vol. 386, The Lancet. Lancet Publishing Group; 2015 [cited 2020 Oct 9]. p. 983–94. Available from: https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(14)61909-7/fulltext

34. Tan EST, Chong WS, Tey HL. Nail psoriasis: A review [Internet]. Vol. 13, American Journal of Clinical Dermatology. Am J Clin Dermatol; 2012 [cited 2020 Oct 9]. p. 375–88. Available from: https://link.springer.com/article/10.2165%2F11597000-000000000-00000

35. Micali G, Verzì AE, Giuffrida G, Panebianco E, Musumeci ML, Lacarrubba F. Inverse psoriasis: From diagnosis to current treatment options [Internet]. Vol. 12, Clinical, Cosmetic and Investigational Dermatology. Dove Medical Press Ltd.; 2019 [cited 2020 Oct 9]. p. 953–9. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6997231/

36. Saleh D, Tanner LS. Psoriasis, Guttate [Internet]. StatPearls. StatPearls Publishing; 2018 [cited 2020 Oct 9]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK482498/

37. Gooderham MJ, Van Voorhees AS, Lebwohl MG. An update on generalized pustular psoriasis [Internet]. Vol. 15, Expert Review of Clinical Immunology. Taylor and Francis Ltd; 2019 [cited 2020 Oct 9]. p. 907–19. Available from: https://www.tandfonline.com/doi/full/10.1080/1744666X.2019.1648209

38. Mansouri B, Benjegerdes K, Hyde K, Kivelevitch D. Pustular psoriasis: pathophysiology and current treatment perspectives. Psoriasis Targets Ther [Internet]. 2016 Sep [cited 2020 Oct 9];Volume 6:131–44. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5683122/

39. Liao W, Singh R, Lee K, Ucmak D, Brodsky M, Atanelov Z, et al. Erythrodermic psoriasis: pathophysiology and current treatment perspectives. Psoriasis Targets Ther [Internet]. 2016 Jul [cited 2020 Oct 9];Volume 6:93–104. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5572467/

40. Langenbruch A, Radtke MA, Krensel M, Jacobi A, Reich K, Augustin M. Nail involvement as a predictor of concomitant psoriatic arthritis in patients with psoriasis. Br J Dermatol [Internet]. 2014 Nov 1 [cited 2020 Oct 10];171(5):1123–8. Available from: https://onlinelibrary.wiley.com/doi/full/10.1111/bjd.13272

41. Ellinghaus D, Ellinghaus E, Nair RP, Stuart PE, Esko T, Metspalu A, et al. Combined analysis of genome-wide association studies for Crohn disease and psoriasis identifies seven shared susceptibility loci. Am J Hum Genet [Internet]. 2012 Apr 6 [cited 2020 Oct 10];90(4):636–47. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3322238/

42. Dowlatshahi EA, Wakkee M, Arends LR, Nijsten T. The prevalence and odds of depressive symptoms and clinical depression in psoriasis patients: A systematic review and meta-analysis. J Invest Dermatol [Internet]. 2014 [cited 2020 Oct 10];134(6):1542–51. Available from: https://www.jidonline.org/article/S0022-202X(15)36822-6/fulltext

43. Singh S, Taylor C, Kornmehl H, Armstrong AW. Psoriasis and suicidality: A systematic review and meta-analysis. J Am Acad Dermatol [Internet]. 2017 Sep 1 [cited 2020 Oct 10];77(3):425-440.e2. Available from: https://www.jaad.org/article/S0190-9622(17)31765-6/fulltext

44. Martínez-García E, Arias-Santiago S, Valenzuela-Salas I, Garrido-Colmenero C, García-Mellado V, Buendía-Eisman A. Quality of life in persons living with psoriasis patients. J Am Acad Dermatol [Internet]. 2014 [cited 2020 Oct 10];71(2):302–7. Available from: https://www.jaad.org/article/S0190-9622(14)01273-0/fulltext

45. Mattei PL, Corey KC, Kimball AB. Psoriasis Area Severity Index (PASI) and the Dermatology Life Quality Index (DLQI): The correlation between disease severity and psychological burden in patients treated with biological therapies. J Eur Acad Dermatology Venereol [Internet]. 2014 Mar [cited 2020 Oct 11];28(3):333–7. Available from: https://onlinelibrary.wiley.com/doi/full/10.1111/jdv.12106

46. Yeung H, Takeshita J, Mehta NN, Kimmel SE, Ogdie A, Margolis DJ, et al. Psoriasis severity and the prevalence of major medical comorbidity: A population-based

study. JAMA Dermatology [Internet]. 2013 Oct [cited 2020 Oct 11];149(10):1173–9. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3800487/

47. Kim WB, Jerome D, Yeung J. Diagnosis and management of psoriasis. Can Fam Physician [Internet]. 2017 [cited 2020 Oct 11];63(4):278–85. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5389757/

48. Ito K, Koga M, Shibayama Y, Tatematsu S, Nakayama J, Imafuku S. Proactive treatment with calcipotriol reduces recurrence of plaque psoriasis. J Dermatol [Internet]. 2016 Apr 1 [cited 2020 Oct 11];43(4):402–5. Available from: http://doi.wiley.com/10.1111/1346-8138.13158

49. Koo J, Tyring S, Werschler WP, Bruce S, Olesen M, Villumsen J, et al. Superior efficacy of calcipotriene and betamethasone dipropionate aerosol foam versus ointment in patients with psoriasis vulgaris - A randomized phase II study. J Dermatolog Treat [Internet]. 2016 Mar 3 [cited 2020 Oct 11];27(2):120–7. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4772687/

50. Yu Z, Wolf P. How It Works: The Immunology Underlying Phototherapy [Internet]. Vol. 38, Dermatologic Clinics. W.B. Saunders; 2020 [cited 2020 Oct 11]. p. 37–53. Available from: https://pubmed.ncbi.nlm.nih.gov/31753191/

51. Chen X, Yang M, Cheng Y, Liu GJ, Zhang M. Narrow-band ultraviolet B phototherapy versus broad-band ultraviolet B or psoralen-ultraviolet A photochemotherapy for psoriasis [Internet]. Vol. 2013, Cochrane Database of Systematic Reviews. John Wiley and Sons Ltd; 2013 [cited 2020 Oct 11]. Available from: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD009481.pub2/full

52. Smith D. Fumaric acid esters for psoriasis: a systematic review [Internet]. Vol. 186, Irish Journal of Medical Science. Springer London; 2017 [cited 2020 Oct 17]. p. 161–77. Available from: https://link.springer.com/article/10.1007%2Fs11845-016-1470-2

53. Kamata M, Tada Y. Safety of biologics in psoriasis [Internet]. Vol. 45, Journal of Dermatology. Blackwell Publishing Ltd; 2018 [cited 2020 Oct 12]. p. 279–86. Available from: https://onlinelibrary.wiley.com/doi/full/10.1111/1346-8138.14096

54. Clark RAF, Ghosh K, Tonnesen MG. Tissue engineering for cutaneous wounds. J Invest Dermatol [Internet]. 2007 [cited 2020 Oct 12];127(5):1018–29. Available from: https://www.jidonline.org/article/S0022-202X(15)33366-2/fulltext

55. Akdeniz M, Gabriel S, Lichterfeld-Kottner A, Blume-Peytavi U, Kottner J. Transepidermal water loss in healthy adults: a systematic review and meta-analysis update [Internet]. Vol. 179, British Journal of Dermatology. Blackwell Publishing Ltd; 2018 [cited 2020 Oct 12]. p. 1049–55. Available from: https://onlinelibrary.wiley.com/doi/full/10.1111/bjd.17025

56. Ye L, Wang Z, Li Z, Lv C, Man MQ. Validation of GPSkin Barrier ® for assessing

epidermal permeability barrier function and stratum corneum hydration in humans. Ski Res Technol [Internet]. 2019 Jan 1 [cited 2020 Oct 12];25(1):25–9. Available from: https://onlinelibrary.wiley.com/doi/full/10.1111/srt.12590

57. Algiert-Zielińska B, Batory M, Skubalski J, Rotsztejn H. Evaluation of the relation between lipid coat, transepidermal water loss, and skin pH. Int J Dermatol [Internet]. 2017 Nov 1 [cited 2020 Oct 12];56(11):1192–7. Available from: https://onlinelibrary.wiley.com/doi/full/10.1111/ijd.13726

58. Yazdanparast T, Yazdani K, Humbert P, Khatami A, Nasrollahi SA, Hassanzadeh H, et al. Comparison of biophysical, biomechanical and ultrasonographic properties of skin in chronic dermatitis, psoriasis and lichen planus. Med J Islam Repub Iran [Internet]. 2018 [cited 2020 Oct 12];32(1). Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6387801/

59. Yamamoto T, Takiwaki H, Arase S, Ohshima H. Derivation and clinical application of special imaging by means of digital cameras and Image J freeware for quantification of erythema and pigmentation. Ski Res Technol [Internet]. 2008 Feb [cited 2020 Oct 12];14(1):26–34. Available from: https://onlinelibrary.wiley.com/doi/full/10.1111/j.1600-0846.2007.00256.x

60. Lazic Strugar T, Kuo A, Seité S, Lin M, Lio P. Connecting the Dots: From Skin Barrier Dysfuntion to Allergic Sensitization, and the Role of Moisturizers in Repaiting the Skin Barrier. J Drugs Dermatol [Internet]. 2019 [cited 2020 Oct 12];18(6):581. Available from: https://jddonline.com/articles/dermatology/S1545961619P0581X

61. Tončić RJ, Kezić S, Hadžavdić SL, Marinović B. Skin barrier and dry skin in the mature patient. Clin Dermatol [Internet]. 2018 Mar 1 [cited 2020 Oct 12];36(2):109–15. Available from: https://pubmed.ncbi.nlm.nih.gov/29566915/

62. Elias PM, Wakefield JS, Man MQ. Moisturizers versus current and next-generation barrier repair therapy for the management of atopic dermatitis [Internet]. Vol. 32, Skin Pharmacology and Physiology. S. Karger AG; 2018 [cited 2020 Oct 12]. p. 1–7. Available from: https://www.karger.com/Article/FullText/493641

63. Torsekar R, Gautam M. Topical therapies in psoriasis. Indian Dermatol Online J [Internet]. 2017 [cited 2020 Oct 12];8(4):235. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5518573/

64. Van Onselen J. An overview of psoriasis and the role of emollient therapy [Internet]. Vol. 18, British Journal of Community Nursing. MA Healthcare Ltd; 2013 [cited 2020 Oct 12]. p. 174–9. Available from: https://www.magonlinelibrary.com/doi/full/10.12968/bjcn.2013.18.4.174

65. Gelmetti C. Therapeutic moisturizers as adjuvant therapy for psoriasis patients [Internet]. Vol. 10, American Journal of Clinical Dermatology. Am J Clin Dermatol; 2009 [cited 2020 Oct 12]. p. 7–12. Available from: https://link.springer.com/article/10.2165%2F0128071-200910001-00002

66. Nikam V, Monteiro R, Dandakeri S, Bhat R. Transepidermal water loss in

psoriasis: A case-control study. Indian Dermatol Online J [Internet]. 2019 [cited 2020 Oct 22];10(3):267. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6536057/

67. Takahashi H, Tsuji H, Minami-Hori M, Miyauchi Y, Iizuka H. Defective barrier function accompanied by structural changes of psoriatic stratum corneum. J Dermatol [Internet]. 2014 [cited 2020 Oct 28];41(2):144–8. Available from: https://onlinelibrary.wiley.com/doi/full/10.1111/1346-8138.12393

68. Cannavò SP, Guarneri F, Giuffrida R, Aragona E, Guarneri C. Evaluation of cutaneous surface parameters in psoriatic patients. Ski Res Technol [Internet]. 2017 Feb 1 [cited 2020 Oct 28];23(1):41–7. Available from: https://onlinelibrary.wiley.com/doi/full/10.1111/srt.12299

69. Lee Y, Young-Jin J, Sang-Sin L, Zheng Jun L, Dae-Kyoung C, Yoo-Bin K, et al. Changes in transepidermal water loss and skin hydration according to expression of aquaporin-3 in psoriasis. Ann Dermatol [Internet]. 2012 [cited 2020 Oct 28];24(2):168–74. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3346907/

70. Delfino M, Russo N, Migliaccio G, Carraturo N. Experimental study on efficacy of thermal muds of Ischia Island combined with blaneotherapy in the treatment of psoriasis vulgaris with plaques. Clin Ter [Internet]. 2003 [cited 2020 Oct 28];154(3):167–71. Available from: https://pubmed.ncbi.nlm.nih.gov/12910806/

71. Choi JW, Kwon SH, Youn J Il, Youn S. Objective measurements of erythema, elasticity and scale could overcome the inter- and intra-observer variations of subjective evaluations for psoriasis severity. Eur J Dermatology [Internet]. 2013 Mar [cited 2020 Oct 28];23(2):224–9. Available from: https://pubmed.ncbi.nlm.nih.gov/23518409/

72. Kim MA, Kim EJ, Lee HK. Use of SkinFibrometer® to measure skin elasticity and its correlation with Cutometer® and DUB® Skinscanner. Ski Res Technol [Internet]. 2018 Aug 1 [cited 2020 Oct 28];24(3):466–71. Available from: https://onlinelibrary.wiley.com/doi/full/10.1111/srt.12455

73. Grän F, Kerstan A, Serfling E, Goebeler M, Muhammad K. Current Developments in the Immunology of Psoriasis. Yale J Biol Med [Internet]. 2020 [cited 2020 Oct 29];93(1):97–110. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7087066/

74. Draelos ZD. Moisturizing cream ameliorates dryness and desquamation in participants not receiving topical psoriasis treatment. Cutis [Internet]. 2008 [cited 2020 Oct 29];82(3):211–6. Available from: https://pubmed.ncbi.nlm.nih.gov/18856161/

75. Danby SG, Al-Enezi T, Sultan A, Chittock J, Kennedy K, Cork MJ. The effect of aqueous cream BP on the skin barrier in volunteers with a previous history of atopic dermatitis. Br J Dermatol [Internet]. 2011 Aug [cited 2020 Oct 29];165(2):329–34. Available from:

https://onlinelibrary.wiley.com/doi/full/10.1111/j.1365-2133.2011.10395.x

76. Leshem YA, Wong A, McClanahan D, Simpson EL. The effects of common over-the-counter moisturizers on skin barrier function: A randomized, observer-blind, within-patient, controlled study. Dermatitis [Internet]. 2020 Sep 1 [cited 2020 Oct 29];31(5):309–15. Available from: https://pubmed.ncbi.nlm.nih.gov/32947459/

77. Simpson E, Böhling A, Bielfeldt S, Bosc C, Kerrouche N. Improvement of skin barrier function in atopic dermatitis patients with a new moisturizer containing a ceramide precursor. J Dermatolog Treat [Internet]. 2013 Apr [cited 2020 Oct 29];24(2):122–5. Available from: https://www.tandfonline.com/doi/full/10.3109/09546634.2012.713461

78. Mohammed D, Matts PJ, Hadgraft J, Lane ME. Influence of Aqueous Cream BP on corneocyte size, maturity, skin protease activity, protein content and transepidermal water loss. Br J Dermatol [Internet]. 2011 Jun [cited 2020 Oct 29];164(6):1304–10. Available from: https://onlinelibrary.wiley.com/doi/full/10.1111/j.1365-2133.2011.10338.x

79. Lehmuskallio E, Anttonen H. Thermophysical effects of ointments in cold: An experimental study with a skin model. Acta Derm Venereol [Internet]. 1999 [cited 2020 Oct 28];79(1):33–6. Available from: https://pubmed.ncbi.nlm.nih.gov/10086855/

13. ANNEXES

ANNEX 1 – DLQI QUESTIONNAIRE

ÍNDICE DE CALIDAD DE VIDA EN DERMATOLOGÍA

DLQI

Hospital núm.: Fecha: Puntuación: ☐

Nombre: Diagnóstico:

Dirección:

El propósito de este cuestionario es medir cuánto ha afectado su problema de la piel a su calidad de vida DURANTE LA ÚLTIMA SEMANA. Marque una casilla por pregunta.

1.	Durante la última semana, ¿cuánta **picazón, molestia, dolor** o **sensación punzante** ha sentido en la piel?	Muchísimo Mucho Un poco Nada en absoluto	☐ ☐ ☐ ☐	
2.	Durante la última semana, ¿qué tan **avergonzado** o **cohibido** se ha sentido debido a su problema de la piel?	Muchísimo Mucho Un poco Nada en absoluto	☐ ☐ ☐ ☐	
3.	Durante la última semana, ¿cuánto ha interferido su problema de la piel con ir de **compras** o cuidar la **casa** o el **jardín**?	Muchísimo Mucho Un poco Nada en absoluto	☐ ☐ ☐ ☐	No es pertinente ☐
4.	Durante la última semana, ¿cuánta influencia ha tenido su problema de la piel en la **ropa** que utiliza?	Muchísimo Mucho Un poco Nada en absoluto	☐ ☐ ☐ ☐	No es pertinente ☐
5.	. Durante la última semana, ¿cuánto ha afectado su problema de la piel a sus actividades **sociales** o **recreativas**?	Muchísimo Mucho Un poco Nada en absoluto	☐ ☐ ☐ ☐	No es pertinente ☐
6.	Durante la última semana, ¿cuánto le ha dificultado su problema de la piel el practicar **deportes**?	Muchísimo Mucho Un poco Nada en absoluto	☐ ☐ ☐ ☐	No es pertinente ☐
7.	Durante la última semana, ¿su problema de la piel le ha impedido **trabajar** o **estudiar**?	sí no	☐ ☐	No es pertinente ☐
	Si la respuesta es "No", durante la última semana, ¿en qué medida su piel ha sido un problema en el **trabajo** o los **estudios**?	Mucho Un poco Nada en absoluto	☐ ☐ ☐	
8.	Durante la última semana, ¿en qué medida su problema de la piel le ha generado dificultades con su **pareja** o con cualquiera de sus **amigos** cercanos o **familiares**?	Muchísimo Mucho Un poco Nada en absoluto	☐ ☐ ☐ ☐	No es pertinente ☐
9.	Durante la última semana, ¿en qué medida su problema de la piel le ha ocasionado **dificultades sexuales?**	Muchísimo Mucho Un poco Nada en absoluto	☐ ☐ ☐ ☐	No es pertinente ☐
10.	Durante la última semana, ¿en qué medida su **tratamiento** para la piel le ha resultado un problema, por ejemplo, desordenando su casa o quitándole tiempo?	Muchísimo Mucho Un poco Nada en absoluto	☐ ☐ ☐ ☐	No es pertinente ☐

Revise que haya respondido TODAS las preguntas. Gracias.

ANNEX 2 – WRITTEN CONSENTIMENT

CONSENTIMIENTO INFORMADO – CONSENTIMIENTO POR ESCRITO DEL PACIENTE

<ESTUDIO HOMEOSTASIS CUTÁNEA EN PACIENTES CON PSORIASIS: IMPACTO DE LAS CREMAS HIDRATANTES**>**

Yo (Nombre y Apellidos):
.....

- He leído el documento informativo que acompaña a este consentimiento (Información al Paciente)
- He podido hacer preguntas sobre el estudio ESTUDIO HOMEOSTASIS CUTÁNEA EN PACIENTES CON PSORIASIS: IMPACTO DE LAS CREMAS HIDRATANTES
- He recibido suficiente información sobre el estudio ESTUDIO HOMEOSTASIS CUTÁNEA EN PACIENTES CON PSORIASIS: IMPACTO DE LAS CREMAS HIDRATANTES. He hablado con el profesional sanitario informador: DANIEL MAROTO MORALES.
- Comprendo que mi participación es voluntaria y soy libre de participar o no en el estudio.
- Se me ha informado que todos los datos obtenidos en este estudio serán confidenciales y se tratarán conforme establece la Ley Orgánica de Protección de Datos de Carácter Personal *3/2018.*
- Se me ha informado de que la información obtenida sólo se utilizará para los fines específicos del estudio.

Comprendo que puedo retirarme del estudio:

- Cuando quiera
- Sin tener que dar explicaciones
- Sin que esto repercuta en mis cuidados médicos

Presto libremente mi conformidad para participar en el *proyecto titulado* ESTUDIO HOMEOSTASIS CUTÁNEA EN PACIENTES CON PSORIASIS: IMPACTO DE LAS CREMAS HIDRATANTES

Firma del paciente:

Firma del profesional sanitario informador:

Nombre y apellidos:…….

Fecha: ……

Nombre y apellidos: ……..

Fecha: ……..

CONSENTIMIENTO INFORMADO – HOJA DE INFORMACIÓN AL PACIENTE

TÍTULO DEL TRABAJO DE FIN DE GRADO: Estudio homeostasis cutánea en pacientes con psoriasis: impacto de las cremas hidratantes.

Alumno: Daniel Maroto Morales

Tutor: Dr. Salvador Antonio Arias Santiago

Este documento tiene por objeto ofrecerle información sobre un estudio de investigación en el que se le invita a participar. Este estudio se va a realizar en el Hospital Universitario Virgen de las Nieves. Si decide participar en el mismo, debe recibir información personalizada del investigador, leer antes este documento y hacer todas las preguntas que sean necesarias para comprender los detalles sobre el mismo.

La participación en este estudio es completamente voluntaria. Vd. puede decidir no participar, o, si acepta hacerlo, cambiar de parecer retirando el consentimiento en cualquier momento sin obligación de dar explicaciones. Le aseguramos que esta decisión no afectará a la relación con su médico ni a la asistencia sanitaria a la que Vd. tiene derecho.

¿Cuál es el propósito del estudio?

El objetivo principal del estudio es estudiar una serie de parámetros determinados a través de unas sondas específicamente validads (Cutometer®, Skin-Thermometer®, Tewameter®, Skin pH-Meter®, Corneometer®), con el fin de ver las diferencias homeostáticas entre la piel sana y afecta en pacientes con psoriasis; así como analizar la posible modificación de dichos parámetros mediante el uso de tratamientos tópicos.

¿Quién puede participar?

Para este estudio se aceptarán a pacientes con psoriasis de ambos sexos y mayores de 18 años, que acudan a su revisión rutinaria en la consulta de psoriasis, siempre y cuando cumpla con los criterios de inclusión definidos para el estudio.

Se espera que participen unas 25-35 personas en el estudio.

¿En qué consiste mi participación?

Se valorarán una serie de parámetros generales: edad, sexo, tiempo de evolución de la enfermedad, antecedentes familiares de psoriasis, tratamiento actual, gravedad de la psoriasis (mediante los índices PASI, BSA y DLQI), hábito tabáquico /enólico, presencia de artropatía psoriásica e hidratación tópica diaria.

También se recogerán todos los datos homeostáticos que consistirán en: elasticidad, temperatura, pérdida transepidérmica de agua, pH e hidratación y eritema recogidas con un sistema de sondas específicamente validadas: Cutometer®, Skin-Thermometer®, Tewameter®, Skin pH-Meter®, Corneometer® (Microcaya S.L. Bilbao, España).

¿Se publicarán los resultados de este estudio?

Los resultados de este estudio serán remitidos a publicaciones científicas para su difusión, pero no se transmitirá ningún dato que pueda llevar a la identificación de los pacientes.

¿Cómo se protegerá la confidencialidad de mis datos?

El tratamiento, comunicación y cesión de sus datos se hará conforme a lo dispuesto por la Ley Orgánica 3/2018, de 5 de diciembre, de protección de datos de carácter personal. En todo momento, Vd. podrá acceder a sus datos, corregirlos o cancelarlos.

Sólo el alumno, el tutor del estudio y las autoridades sanitarias, que tienen deber de guardar la confidencialidad, tendrán acceso a todos los datos recogidos por el estudio. Se podrá transmitir a terceros la información que no pueda ser identificada.

¿Qué ocurrirá si hay alguna consecuencia negativa de la participación?

Dado que las pruebas realizadas no son invasivas, no se requerirá ningún seguro adicional a los ya disponibles para cubrir la tarea asistencial habitual. En todo caso, se pondrán todos los medios necesarios para eliminar o minimizar los daños provocados por la participación.

¿Existen intereses económicos en este estudio?

Esta investigación forma parte de un Trabajo de Fin de Grado como parte del Grado de Medicina en la Universidad de Girona. Por tanto, no hay intereses económicos vinculados y vd. no será retribuido por participar.

¿Quién me puede dar más información?

Puede contactar con el alumno Daniel Maroto Morales por correo electrónico (danielmarotomorales@gmail.com) o con el Dr. Salvador Antonio Arias Santiago en el email (salvadorarias@ugr.es).

ANNEX 3 – PSORIATIC PATIENTS RECOMPILATION DATA SHEET

Plantilla recopilación de datos - *paciente con psoriasis*

Número de identificación: **Edad:** **Sexo:**

Tiempo de evolución de la enfermedad:

Antecedentes familiares de psoriasis:

Gravedad de la psoriasis:
PASI: **BSA:** **DLQI:**

Tratamiento actual:
-Tópico:
-Sistémico:
-Biológico:

Fumador/a: **Sí** □ **No** □
Consumo de alchohol: **Sí** □ **No** □
Artropatía psoriásica: **Sí** □ **No** □
Hidratación diaria: **Sí** □ **No** □

Peso (kg): **Temperatura ambiente (ºC):**
Altura (m): **Humedad ambiente (%):**
Perímetro abdominal (cm):

	Placa (pre hidratación)	**Placa (post vaselina)**	**Placa (post solución acuosa**	**Piel sana (pre hidratación)**	**Piel sana (post vaselina)**	**Piel sana (post solución acuosa)**
TEWL						
Hidratación						
Temperatura						
pH						
Elasticidad						
Eritema						

Observaciones:

ANNEX 4 – CONTROL GROUP RECOMPILATION DATA SHEET

Plantilla recopilación de datos - *control*

Número de identificación: **Edad:** **Sexo:**

Antecedentes familiares de psoriasis:

Fumador/a: **Sí** □ **No** □
Consumo de alchohol: **Sí** □ **No** □
Hidratación diaria: **Sí** □ **No** □

Peso (kg): **Temperatura ambiente (ºC):**
Altura (m): **Humedad ambiente (%):**
Perímetro abdominal (cm):

	Piel sana (pre hidratación)	**Piel sana (post vaselina)**	**Piel sana (post solución acuosa)**
TEWL			
Hidratación			
Temperatura			
pH			
Elasticidad			
Eritema			

Observaciones:

ANNEX 5 – CLINICAL RESEARCH ETHICAL COMMITTEE APROVAL

JUNTA DE ANDALUCIA CONSEJERÍA DE SALUD Y FAMILIAS

DICTAMEN ÚNICO EN LA COMUNIDAD AUTÓNOMA DE ANDALUCÍA

D/Dª: CRISTINA LUCIA DAVILA FAJARDO como secretario/a del CEIM/CEI Provincial de Granada

CERTIFICA

Que este Comité ha evaluado la propuesta del promotor/investigador (No hay promotor/a asociado/a) para realizar el estudio de investigación titulado:

TÍTULO DEL ESTUDIO:	Impacto del tratamiento tópico, sistémico o físico en la homeostoasis cutánea de pacientes con enfermedades cutáneas .(Cambios en la homeostasis cutánea en los pacientes dermatológicos)
Protocolo, Versión:	V01
HIP, Versión:	V01
CI, Versión:	V01

Y que considera que:

Se cumplen los requisitos necesarios de idoneidad del protocolo en relación con los objetivos del estudio y se ajusta a los principios éticos aplicables a este tipo de estudios.

La capacidad del/de la investigador/a y los medios disponibles son apropiados para llevar a cabo el estudio.

Están justificados los riesgos y molestias previsibles para los participantes.

Que los aspectos económicos involucrados en el proyecto, no interfieren con respecto a los postulados éticos.

Y que este Comité considera, que dicho estudio puede ser realizado en los Centros de la Comunidad Autónoma de Andalucía que se relacionan, para lo cual corresponde a la Dirección del Centro correspondiente determinar si la capacidad y los medios disponibles son apropiados para llevar a cabo el estudio.

Lo que firmo en Granada a 08/05/2020

D/Dª. CRISTINA LUCIA DAVILA FAJARDO, como Secretario/a del CEIM/CEI Provincial de Granada

Código Seguro De Verificación:	1f7414a95ce0a2f004cec2442ed089010fa8e7a0	Fecha	08/05/2020
Normativa	Este documento incorpora firma electrónica reconocida de acuerdo a la Ley 59/2003, de 19 de diciembre, de firma electrónica.		
Firmado Por	Cristina Lucia Davila Fajardo		
Url De Verificación	https://www.juntadeandalucia.es/salud/portaldeetica/xhtml/ayuda/verificarFirmaDocumento.iface/code/1f7414a95ce0a2f004cec2442ed089010fa8e7a0	Página	1/3

CERTIFICA

Que este Comité ha ponderado y evaluado en sesión celebrada el 30/03/2020 y recogida en acta 4/2020 la propuesta del/de la Promotor/a (No hay promotor/a asociado/a), para realizar el estudio de investigación titulado:

TÍTULO DEL ESTUDIO:	Impacto del tratamiento tópico, sistémico o físico en la homeostoasis cutánea de pacientes con enfermedades cutáneas ,(Cambios en la homeostasis cutánea en los pacientes dermatológicos)
Protocolo, Versión:	V01
HIP, Versión:	V01
CI, Versión:	V01

Que a dicha sesión asistieron los siguientes integrantes del Comité:

Presidente/a

D/Dª. José Darío Sánchez López

Vicepresidente/a

D/Dª. Francisco Manuel Luque Martínez

Secretario/a

D/Dª. CRISTINA LUCIA DAVILA FAJARDO

Vocales

D/Dª. Jesús Martínez Tapias
D/Dª. Juan Ramón Delgado Pérez
D/Dª. Berta Gorlat Sánchez
D/Dª. José Cabeza Barrera
D/Dª. Sonia Domínguez Almendros
D/Dª. Juan Mozas Moreno
D/Dª. José Uberos Fernández
D/Dª. MARIA ESPERANZA DEL POZO GAVILAN
D/Dª. AURORA BUENO CAVANILLAS
D/Dª. Paloma Muñoz de Rueda
D/Dª. Manuel Gálvez Ibáñez
D/Dª. Esther Espínola García
D/Dª. ANTONIO MORALES ROMERO
D/Dª. Encarnación Martínez García
D/Dª. FRANCISCO LUIS MANZANO MANZANO
D/Dª. MIGUEL LÓPEZ GUADALUPE
D/Dª. JUAN ROMERO COTELO
D/Dª. MANUEL MARTIN DIAZ
D/Dª. JOSÉ LUIS MARTÍN RODRÍGUEZ
D/Dª. JUAN DIAZ GARCIA
D/Dª. LUIS MIGUEL DOMENECH GIL
D/Dª. Luis Javier Martínez González
D/Dª. JESÚS CARDONA CONTRERAS
D/Dª. Pilar Guijosa Campos
D/Dª. José Luis Martín Ruiz
D/Dª. MARIANA FÁTIMA FERNÁNDEZ CABRERA
D/Dª. MARÍA DOLORES GARCÍA VALVERDE
D/Dª. ESTHER MOLINA RIVAS
D/Dª. ANTONIO JUAN PÉREZ FERNÁNDEZ
D/Dª. JOAQUINA MARTINEZ GALAN

Código Seguro De Verificación:	1f7414a95ce0a2f004cec2442ed089010fa8e7a0	**Fecha**	08/05/2020
Normativa	Este documento incorpora firma electrónica reconocida de acuerdo a la Ley 59/2003, de 19 de diciembre, de firma electrónica.		
Firmado Por	Cristina Lucia Davila Fajardo		
Url De Verificación	https://www.juntadeandalucia.es/salud/portaldeetica/xhtml/ayuda/verificarFirmaDocumento.iface/code/1f7414a95ce0a2f004cec2442ed089010fa8e7a0	**Página**	2/3

Que dicho Comité, está constituido y actua de acuerdo con la normativa vigente y las directrices de la Conferencia Internacional de Buena Práctica Clínica.

Lo que firmo en Granada a 08/05/2020

Código Seguro De Verificación:	1f7414a95ce0a2f004cec2442ed089010fa8e7a0	Fecha	08/05/2020
Normativa	Este documento incorpora firma electrónica reconocida de acuerdo a la Ley 59/2003, de 19 de diciembre, de firma electrónica.		
Firmado Por	Cristina Lucia Davila Fajardo		
Url De Verificación	https://www.juntadeandalucia.es/salud/portaldeetica/xhtml/ayuda/verificarFirmaDocumento.iface/code/1f7414a95ce0a2f004cec2442ed089010fa8e7a0	Página	3/3