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Skin barrier function: The impact of inflammatory skin diseases and personal protective equipment.

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Skin barrier function: The impact of inflammatory skin diseases and personal protective equipment

Tesis Doctoral que presenta **Trinidad Montero Vílchez** para aspirar al Título de Doctor con Mención Internacional

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“El secreto de la felicidad no está en hacer lo que a uno le gusta, sino en que a uno le guste lo que hace”

James Matthew Barrie (1860- 1937)

“Si no conozco una cosa, la investigaré”

Louis Pasteur (1822-1895)

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3) **Montero-Vilchez T**, Soler-Góngora M, Martínez-López A, Ana FG, Buendía-Eisman A, Molina-Leyva A, Arias-Santiago S. Epidermal barrier changes in patients with psoriasis: The role of phototherapy. *Photodermatol Photoimmunol Photomed* 2021;37:285-292. doi: 10.1111/phpp.12650. **Impact factor: 3.135. Dermatology – SCIE Q2 (31/69).**
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5) **Montero-Vilchez T**, Martinez-Lopez A, Cuenca-Barrales C, Rodriguez-Tejero A, Molina-Leyva A, Arias-Santiago S. Impact of Gloves and Mask Use

on Epidermal Barrier Function in Health Care Workers. *Dermatitis* 2021;32:57-62. doi: 10.1097/DER.0000000000000682. **Impact factor: 4.845. Dermatology – SCIE Q1 (11/69).**

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Speaker Presentation

1) **Montero-Vílchez T.** Trabajo investigación propio 3: Epidermal barrier changes in patients with psoriasis: The role of phototherapy. En la session Simposio: 2ª Parte: Actualizaciones / Nuestra Investigación. *7º Congreso de Psoriasis Presencial-Virtual.* Madrid, Spain, 21-22.01.2022.
2) **Montero-Vílchez T**, Díaz-Calvillo P, Rodríguez-Pozo JA, Sánchez-Díaz M, Molina-Leyva A, Arias-Santiago S. Diferencias en efectividad, disfunción epidérmica y tolerabilidad de tres productos para la higiene de manos: un ensayo clínico aleatorizado. *Reunión Grupo de Trabajo AEDV: Epidemiología y Promoción de la salud. Congreso AEDV. 48 Congreso Nacional de Dermatología y Venereología*. Bilbao, Spain, 01-03.12.2021.
3) ¿Cómo influyen los equipos de protección individual en la función barrera epidérmica y las enfermedades de la piel? *Los Jueves de la AEDV, del Grupo de Epidemiología y Promoción de la Salud en Dermatología*. Ponentes: **Trinidad Montero Vílchez** y Eliseo Martínez García. Moderadores: Agustín Buendía Eisman y Salvador Arias Santiago. Organizador: Academia Española de Dermatología. Virtual. 18.03.2021.
4) **Montero-Vilchez T**, Martínez-López A, Cuenca-Barrales C, Molina-Leyva A, Arias-Santiago S. Impacto del uso de guantes y mascarillas en la función de la barrera epidérmica del personal sanitario. *Reunión Grupo de Trabajo AEDV: Epidemiología y Promoción de la salud. Congreso AEDV. Virtual Otoño*. Virtual, 2020. 29-19-21.11.2020.

Oral communications and posters presented

1) **Montero-Vílchez T**, Sánchez-Díaz M, Rodríguez-Pozo JA, Cuenca-Barrales C, Molina Leyva A, Arias Santiago S. Impacto de la higiene de manos en la barrera cutánea durante la pandemia de la COVID-19: un ensayo clínico aleatorizado. *48 Congreso Nacional de Dermatología y Venereología*. Bilbao, Spain, 01-03.12.2021.
2) Arias-Santiago S, **Montero-Vílchez T**, Díaz-Calvillo P, Salazar-Nievas M, Tercedor-Sánchez J, Molina-Leyva A. Impacto del dupilumab en la función de barrera epidérmica: un estudio observacional prospectivo. *48 Congreso Nacional de Dermatología y Venereología*. Bilbao, Spain, 01-03.12.2021.
3) **Montero-Vílchez T**, Montero-Vílchez C, Sánchez-Díaz M, Molina-Leyva A, Arias-Santiago S. Age and skin barrier function in atopic dermatitis. *30th Congress of the European Academy of Dermatology and Venereology*. Virtual, 29.09-02.10.2021.
4) **Montero-Vilchez T**, Martinez-Lopez A, Cuenca-Barrales C, Pérez-Rodríguez I, Molina-Leyva A, Arias-Santiago S. Skin barrier function in atopic dermatitis: temperature and transepidermal water loss as useful tools to assess disease severity. *30th Congress of the European Academy of Dermatology and Venereology*. Virtual, 29.09-02.10.2021.
5) **Montero-Vilchez T**, Sánchez-Díaz M, Rodríguez-Pozo JA, Díaz-Calvillo P, Molina-Leyva A, Arias-Santiago. Función de barrera epidérmica en los pacientes con dermatitis atópica. *66 Reunión del Grupo Español en Investigación de Dermatitis de Contacto y Alergia Cutánea*. Murcia, Spain, 24-25.09.2021.

6) **Montero-Vilchez T**, Martínez-López A, Rodríguez-Tejero A, Pérez-Rodríguez I, Molina-Leyva A, Arias-Santiago S. La temperatura y la pérdida transepidérmica de agua como herramientas para evaluar objetivamente la gravedad de la psoriasis. *6º Congreso de Psoriasis. Reunión del Grupo de Psoriasis de la AEDV*. Madrid, Spain, 23.01.2021.

7) **Montero-Vilchez T**, Martínez-López A, Salvador-Rodríguez L, Rodríguez Tejero A, Molina Leyva A, Arias Santiago S. Cambios en la barrera epidérmica, la homeostasis cutánea y el estrés oxidativo en los pacientes con psoriasis tratados con fototerapia. *Congreso AEDV Virtual Otoño 2020*. Virtual, 19-21.09.2020.

8) Soler-Gongora M, **Montero-Vilchez T**, Martinez-Lopez A, Salvador-Rodriguez L, Molina-Leyva A, Arias-Santiago S. Analysis of cutaneous homeostasis and epidermal barrier functions in patients with psoriasis: impact of phototherapy. *2020 American Academy of Dermatology Annual Meeting*. Virtual, 20-24.03.2020.

9) Espinosa-Rueda MI, **Montero-Vilchez T**, Martinez-Lopez A, Molina-Leyva A, Arias-Santiago S, Buendia-Eisman A. Influence of skin anatomical location on cutaneous homeostasis. *2020 American Academy of Dermatology Annual Meeting*. Virtual, 20-24.03.2020.

Stays abroad related to the development of this doctoral thesis

International Clinical Fellow for 3 months at the Department of Dermatology and Venereology of the Centro Hospitalar e Universitário de Coimbra, Portugal, a reference centre for care and research in Cutaneous Allergy and Oncological Surgery.

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ABBREVIATIONS

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ABHS: Alcohol-based hand sanitizers

AD: Atopic dermatitis

AU: Arbitrary units

BSA: Body Surface Area

BB-UVB: Broadband ultraviolet

CFU: Colony-forming unit

CH: Cutaneous homeostasis

COVID-19: Novel Coronavirus-2019 disease

DLQI: Dermatology Life Quality Index

EASI: Eczema Area and Severity Index

ECM: Extracellular matrix

EBF: Epidermal barrier function

FLG: Filaggrin

FFP2: Filtering Facepiece 2

HCWs: Healthcare workers

NB-UVB: Narrowband ultraviolet B

PASI: Psoriasis Area Severity Index

PPE: Personal Protective Equipment

PUVA: Psoralen ultraviolet A photochemotherapy

ROC: Receiver Operating Characteristic

SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2

SD: Standard deviation

SCH: Stratum corneum hydration

SCORAD: SCORing Atopic Dermatitis

TAC: Total antioxidant capacity

TEWL: Transepidermal water loss

UVB: Ultraviolet B

RESUMEN

RESUMEN

Antecedentes

La piel es el órgano más grande del cuerpo humano y cumple múltiples funciones defensivas y reguladoras. Es posible evaluar de forma objetiva y no invasiva la función de barrera epidérmica (FBE) y los parámetros de homeostasis cutánea (HC) que podrían diferir entre regiones anatómica. Estos parámetros incluyen la pérdida de agua transepidérmica (transepidermal water loss, TEWL) -la variable principal para determinar la función de la barrera cutánea -, la hidratación del estrato córneo (stratum corneum hydration, SCH), el pH, el eritema, la melanina, la temperatura, la elasticidad y la capacidad antioxidante. Es necesario realizar un abordaje global y multiparamétrico para evaluar toda la gama de funciones biofísicas de la barrera cutánea.

La FBE puede verse alterada en la psoriasis -debido a la hiperproliferación epidérmica y a la diferenciación defectuosa de los queratinocitos-, y en la dermatitis atópica (DA), -principalmente a causa de las mutaciones de la filagrina (FLG)-, traduciéndose en alteraciones de la FBE y la HC. En la actualidad, no existe una escala objetiva para valorar la gravedad de estas enfermedades y evaluar la respuesta al tratamiento. Los parámetros de FBE y HC podrían relacionarse con la gravedad de la enfermedad y ayudar a los médicos a resolver este problema.

La fototerapia es un tratamiento eficaz para la psoriasis, pero se necesitan muchas visitas médicas para conseguir una mejora significativa. Además, actualmente existen otras opciones terapéuticas que producen tasas más altas de respuesta en un periodo de tiempo más corto. El efecto beneficioso de la fototerapia se explica por una inhibición de la hiperproliferación epidérmica y un efecto inmunomodulador, que probablemente modifique los parámetros de la FBE y la HC. Así pues, los cambios objetivos en la FBE y la HC podrían ayudar a los clínicos a predecir la mejora de la psoriasis tras la fototerapia.

El uso de equipos de protección individual (EPIs), incluyendo las mascarillas y los guantes, y el interés por las estrategias de higiene de manos han aumentado tras la aparición de la enfermedad por Coronavirus 2019 (COVID-19). El uso de EPIs y la higiene de manos se han relacionado con varios tipos de trastornos cutáneos, pero su frecuencia varía en función del estudio. Además, se desconoce la repercusión del uso de mascarillas sobre la FBE y la HC, el efecto de los guantes es controvertido y hay escasa evidencia sobre el impacto en la barrera cutánea utilizando diferentes estrategias de higiene de manos en la práctica clínica.

Por lo tanto, nos planteamos las siguientes preguntas: ¿Podrían diferir la FBE y la HC entre regiones anatómicas? ¿Podría la función de barrera cutánea estar alterada en pacientes con psoriasis y DA y podrían los parámetros de FBE y HC estar relacionados con la gravedad de la enfermedad? ¿Podrían cambiar la FBE y la HC tras la fototerapia? ¿Podrían estos cambios ayudar a los médicos a seleccionar los pacientes más adecuados para ser tratados con fototerapia? ¿Podrían las mascarillas y los guantes perjudicar la función de la barrera cutánea? ¿Cuál podría ser el procedimiento de higiene de manos menos agresivo y más eficaz? ¿Cuál es la prevalencia real de los acontecimientos adversos relacionados con los EPIs?

Participantes y métodos

Nuestra investigación se dividió en siete etapas: 1) Un estudio transversal para comparar la FBE y la HC en individuos sanos en tres regiones anatómicas (la mejilla, la región volar del antebrazo y la palma de la mano). 2) Un estudio transversal para comparar la FBE y la HC entre individuos sanos, pacientes con psoriasis y DA y para explorar la relación entre la disfunción de la barrera cutánea y la gravedad de la enfermedad. 3 y 4) Un estudio observacional prospectivo en pacientes con psoriasis para

evaluar los cambios en la FBE y la HC tras la fototerapia y explorar su potencial como parámetros predictivos de respuesta al tratamiento. 5) Un estudio transversal con sanitarios sanos para comparar las zonas cubiertas y no cubiertas por mascarillas y guantes. 6) Un ensayo clínico para evaluar las diferencias entre tres estrategias diferentes de higiene de manos -gel hidroalcohólico, agua y jabón, y toallitas desinfectantes- en la disfunción de la barrera cutánea, la efectividad antimicrobiana y la tolerabilidad de los usuarios. 7) Una revisión sistemática y un metaanálisis para explorar la evidencia científica disponibles sobre los efectos adversos en la piel asociados a los EPIs.

Etapa 1-6. La investigación se llevó a cabo entre abril de 2019 y enero de 2021 en el Servicio de Dermatología del Hospital Universitario Virgen de las Nieves de Granada, España, y en el Departamento de Dermatología de la Universidad de Granada, Granada, España. Se incluyeron individuos sanos, pacientes con psoriasis y DA que acudieron a nuestro Servicio de Dermatología (estadio 1-4) y sanitarios sanos (estadio 5-6). Se midieron variables de FBE y HC, como la TEWL, la SCH, el pH, el índice de eritema y melanina, la temperatura de la piel, la elasticidad y la capacidad antioxidante total (CAT). Los datos sociodemográficos y las características clínicas de los pacientes con psoriasis y DA se registraron a través de una historia clínica y una exploración física. También se recogieron muestras microbiológicas y las tasas de tolerabilidad y aceptabilidad de los procedimientos de higiene de manos.

Etapa 7. Se realizó una revisión sistemática y un metaanálisis siguiendo las directrices PRISMA utilizando las bases de datos Medline, Scopus y Embase desde su concepción hasta el 21 de enero de 2021. La búsqueda se limitó a: (i) datos en humanos, (ii) estudios in vivo, (iii) eventos adversos cutáneos relacionados con los EPIs, (iv) artículos escritos en inglés. Las variables evaluadas fueron el diseño del estudio, la tasa y el tipo de acontecimientos adversos cutáneos relacionados con los EPI, los factores de

riesgo para desarrollar manifestaciones cutáneas, el número de participantes, el autor, el país, la edad, el sexo, las herramientas de evaluación, las regiones anatómicas dañadas y el tipo de medidas preventivas. La prevalencia global de los eventos cutáneos relacionados con los EPIs se calculó mediante un metaanálisis de efectos aleatorios ponderado por el tamaño de la muestra del estudio. Se construyeron diagramas de bosque para resumir las estimaciones de prevalencia y sus intervalos de confianza del 95%.

Resultados

Etapa 1. Se incluyeron 87 individuos sanos en el estudio. La TEWL fue menor en la región volar del antebrazo que en la mejilla y la palma (9,69 vs. 15,16 vs. 49,32 $g \cdot m^{-2} \cdot h^{-1}$, p<0,001). La SCH fue menor en la región volar del antebrazo que en la mejilla y la palma (43,46 vs. 52,23 vs. 60,06 unidades arbitrarias (UA), p<0,001). El pH fue menor en la palma que en la mejilla y la región volar del antebrazo (5,58 vs. 5,72 vs. 5,74, p<0,001). El eritema fue mayor en la mejilla que en la palma o la región volar del antebrazo (413,51 vs. 259,98 vs. 252,02 UA, p<0,001). La melanina fue menor en la palma de la mano que en la mejilla y la región volar del antebrazo (92,72 vs. 147,63 vs. 151,07AU, p<0,001). Cada aumento de un año en la edad se asoció con un aumento de la TEWL de 0,45 $g \cdot m^{-2} \cdot h^{-1}$ en la mejilla y de 0,32 $g \cdot m^{-2} \cdot h^{-1}$ en la palma.

Etapa 2. Se incluyeron 314 participantes en el estudio, de los cuales 92 eran pacientes con psoriasis y 92 sus controles, y 65 eran pacientes con DA y 65 sus controles. La TEWL fue mayor en las placas de psoriasis que en la piel psoriásica no afecta y en la piel sana (18,45 vs. 12,06 vs. 12,34 $g \cdot m^{-2} \cdot h^{-1}$, p<0,001), mientras que no se encontraron diferencias entre la piel psoriásica no afecta y la piel sana. La SCH fue significativamente menor en las placas de psoriasis que en la piel psoriásica no afecta y en la piel sana (8,71 vs. 38,43 vs. 44,39 UA). La temperatura fue mayor en las placas de psoriasis que en la

piel psoriásica no afecta (30,95 vs. 30,57 °C, p=0,046). El índice de eritema fue significativamente mayor en las placas de psoriasis que en la piel psoriásica no afecta y en los controles sanos (408,44 vs. 311,56 vs. 285,91 UA). No se encontraron diferencias en el pH o la elasticidad. En las placas de psoriasis, un valor de temperatura superior a 30,85 °C, con una sensibilidad del 72,7%; y un valor de TEWL superior a 13,85 $g \cdot m^{-2} \cdot h^{-1}$, con una sensibilidad del 81,8%; indicaban que un paciente tenía psoriasis moderada/grave, índice de gravedad del área de psoriasis (PASI) ≥ 7.

En cuanto a los pacientes con DA, la TEWL fue significativamente mayor en las lesiones eczematosas que en la piel no afecta y la piel sana (28,68 frente a 13,15 vs. 11,60 $g \cdot m^{-2} \cdot h^{-1}$). La SCH fue más baja en las lesiones eczematosas que en la piel no afecta y en la piel sana (20,20 vs. 40,95 vs. 50,73 UA, p<0,001). La temperatura fue significativamente mayor en las lesiones eccematosas que en la piel no afecta y en la piel sana (32,05 vs. 31,35 vs. 31,37 °C), mientras que no se encontraron diferencias entre la piel no afecta y la piel sana. El índice de eritema fue significativamente mayor en las lesiones eczematosas que en la piel sana (387,21 vs. 244,44 UA). La elasticidad fue significativamente menor en las lesiones eccematosas de la DA que en la piel sana (69% vs. 74% vs. 76%), mientras que no se encontraron diferencias entre la piel no afecta de la DA y la piel sana. No se encontraron diferencias en el pH. En las lesiones eczematosas, un valor de temperatura superior a 31,75 °C, con una sensibilidad del 81,8%; y un valor de TEWL superior a 23,19 $g \cdot m^{-2} \cdot h^{-1}$, con una sensibilidad del 73,5%; indicaban que un paciente tenía DA moderada/grave, índice de gravedad de la DA (SCORing Atopic Dermatitis, SCORAD) ≥ 37.

Etapa 3. Tras una sesión de fototerapia, la temperatura aumentó 0,81ºC en la piel no afectada (p=0,001) y 0,64ºC en las placas de psoriasis (p=0,003). La SCH y el eritema aumentaron 1,15 UA y 9,63 UA en las placas de psoriasis, respectivamente, mientras que

no se observó ningún cambio en la piel no afecta. Se observó una tendencia a la disminución de los valores de la TEWL en ambas localizaciones. No se encontraron cambios en el pH ni en la elasticidad.

Tras quince sesiones de fototerapia, la temperatura y el eritema aumentaron en la piel no afecta y en las placas de psoriasis. La SCH aumentó en las placas de psoriasis. La TEWL disminuyó en 3,50 $g \cdot m^{-2} \cdot h^{-1}$ en la piel no afecta ($p = 0,021$) y en 5,19 $g \cdot m^{-2} \cdot h^{-1}$ en las placas de psoriasis ($p = 0,016$). No se encontraron cambios en la piel sana no expuesta.

Etapa 4. Tras la primera sesión de fototerapia, los pacientes con una mejora del PASI ≥3 mostraron un mayor aumento del eritema en comparación con los pacientes que no alcanzaron esta mejoría (71,08 vs. 11,54 UA, $p = 0,011$). Se generó una curva ROC para determinar un valor de corte óptimo para los aumentos de eritema tras una sesión de fototerapia, que permitía a los médicos predecir la mejora después de 15 sesiones de fototerapia (área bajo la curva = 0,789, $p = 0,026$). Un incremento del eritema superior a 53,23 UA después de la primera sesión de fototerapia, con una sensibilidad del 71,4% y una especificidad del 84,2%, indicaba que un paciente mejoraría su PASI ≥3 puntos después de quince sesiones de fototerapia.

Etapa 5. Se incluyeron 34 sanitarios. La TEWL (31,11 vs. 14,24 $g \cdot m^{-2} \cdot h^{-1}$, $p<0,001$), la SCH (43,26 vs. 58,28 AU, $p<0,001$), la temperatura (33,29 vs. 32,57ºC, $p<0,001$) y el eritema (243,97 vs. 215,55 AU, $p<0,001$) fueron mayores en la zona cubierta por los guantes en comparación con la zona no cubierta, respectivamente. La TEWL (22,82 vs. 13,69 $g \cdot m^{-2} \cdot h^{-1}$, $p<0,001$), la temperatura (33,19 vs. 32,54ºC, $p<0,001$) y el eritema (411,43 vs. 335,52 UA, $p<0,001$) fueron mayores en la zona cubierta por las mascarillas en comparación con la no cubierta, mientras que la SCH fue menor (53,87 vs.

59,50 UA, p=0,058). La TEWL fue mayor en la zona cubierta por la mascarilla quirúrgica que en la FFP2 (27,09 vs. 18,02 $g \cdot m^{-2} \cdot h^{-1}$, p=0,034).

Etapa 6. Se incluyeron en el estudio 62 sanitarios, 20 de ellos en el grupo de agua y jabón, 21 en el de gel hidroalcohólico y 21 en el de toallitas desinfectantes. La TEWL aumentó en 5,45 $g \cdot m^{-2} \cdot h^{-1}$ en el grupo de toallitas desinfectantes y en 3,87 $g \cdot m^{-2} \cdot h^{-1}$ en el grupo de agua y jabón, mientras que se redujo en 1,46 $g \cdot m^{-2} \cdot h^{-1}$en el grupo de gel hidroalcohólico, con diferencias significativas entre los grupos (p=0,020). Tras construir un modelo de regresión lineal, se observó que el agua y el jabón (β=4,77, p=0,05) y las toallitas desinfectantes (β=6,14, p=0,016) se asociaban de forma independiente con un aumento de la TEWL. La reducción del recuento de unidades formadoras de colonias (UFC) de bacterias y hongos fue menor en el grupo de agua y jabón que en el de gel hidroalcohólico y toallitas desinfectantes. Las toallitas desinfectantes se consideraron más difíciles de usar (p=0,013) en comparación con el agua y el jabón y el gel hidroalcohólico.

Etapa 7. La búsqueda bibliográfica identificó 1.007 artículos, 35 de las cuales cumplieron los criterios de elegibilidad y fueron incluidos en el análisis, representando a 31.453 participantes. La media de eventos adversos cutáneos relacionados con el EPI fue de 75,13%. La tasa de eventos adversos cutáneos relacionados con las mascarillas fue del 57,71% y los asociados a los guantes y productos de higiene de manos fue del 49,16%. Los acontecimientos adversos cutáneos más comunes fueron la dermatitis de contacto, el acné y el picor. Las regiones anatómicas más dañadas fueron el puente nasal, las mejillas y las manos. Una larga duración del uso del EPIs fue el factor de riesgo más común. El lavado frecuente de las manos, los guantes y las mascarillas fueron los agentes más frecuentemente relacionados con las reacciones cutáneas. Las mascarillas N95 fueron el tipo de mascarilla más perjudicial para la piel. El uso de hidrocoloides evitó el desarrollo de acontecimientos adversos cutáneos relacionados con las mascarillas

Conclusión

Los parámetros de FBE y HC en individuos sanos son diferentes en la mejilla, la región volar del antebrazo y la palma de la mano. La FBE y la HC difieren entre los individuos sanos, los pacientes con psoriasis y los pacientes con DA; y la temperatura y la TEWL pueden ayudar a los médicos a determinar objetivamente la gravedad de la enfermedad. La FBE y la HC se modifican con la fototerapia. Un punto de corte en el incremento del eritema tras la primera sesión de fototerapia podría ayudar a los clínicos a seleccionar a los pacientes con psoriasis con mayor probabilidad de responder a quince sesiones de fototerapia. El uso de guantes y mascarillas deteriora la barrera cutánea, siendo las mascarillas quirúrgicas más perjudiciales que las FFP2. La higiene diaria de las manos con gel hidroalcohólico mostró las tasas más bajas de alteración de la barrera cutánea, la mayor reducción de la carga microbiana y las tasas más altas de tolerabilidad. La prevalencia de acontecimientos adversos cutáneos relacionados con el uso de EPIs es alta, siendo la mayoría de ellos leves.

ABSTRACT

ABSTRACT

Background

Skin is the largest organ of the human body and accomplishes multiple defensive and regulatory functions. It is possible to assess objectively and non-invasively epidermal barrier function (EBF) and cutaneous homeostasis (CH) parameters on the skin and they could differ between each anatomic region. These parameters include transepidermal water loss (TEWL) - the key characteristic to assess skin barrier function-, stratum corneum hydration (SCH), pH, erythema, melanin, temperature, elasticity and antioxidant capacity. An integrated and a multiparametric approach is needed to evaluate the full range of biophysical functions of the skin barrier.

Skin barrier function may be disrupted in psoriasis -due to epidermal hyperproliferation and defective keratinocyte differentiation-, and atopic dermatitis (AD), -mainly because of filaggrin (FLG) mutations, being translated into EBF and CH alterations. Currently, there is no objective scale to assess objectively these diseases severity and evaluate clinical outcomes. EBF and CH parameters could be related to disease severity and help clinicians to solve this problem.

Phototherapy is an effective therapy for psoriasis, but many medical appointments are needed to see a significant improvement and there are currently other treatments options with higher and faster effect. The beneficial effect of phototherapy is explained by the inhibition of epidermal hyperproliferation and an immunomodulatory effect, likely modifying EBF and CH parameters. So, objective changes in the EBF and CH may help could help physicians to predict psoriasis improvement after phototherapy.

The use of personal protective equipment (PPE), including masks and gloves, and the interest in hand hygiene strategies has increased after the COVID-19 outbreak. PPE and hand hygiene have been related to several type of skin disorders, but its frequency

varies depending on the research. Moreover, it is unknown the effect of masks wearing on EBF and CH, the impact of gloves is controversial in there is scarce evidence about the impact on skin barrier using different hand hygiene strategies in the clinical practice.

Thus, we asked ourselves the following questions: Could EBF and CH differ between anatomical regions? Could skin barrier function be impaired in patients with psoriasis and AD and could EBF and CH parameters be related to disease severity? Could EBF and CH change after phototherapy? Could these changes help physicians to select the most appropriate patients to be treated with phototherapy? Could mask and gloves impair skin barrier function? Which could be the least aggressive and the most effective hand hygiene procedure? What is the real prevalence of adverse events related to PPE?

Participants and methods

Our research was divided in seven stages: 1) A cross-sectional study to compare EBF and CH in healthy individuals at three anatomic regions (the cheek, the volar forearm and the palm). 2) A cross-sectional study to compare EBF and CH between healthy individuals, patient with psoriasis and AD and to explore the relation between skin barrier dysfunction and disease severity. 3 and 4) A prospective observational study in patients with psoriasis to evaluated changes in EBF and CH after phototherapy and to explore them as potentially predictive parameters of treatment response. 5) A cross-sectional study including healthy healthcare workers (HCWs) to compared areas covered and non-covered by masks and gloves. 6) A clinical trial to assess differences between three different hand hygiene strategies- alcohol based hand sanitizer (ABHS), water and soap, and disinfectant wipes- in skin barrier dysfunction, microbial load and users' tolerability. 7) A systematic review and metanalysis to explore the available scientific evidence regarding skin adverse events associated with PPE.

Stage 1-6. The research was conducted between April 2019 and January 2021 in the Dermatology Department of the Hospital Universitario Virgen de las Nieves in Granada, Spain, and in the Dermatology Department of Granada University, Granada, Spain. Healthy individual, patients with psoriasis and AD that attended to our Dermatology Department (stage 1-4) and healthy HCWs (stage 5-6) were included. EBF and CH variables were measured, including TEWL, SCH, pH, erythema and melanin index, skin temperature, elasticity, and total antioxidant capacity (TAC). Sociodemographic data were recorded by clinical interview. Clinical characteristics for patients with psoriasis and AD were included by means of clinical interview and physical examination. Microbiological samples and tolerability and acceptability rates for hand hygiene procedures were also collected.

Stage 7. A systematic review and meta-analysis were conducted following PRISMA guidelines using Medline, Scopus and Embase databases from conception to 21st January 2021. The search was limited to: (i) human data, (ii) *in vivo* studies, (iii) skin adverse events related to PPE, (iv) articles written in English. The variables assessed were study design, rate and type of skin adverse events related to PPE, risk factors for developing skin manifestations, number of participants, author, country, age, sex, assessment tools, anatomical regions damaged, kind of preventive measures. The overall prevalence of skin cutaneous events related to PPE was calculated by a random effect meta-analysis weighted by the study sample size. Forest plots were constructed to summarize the prevalence estimates and their 95% CIs.

Results

Stage 1. We included 87 healthy individuals. TEWL was lower on the volar forearm than the cheek and the palm (9.69 vs. 15.16 vs. 49.32 $g \cdot m^{-2} \cdot h^{-1}$, p<0.001). SCH was lower on the volar forearm than check and palm (43.46 vs. 52.23 vs. 60.06 arbitrary units (AU), p<0.001). pH was lower on the palm than on the cheek and the volar forearm (5.58 vs. 5.72 vs. 5.74, p<0.001). Erythema was higher on the cheek than on the palm or volar forearm (413.51 vs. 259.98 vs. 252.02 AU, p<0.001). Melanin was lower on the palm than on the cheek and the volar forearm (92.72 vs. 147.63 vs. 151.07AU, p<0.001). Each one-year increase in age was associated with an increase in TEWL of 0.45 $g \cdot m^{-2} \cdot h^{-1}$ on the cheek and 0.32 $g \cdot m^{-2} \cdot h^{-1}$ on the palm.

Stage 2. We included 314 participants, consisting of 92 patients with psoriasis and their 92 controls and 65 with AD and their 65 controls. TEWL was higher at psoriatic plaques than at uninvolved psoriatic skin and healthy skin (18.45 vs. 12.06 vs. 12.34 $g \cdot m^{-2} \cdot h^{-1}$, p<0.001) while no differences were found between uninvolved psoriatic skin and healthy skin. SCH was significantly lower at psoriatic plaques than uninvolved psoriatic skin and healthy skin (8.71 vs. 38.43 vs. 44.39 AU). Temperature was higher at psoriatic plaques than at uninvolved psoriatic skin (30.95 vs. 30.57 °C, p = 0.046). The erythema index was significantly higher at psoriatic plaques than at uninvolved psoriatic skin and healthy controls (408.44 vs. 311.56 vs. 285.91 AU). No differences in pH or elasticity were found. On psoriatic plaques, a value for temperature exceeding 30.85 °C, with a sensitivity of 72.7%; and a TEWL value higher than 13.85 $g \cdot m^{-2} \cdot h^{-1}$, with a sensitivity of 81.8%; indicated that a patient had moderate/severe psoriasis, psoriasis area severity index (PASI) ≥ 7.

Regarding patients with AD, TEWL was significantly higher at AD eczematous lesions than at uninvolved AD skin and healthy skin (28.68 vs. 13.15 vs. 11.60 $g \cdot m^{-2} \cdot h^{-1}$). SCH was lower at AD eczematous lesions than at uninvolved AD skin and healthy skin

(20.20 vs. 40.95 vs. 50.73 AU, p<0.001). Temperature was significantly higher at AD eczematous lesions than at uninvolved AD skin and healthy skin (32.05 vs. 31.35 vs. 31.37 °C), while no differences were found between uninvolved AD skin and healthy skin. The erythema index was significantly higher at AD eczematous lesions than healthy skin (387.21 vs. 244.44 AU). Elasticity was significantly lower at AD eczematous lesions than healthy skin (69% vs. 74% vs. 76%), while no differences were found between uninvolved AD skin and healthy skin. No differences in pH were found. On eczematous lesions, a value for temperature exceeding 31.75 °C, with a sensitivity of 81.8%; and a TEWL value higher than 23.19 $g \cdot m^{-2} \cdot h^{-1}$, with a sensitivity of 73.5%; indicated that a patient had moderate/severe AD, SCORing Atopic Dermatitis (SCORAD) ≥ 37.

Stage 3. After one phototherapy session, temperature increased by 0.81ºC at uninvolved skin (p=0.001) and 0.64ºC at psoriatic plaques (p=0.003). SCH and erythema increased by 1.15 AU and by 9.63 AU at psoriatic plaques, respectively, while no effect was reported for uninvolved skin. A decreasing trend was observed for TEWL values at both locations. No changes in pH or elasticity were found.

After fifteen phototherapy sessions, temperature and erythema increased at uninvolved skin and psoriatic plaques. SCH increased at psoriatic plaques. TEWL decreased by 3.50 $g \cdot m^{-2} \cdot h^{-1}$ at uninvolved skin (p = 0.021) and by 5.19 $g \cdot m^{-2} \cdot h^{-1}$ at psoriatic plaques (p = 0.016). No effect was observed at healthy non-exposed skin.

Stage 4. After the first phototherapy session, patients with a PASI improvement ≥3 showed a higher erythema increase (71.08 vs. 11.54 AU, p = 0.011). A ROC curve was generated to determine an optimum cut-off value for erythema increases after one phototherapy session, which allowed clinicians to predict the improvement after 15 phototherapy sessions (area under the curve = 0.789, p = 0.026). A value for erythema increases exceeding 53.23 AU after the first phototherapy session, with a sensitivity of

71.4% and specificity of 84.2%, indicated that a patient may improve PASI by ≥3 points after fifteen phototherapy sessions.

Stage 5. Thirty-four HCWs were included. TEWL (31.11 vs 14.24 $g \cdot m^{-2} \cdot h^{-1}$, p<0.001), SCH (43.26 vs 58.28 AU, p<0.001), temperature (33.29 vs 32.57ºC, p<0.001) and erythema (243.97 vs 215.55 AU, p<0.001) were higher at the area covered by the gloves compared to the non-covered area, respectively. TEWL (22.82 vs 13.69 $g \cdot m^{-2} \cdot h^{-1}$, p<0.001), temperature (33.19 vs 32.54ºC, p<0.001) and erythema (411.43 vs 335.52 AU, p<0.001) were higher at the area covered by the mask compared to the non-covered, while SCH was lower (53.87 vs 59.50 AU, p=0.058). TEWL was higher at the area covered by a surgical mask than at the FFP2 one (27.09 vs 18.02 $g \cdot m^{-2} \cdot h^{-1}$, p=0.034).

Stage 6. Sixty-two HCWs were included in the study, 20 of them in the water and soap group, 21 in ABHS group and 21 in disinfectant wipes group. TEWL increased by 5.45 $g \cdot h^{-1} \cdot m^{-2}$ in disinfectant wipes group and 3.87 $g \cdot h^{-1} \cdot m^{-2}$ in water and soaps group while it was reduced by 1.46 $g \cdot h^{-1} \cdot m^{-2}$ in the ABHS group with significant differences between groups (p=0.020). After constructing a linear regression model, it was observed that water and soap (β=4.77, p=0.05) and disinfectant wipes (β=6.14, p=0.016) were independently associated with a TEWL increase. Bacteria and fungi colony-forming unit (CFU) count reduction was lower for water and soap group than for ABHS and disinfectant wipes. Disinfectant wipes were considered more difficult to use (p=0.013) compared to water and soap and ABHS.

Stage 7. The literature search identified 1,007 references, 35 of them met the eligible criteria and were included for analysis, representing 31,453 participants. The media of skin side events related to PPE was 75.13%. The rate of cutaneous adverse events related to mask was 57.71% and those associated with gloves and hand hygiene products was 49.16%. Most common skin adverse events were contact dermatitis, acne

and itching. The most damaged anatomical regions were the nasal bridge, the cheeks and the hands. The duration of PPE wearing was the most common risk factor. Frequent hand washing, gloves and masks were the agents most frequently related to skin reactions. N95 respirators were the most harmful mask type for the skin. Hydrocolloid use prevented from developing skin adverse events related to masks

Conclusion

EBF and CH parameters in healthy individuals are different in the volar forearm, the cheek and the palm. EBF and CH differs between healthy individuals, patients with psoriasis and patients with AD; and temperature and TEWL may help clinicians to determinate objectively disease severity. EBF and CH change after phototherapy. A cut-off point in erythema increases after the first phototherapy session could help clinicians to select psoriasis patients with more likelihood of responding to fifteen phototherapy sessions. Gloves and mask wearing impair skin barrier, being surgical masks more harmful than FFP2 one. Daily hand hygiene with ABHS showed the lowest rates of skin barrier disruption, the highest microbiologic load reduction and the highest tolerability rates. The rate of cutaneous adverse events related to PPE use is high, being most of them mild and being dryness, pressure related symptoms and itching the most frequent one.

1. INTRODUCTION

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1.1. Skin barrier function

Skin is the largest organ of the human body and accomplishes multiple defensive and regulatory functions[1]. Skin is composed by three layers: the epidermis, dermis, and hypodermis. The epidermis is the most superficial sheet and it is form by keratinocytes organized in four epidermal layers (stratum basal, stratum spinosum, stratum granulosum and stratum corneum). The dermis resides below the epidermis and consists of a fibrous extracellular matrix (ECM), composed by collagens and elastin fibers between other elements, with fibroblasts and immune cells. The hypodermis is the deepest layer and is mainly form by fatty tissue[2].

The barrier function of skin resides mainly in the epidermis, especially in the stratum corneum, its most superficial layer[3]. This epidermal barrier maintains cutaneous homeostasis (CH) and protects the body against numerous external stressors, including chemical, environmental, and physical stress, such as ultraviolet (UV) radiation[4]. The regulation of epidermal barrier function (EBF) and cutaneous homeostasis remains poorly understood, and knowledge of the patterns of homeostatic parameters that regulate healthy skin is important to support clinical decision-making in patients with cutaneous diseases[5].

Transepidermal water and retained water make up the water content of skin. Transepidermal water from circulating blood migrates through the dermis into the epidermis, eventually evaporating on the skin surface, and it plays an essential role in the supply of nutrients to the epidermis, which is devoid of blood vessels[6]. Retained water in the stratum corneum is localized within corneocytes between lipid bilayers, and it maintains the mechanical properties of the cornified layer, increases the plasticity of the epidermis, and enhances the hydrophilic properties of keratin[7]. Transepidermal water loss

(TEWL), i.e., the diffusion of condensed water through the stratum corneum, is a key characteristic to assess skin barrier function[8]. Greater TEWL is often associated with skin barrier impairments and has been observed in some skin diseases[9]. Stratum corneum hydration (SCH), i.e., the water content of the stratum corneum, is another important parameter, and a lower value is frequently associated with skin barrier dysfunction[7]. In addition, an elevated TEWL value in a disturbed skin barrier is frequently correlated with a reduced SCH value[10].

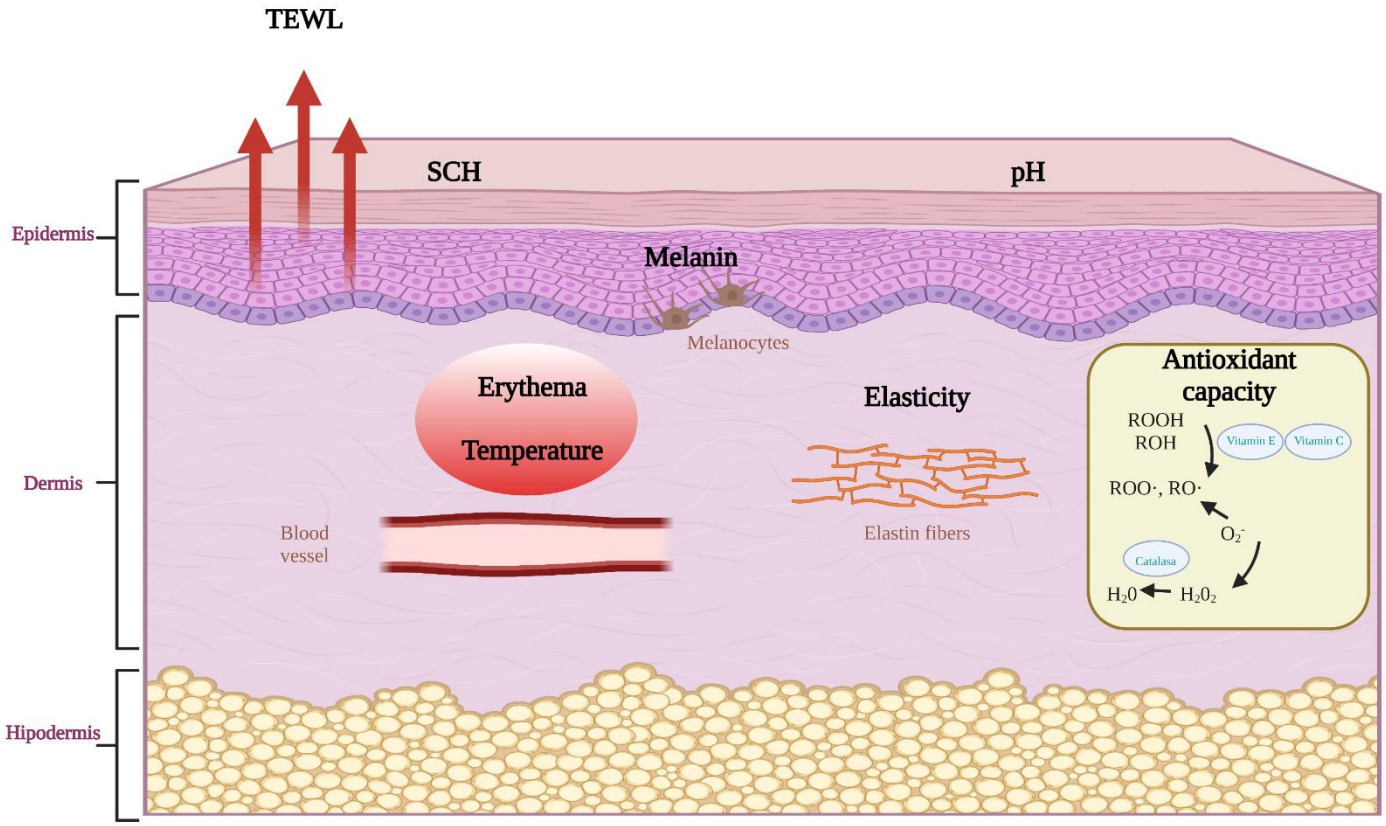
The skin surface pH is also considered in the assessment of epidermal functions, as acidic pH of the stratum corneum is considered to present an antimicrobial barrier preventing colonization and is essential to preserve metabolic and enzymatic activity and maintain the structure of lipids[11]. Thus, neutralization of the stratum corneum produces abnormalities in its function, with aberrant permeability barrier homeostasis and decreased stratum corneum integrity and cohesion[12].

Erythema, temperature and melanin are also determinants of skin health[13]. Increases in erythema and temperature results from the exposure of skin to irritants such as chemical substances, cleansers, allergens, or UV, among others[14], and they could be translating an increased in skin permeability due to an inflammatory[15]. Melanin production is stimulated by ultraviolet B (UVB) light and it is a skin defense mechanism against sun radiation[16]. Melanin is formed in melanocytic melanosomes and is transferred to the keratinocytes, migrating with the desquamation cycle. There is a higher density of melanocytes on the face and genitals. However, differences in pigmentation among anatomic areas are not related to their density but rather to the proportion of mature melanosomes and their distribution and activity, which is influenced by endocrine factors, radiation, and the pH[17].

Furthermore, the skin is a potential target of oxidative damage as it is continuously exposed to environmental factors such as air pollution, solar radiation, chemicals and microorganism, inducing free radicals' formation[18]. Antioxidants remove free radical and protect cells against the oxidative stress[19]. The stratum corneum contains high levels of water- and lipid-soluble antioxidants such as glutathione, vitamin C, tocopherol, squalene and coenzyme Q[18]. An imbalance between the antioxidants and oxidative free radicals cause injury to cell membranes and DNA leading to cytotoxicity, cell death, lipid peroxidation and protein breakdown leading to an impaired skin barrier[20]. Elasticity is another important property of the skin that resides mainly in the elastic fibers of the inner dermal layer[21]. Elastin is the major component of elastic fibers, and it is a particularly vulnerable protein because of its slow turnover[22]. A normal production of elastic fiber and their integration with other ECM proteins, such as proteoglycans and glycosaminoglycans, is necessary to preserve a functional skin structure[23]. Elastin production is susceptible to be damaged by environmental exposure or inflammation due to a recruitment of elastases, elastolytic enzymes, that degrade elastin fibers[22].

An integrated and a multiparametric approach is needed to evaluate the full range of biophysical functions of the skin barrier[13,24] (Figure 1). Despite their importance for the accurate evaluation and treatment of skin conditions, few normative data are available on cutaneous homeostasis parameters in healthy individuals.

Figure 1. Epidermal barrier function and cutaneous homeostasis parameters that can be assessed non-invasively on the skin.



SCH: stratum corneum hydration; TEWL: transepidermal water loss

This figure has been created using BioRender.com

1.2. Skin barrier impairment in psoriasis and atopic dermatitis

Psoriasis is a chronic, recurrent, multisystemic inflammatory disease[25] caused by a combination of immunological imbalances, genetic associations, and environmental factors[26]. Its prevalence around the word has been estimated at between 0.51% and 11.43%[27]. There are several types of psoriasis, including plaque psoriasis, guttate psoriasis, erythrodermic psoriasis, and pustular psoriasis[28]. Plaque psoriasis is the most common variant of psoriasis and clinically it is characterized by erythematous, scaly and raised plaques[29]. Skin manifestations are often the only recognized symptoms of psoriasis[30], but it is associated with multiple comorbidities, including cardiovascular disease, arthritis and inflammatory bowel disease[31-35], and with and impairment in patients and cohabitants' quality of life[36-38]. Epidermal barrier dysfunction has not been considered in detail in psoriasis pathophysiology although epidermal hyperproliferation and defective keratinocyte differentiation may impair skin barrier function[39-41]. Hyperproliferation of keratinocytes generates a thicker epidermis and the aberrant epidermal differentiation in response to inflammatory cytokines decreased tight junction protein expression and dysregulate ceramide production in the ECM[42].

Atopic dermatitis (AD) is a chronic cutaneous inflammatory disease caused by genetic and environmental factors[43,44]. It is one of the most prevalent skin diseases and its prevalence ranges from 0.96% to 22.6% in children and from 1.2% to 17.1% in adults[45], with higher prevalence in industrialized countries[46]. Clinically, it is characterized by recurrent and itchy eczematous lesions, excoriations, scaling and dry skin[43]. AD is also related to other comorbidities including allergic disorders, such as asthma, hay fever, food allergy and eosinophilic esophagitis; and psychosocial disturbances, such as depression and anxiety[47]. So, it is a disease with greatly impairment in patients and cohabitant patients quality of life[48]. Epidermal barrier dysfunction, immune dysregulation, and gut

dysbiosis may play roles in this disease[49]. Skin barrier dysfunction is considered the first step in the development of AD[50,51]. Filaggrin (FLG) mutations leads to alterations in the differentiation and growth of a normal stratum corneum, increasing cutaneous water loss from normal levels[52]. Skin barrier dysfunction in AD includes abnormalities in the cornified envelope, tight junctions, lipid lamellae, and cutaneous microbiome[53]. Moreover, impairment in skin barrier increases allergic sensitization to antigens[54] and is an independent risk factor for developing food sensitization[55].

The assessment of EBF and CH in psoriasis and AD could evaluate qualitative and quantitative skin alterations of lesioned and non-lesioned skin and help to better understand the complex and still incomplete etiopathogenesis of these diseases[42,53]. Furthermore, there is a need to develop objective tools to assess psoriasis and AD severity in therapeutics and outcome research[56,57]. Despite multiple diagnostic tools have been used to evaluate severity in patients with psoriasis and AD, all of them have a subjective component that could lead to a high intra- and inter-observer variability[58,59]. The psoriasis area severity index (PASI) is the most widely used scale for assessing psoriasis severity[60]. This score quantifies extent (the percentage of involvement of the four anatomical regions: head, trunk, and upper and lower extremities) and intensity of the psoriatic plaques (evaluating erythema, desquamation, and induration separately for the four anatomical regions)[61]. The Eczema Area and Severity Index (EASI) and the SCORing Atopic Dermatitis (SCORAD) are the most common index used to assess AD severity[62]. The EASI tabulates body surface area in four areas (head and neck, upper extremities, trunk, and lower extremities) and assesses separately in each one the erythema, induration/papulation/edema, excoriations, and lichenification, assigning a score of 0 to 3 (none, mild, moderate, and severe, respectively)[63]. The SCORAD evaluates the extent of the disorder, the intensity (composed of six items: erythema, oedema/papules, effect

of scratching, oozing/crust formation, lichenification, and dryness) and subjective symptoms (itch, sleeplessness)[64]. As all these scales have an observer-dependent component, the measurement of EBF and CH could help clinicians to assess the disease severity objectively[65,66].

1.3. The role of phototherapy in skin restoration

Phototherapy is an effective, safe, and low-cost therapy for mild–moderate plaque psoriasis[67]. Nevertheless, many medical appointments are needed to see a significant improvement[68] and there are currently other treatments options for psoriasis that have a higher and faster effect[69]. Several types of light and lasers are useful for treating psoriasis, including narrowband ultraviolet B (NB-UVB); broadband ultraviolet B (BB-UVB); and psoralen ultraviolet A photochemotherapy (oral or bath PUVA)[70]. NB-UVB, wavelengths ranging from 311 to 313 nm, is the most effective type of phototherapy for psoriasis and the most frequently used[71]. The starting dose is based on skin phototype or minimal erythema dose (MED) and two or three sessions per week are recommended, reaching clearance after two- or three-months treatment[71,72]. The beneficial effect of phototherapy for psoriasis is explained by the inhibition of epidermal hyperproliferation and an immunomodulatory effect[73]. Previously, it has been shown that phototherapy increases TEWL and decrease SCH[66,74]. So, objective changes in the EBF may help clinicians to select the right patient for phototherapy and to predict disease improvement.

1.4. Skin impairment related to personal protective equipment

The use of personal protective equipment (PPE) between healthcare workers (HCWs) and the general population has increased due to the Novel Coronavirus-2019

disease (COVID-19) outbreak[75]. COVID-19 is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a novel virus, emerged in December 2019 in Wuhan, China Popular Republic[76]. This virus rapidly spread around the world, causing multiple deaths and a saturation of health systems[77].

To fight against the pandemic and avoid the virus transmission HCWs should wear adequate PPE, including gloves, facial masks, goggles or face shields and plastic gowns and perform frequent and proper hand washing[78]. Daily use of the PPE can lead to physical and psychological disturbances, such as headache, depression, anxiety or insomnia[79,80]. Skin disorders are one of the most frequent side events related to PPE[81]. Their prevalence range between 42.8% and 74%, with high differences between studies[82-85]. Moreover, there is scarce evidence regarding the most common skin side events, the type of equipment most likely to cause skin damage or preventive measures to avoid these adverse cutaneous events related to PPE[86,87].

The need of face masks wearing has been widespread to the whole population after COVID-19 pandemic, having to use them for long-period as it is a compulsory measure in many countries[88,89]. Facial masks can lead to erosion, abrasion, maceration and ecchymosis in the cheeks, forehead and nasal bridge[90], and it has been also reported an overall 21% of work absenteeism due to these facial lesions[91]. Despite being related to several skin conditions, mask impact on EBF and CH has hardly been evaluated and it is controversial the type of mask that cause higher cutaneous impairment[92]. The prolonged use of gloves can cause different skin conditions, including irritant and allergic contact dermatitis, glove-related hand urticaria[93], pompholyx or secondary infections[90], but the effect of gloves in EBF and CH is controversial in the literature[94,95].

The frequent use of hand washing products is also associated with skin damage[96]. Hands are the main vector for infectious diseases transmission in a hospital environment[97]

and injured skin facilitates microorganism penetration, including SARS-CoV-2[98]. Currently, there are several hand hygiene products available, including soaps, alcohol-based hand sanitizers (ABHS) and disinfectant wipes[97,99-101]. ABHS reduce skin pathogens more efficiently[102,103] and, therefore, frequent application of ABHS containing at least 60% alcohol or, if unavailable, hand washing with soap and water for at least 30 seconds, are recommended[104,105]. Regarding EBF and CH, it has been reported that TEWL increased with soaps[14] and decreased with ABHS[106], but there is only one study comparing the impact of different hand hygiene products on EBF and CH in the clinical practice[107]. An adequate hand hygiene procedure should be effective -eliminating microorganism from the skin and avoiding disease transmission-, non-harmful for the skin and tolerable for the user. Nevertheless, there are scarce studies that compare these three factors when using different hand hygiene strategies in a clinical setting.

2. JUSTIFICATION AND HYPOTHESIS

2. JUSTIFICATION AND HYPOTHESIS

Epidermal barrier function (EBF) and cutaneous homeostasis (CH) may be different depending on the anatomical location because the skin structure is different in each body region. EBF and CH might be disrupted in patients with psoriasis and atopic dermatitis (AD). The changes in EBF and CH could be related to disease severity and could be improved with the therapies for these diseases. Currently, it is not well defined which is the most appropriate treatment for each patient with psoriasis or AD. The measurement of EBF and CH parameters could help clinicians to choose the right patient profile for each treatment, facilitating an effective and early approach and preventing disease progression and development of associated complications. Therefore, we asked ourselves the following questions: Could EBF and CH differ between anatomical regions? Could skin barrier function be impaired in patients with psoriasis and AD and could EBF and CH parameters be related to disease severity? Could EBF and CH change after phototherapy? Could these changes help physicians to select the most appropriate patients to be treated with phototherapy?

Personal protective equipment (PPE), including gloves and masks, and hand hygiene products might impair EBF and CH. Currently, it is not well known the effect that gloves, masks and hand hygiene products have on EBF and CH. This knowledge could help to provide appropriate materials and develop adequate measures to prevent skin damage associated with these products use. A skin damage reduction could contribute to increase the compliance with protection protocols and decrease the risk of disease transmission. Thus, we asked ourselves the following questions: Could mask and gloves impair skin barrier function? Which could be the least aggressive and the most effective hand hygiene procedure? What is the real prevalence of adverse events related to PPE?

3. OBJECTIVES

3. OBJECTIVES

General objective

To assess epidermal barrier function (EBF) and cutaneous homeostasis (CH) in patients with psoriasis and atopic dermatitis (AD) and in healthcare workers (HCWs) using personal protective equipment (PPE).

Specific objectives

1) To evaluate EBF and CH in healthy individuals in different anatomical regions.
2) To assess differences in EBF and CH between healthy individuals, patients with psoriasis and patients with AD and to explore the relation between skin barrier dysfunction and disease severity.
3) To evaluate changes in EBF and CH in patients with psoriasis after phototherapy.
4) To explore EBF and CH as potentially predictive parameters of response to phototherapy.
5) To evaluate the impact of gloves and masks use on EBF and CH.
6) To assess the effect of hand hygiene strategies on EBF and CH, on the microbial load and on users' tolerability and acceptability.
7) To explore the available scientific evidence regarding skin adverse events associated with PPE.

4. PARTICIPANTS AND METHODS

4. PARTICIPANTS AND METHODS

4.1. Objectives 1-6

4.1.1. Design

Objective 1 and 2. A cross-sectional study was designed including healthy individuals, patient with psoriasis and atopic dermatitis (AD).

Objective 3 and 4. A prospective observational study was carried out on patients with psoriasis and healthy individuals.

Objective 5. A cross-sectional study including healthy healthcare workers (HCWs) was designed.

Objective 6. An observer-blinded randomised comparative study following CONSORT guidelines including HCWs was conducted.

4.1.2. Setting

This research was conducted between April 2019 and January 2021 in the Dermatology Department of the Hospital Universitario Virgen de las Nieves in Granada, Spain, and in the Dermatology Department of Granada University, Granada, Spain.

4.1.3. Participants and inclusion / exclusion criteria

Objective 1. Participants were student that attended the Dermatology Department of Granada University, Granada, Spain. Inclusion criteria: 1) age between 20-40 years, 2) absence of concomitant inflammatory skin disease, 3) absence of any medication. Exclusion criteria: 1) having applicated a topical product 12 hours before measurements, 2) not signing the informed consent form.

Objective 2-4. Participants were healthy individuals, patients with psoriasis and AD that attended the Dermatology Department of the Hospital Universitario Virgen de las Nieves in Granada, Spain.

- Inclusion Criteria:
  - ✓ Male or female.
  - ✓ Age between 18-65.
  - ✓ Healthy volunteers were people who attended the Dermatology Service for common conditions, such as melanocytic nevi or seborrheic keratoses, and did not have previous personal or family history of any inflammatory skin disease.
  - ✓ Patients with psoriasis were patients with an established clinical diagnosis of active moderate-to-severe plaque-type psoriasis (minimum Psoriasis Area and Severity Index (PASI) score of 4)[25] and had a psoriasis plaque on their elbows. Moreover, for resolving objective 3 and 4, these patients had to be selected by clinical criteria to attend phototherapy treatment with UVB narrowband (NB-UVB)[68].
  - ✓ Patients with AD were patients with established clinical diagnosis of mild to severe AD[108] and had an eczematous lesion on their volar forearms.
- Exclusion Criteria:
  - ✓ Psoriasis patients currently having non-plaque forms of psoriasis, e.g., erythrodermic, guttate, or pustular psoriasis, or a drug-induced form of psoriasis.
  - ✓ Healthy volunteers who had previous personal history of any inflammatory skin disease.
  - ✓ Having applicated a topical product 12 hours before measurements

- ✓ Clinical infection on the measured area.
- ✓ History of allergy, cancer or an immunocompromised disease.
- ✓ Not signing the informed consent form.

Objective 5-6. Participants were healthy HCWs working at the Dermatology Department of the Hospital Universitario Virgen de las Nieves in Granada, Spain.

- Inclusion criteria:
  - ✓ Male or female.
  - ✓ Age between 18-65.
  - ✓ To resolve the objective 5, participants should also be wearing for at least two hours nitrile gloves and a mask (a surgical mask or a filtering respirator mask coded filtering facepiece 2 (FFP2))
- Exclusion criteria:
  - ✓ Having previous personal history of any inflammatory skin disease (psoriasis, atopic dermatitis, hidradenitis suppurativa, acne or seborrheic dermatitis).
  - ✓ Having applicated a topical product 12 hours before measurements.
  - ✓ Clinical infection on the measured area.
  - ✓ History of allergy, cancer or an immunocompromised disease.
  - ✓ Not signing the informed consent form.

4.1.4. Specific characteristics for longitudinal studies: randomization, follow-up and exposure (only for objective 3,4 and 6)

Objective 3 and 4. Patients with psoriasis (exposed subjects) were evaluated before and after receiving the first phototherapy session and before and after the 15th phototherapy session. The starting dose for NB-UVB therapy and the dosage schedule

were based on skin phototype following the current guidelines[71]. The frequency was two or three times a week depending on the patient's availability. Non-exposed subjects were evaluated twice, on the same days as their exposed pair.

Objective 6. Participants were randomized in a 1:1:1 ratio (computerized randomization) to use for their hand hygiene between every patient, either washing with water and soap, applying and rubbing their hands with an alcohol alcohol-based hand sanitizer (ABHS) or using disinfectant wipes for 20 seconds at least. Intervention assignments were allocated by the study coordinator (SAS). The evaluator (TMV) was blinded to the assignments. After randomization, baseline measurements were taken at around 08:00 a.m. (before participants had started their work shift) and final measurements were recorded after a full working day (around 03:00 p.m.).

4.1.5. Variables

Epidermal barrier function and cutaneous homeostasis variables

Transepidermal water loss (TEWL) was measured in $g \cdot m^{-2} \cdot h^{-1}$ using Tewameter® TM 300, stratum corneum hydration (SCH) in arbitrary units (AU) using Corneometer® CM 825, pH using Skin-pH-Meter® PH 905, erythema and melanin index in AU using Mexameter® MX 18, skin temperature in °C using Skin-Thermometer ST 500, and elasticity, assessed by R2 value, in % using Cutometer® Dual MPA 580. All these sensors were connected to a Multi Probe Adapter (MPA, Courage + Khazaka electronic GmbH, Mirocaya, Bilbao, Spain). Elasticity parameters were measured four times and the other variables were measured ten times, using their average for analysis.

Total antioxidant capacity (TAC), both fast antioxidants (Q1), that have a lower oxidation potential, and slow antioxidants (Q2), were measured using eBQC electrochemical method (Bioquochem S.L. (BQCkit), Asturias, Spain), and expressed in

micro-coulombs. Briefly, a conductive hydrogel, designed for direct measurement of the antioxidant capacity, is stuck to the skin surface and maintained in contact for five minutes and then peeled off and placed on the measurement area of the e-BQC strips[109].

All of these measurements were taken following the same order, in the same room at a mean room temperature of 23 ± 1 °C and ambient air humidity of 45% (range, 40–50%). All participants underwent an adaptation period of at least 20 min before the measurements were taken.

Measurement location:

- Objective 1. EBF and CH parameters were evaluated at three body sites: cheek, volar forearm, and palm.
- Objective 2-4. EBF and CH parameters were measured at two anatomical locations in healthy individuals (the elbow and the volar forearm), at two body sites in psoriatic patients (on a psoriatic plaque and on an uninvolved skin area at the elbow) and at two body sites in AD patients (on an eczematous lesion and on an uninvolved skin area at volar forearm).
- Objective 5. Measurements were taken at four anatomic areas: at the distal right volar forearm covered by the glove and in another area 2 cm far from not covered; and at the right cheek covered by the mask and in another area 2 cm far from not covered.
- Objective 6. EBF and CH parameters were measured on the dominant palm

Sociodemographic data

Sex, age, comorbidities, smoking and alcohol habit, previous history of inflammatory disorders, skincare habits (moisturizing or suntan lotion use), professional group (doctor, nurse, miscellaneous) and work-related activities likely to cause skin

damage were recorded by a clinical interview. The phototype was assessed by a dermatologist using Fitzpatrick grading[110].

Clinical data *(*objective 2-4)

Psoriasis severity was assessed by the psoriasis area and severity index (PASI). AD severity was assessed by SCORing Atopic Dermatitis (SCORAD). The body surface area (BSA) was also recorded. All these scales were calculated by a dermatologist after physical exploration. The dermatology life quality index (DLQI) was also collected using a self-reported questionary.

Age at diagnosis, psoriasis and AD family history, previous treatments, and disease duration were gathered by means of clinical interview. Information about the previous number of phototherapy sessions, session dose and total cumulative dose was also collected.

Microbiological evaluation (objective 6)

Microbiological samples were obtained by direct application of the 4 fingertips in a Petri dish with culture medium, either for bacteria (right hand) or fungi (left hand). For bacteria, smears were placed in Trypcase Soy 3P Irradiated Trypcase Soy Agar (TSA3), a non-selective method, between 28-32ºC for 72 hours and for fungi in Sabouraud Dextrose 3PTM Agar with irradiated neutralisers (SN3P) between 20-25ºC for 96 hours. The total number of CFU per plate were counted after 72 or 96 hours of incubation, and differences between baseline and end of the working day were used to assess the microbial load.

Tolerability and acceptability (objective 6)

Tolerability and acceptability of the hand hygiene procedures were assessed after the workday using the protocol proposed by the WHO that allowed both objective evaluation by an observer and subjective evaluation by the participants[111]. Briefly, on a seven-point Likert scale, participants assessed the product's: colour (unpleasant-pleasant), smell (unpleasant-pleasant), texture (sticky-non-sticky), irritation (very irritating-not irritating), drying effect (very much-not at all), ease of use (very difficult-very easy), speed of drying (very slow-very fast), application (unpleasant-pleasant), and overall evaluation (dissatisfied-satisfied). Likewise, on a seven-point scale, participants rated the skin condition of their hands: appearance (abnormal-normal); intactness (abnormal-normal); moisture content (abnormal-normal); sensation (abnormal-normal); overall integrity of the skin (very altered-not altered). Skin condition was also assessed by the dermatologist evaluator, as follows: redness (0–3, no redness-very bright with oedema), scaling (0–3, no scaling-very pronounced desquamation), fissures (0–3, no fissure-extensive cracks with bleeding or seeping), visual scoring of skin scale (0, no observable scale or irritation of any kind; 1, occasional scale that is not necessarily uniformly distributed; 2, dry skin and/or redness; 3, very dry skin with whitish appearance, rough to touch, and/or redness, but without fissures; 4, cracked skin surface but without bleeding/seeping; 5, extensive cracking of skin surface with bleeding/seeping). All evaluations were carried out at baseline and after the working day using the hand-hygiene product.

4.1.6. Statistical analysis

In a descriptive analysis, continuous variables were expressed as means ± standard deviation (SD) and qualitative variables as absolute and relative frequency distributions.

The Shapiro-Wilk test was used to check the normality of data distribution and Levene's test was used to check the homogeneity of variance.

The chi-square test or Fisher's exact test, as appropriate, were used for qualitative data. The Student's t-test for paired samples or the Wilcoxon test, as appropriate, was used to compare EBF and CH parameters in the same individual- cheek vs. volar forearm vs. palm (objective 1); uninvolved psoriatic skin vs. psoriatic plaques and uninvolved atopic skin vs. eczematous lesions (objective 2); before vs. after phototherapy (objective 3 and 4); covered vs non-covered areas (objective 5); before and after hand hygiene procedure (objective 6). The Student's t-test for independent samples or the or the Mann-Whitney test, as appropriate, was used for comparisons of continuous variables between participants. One-way analysis of variance (ANOVA), post-hoc Bonferroni correction, was used to compare quantitative variables between more than two groups (different hand hygiene procedure). When necessary, adjusted regression models were constructed to compare continuous data between participants. The effect of phototherapy by time (before, after) and skin involvement (uninvolved skin, psoriatic plaque), adjusted by total cumulative dose, was analysed using repeated measures ANOVA (RM-ANOVA) with post hoc Bonferroni correction.

The Pearson correlation coefficient was calculated to test for possible correlations between continuous variables. Linear regression models were also constructed for predictive analysis. PASI and SCORAD respectively, were analyzed to establish cut-off points using receiver operating characteristic (ROC) curves for the values of temperature, TEWL, and SCH. The results of ROC curves were used to calculate sensitivity and specificity for various criteria together. To predict PASI improvement after fifteen phototherapy sessions, cut-off points were generated using ROC curves for the changes of erythema and SCH after the first phototherapy session. To produce these ROC curves,

the sensitivities and specificities for changes of erythema and SCH values after the first phototherapy that predict an improvement in PASI of ≥3 after the fifteenth phototherapy session were tabulated and the graphical ROC curve was generated by plotting true positive rate (sensitivity) on the y-axis against false positive rate (1-specificity) on the x-axis for the various values tabulated. To select the optimal cut-off point, the point nearest to the top-left-most corner of the ROC curve was chosen, giving equal weight to the importance of sensitivity and specificity.

A p-value of <0.05 was considered statistically significant. Statistical Analyses were performed using the SPSS package (SPSS for Windows, Version 24.0 Chicago: SPSS Inc.).

4.1.7. Ethics

All participants included in the research were volunteers. The nature of the study was explained to all the participants, who agreed to participate and signed the informed consent form. All measurements employed were non-invasive, so participants did not suffer any damage due to the inclusion in the study. Participant's data was kept confidential. This doctoral thesis was conducted according to the guidelines of the Declaration of Helsinki, and its protocol was approved by the Ethics Committee of Hospital Universitario Virgen de las Nieves, Granada, Spain (protocol code HC01 / 0442-N-20).

4.2. Objective 7

A systematic review and meta-analysis were conducted following PRISMA guidelines. A literature search was performed using Medline, Scopus and Embase databases from conception to 21st January 2021. The following search algorithm was used: ((PERSONAL PROTECTIVE EQUIPMENT) OR GLOVES OR MASK OR FACEMASK OR (RESPIRATORY EQUIPMENT) OR (ALCOHOL-BASED HAND RUB) OR SOAP OR ALCOHOL) AND (SKIN OR CUTANEOUS OR DERMATOLOGY OR (SKIN REACTION) OR (SKIN ADVERSE EVENTS)) AND (COVID-19 OR (CORONAVIRUS DISEASE 2019)).

The search was limited to: (i) human data, (ii) *in vivo* studies, (iii) skin adverse events related to PPE, (iv) articles written in English. All types of epidemiological studies (clinical trials, cohort studies, case-control studies and cross-sectional studies) regarding skin adverse events related to PPE were included and analyzed. Reviews, guidelines, protocols, case series, case reports and conference abstracts were excluded.

Two researchers (TMV and CCB) independently reviewed the titles and abstracts of the articles obtained in the first search to assess relevant studies. The full texts of all articles meeting the inclusion criteria were reviewed, and their bibliographic references were checked for additional sources. The articles considered relevant by both researchers were included in the analysis. Disagreements about inclusion or exclusion of articles were subjected to discussion until a consensus was reached. If not reached, resolution was achieved by discussion with a third researcher (AMLo).

The variables assessed were study design, rate and type of skin adverse events related to PPE, risk factors for developing skin manifestations, number of participants, author, country, age, sex, assessment tools, anatomical regions damaged, kind of preventive measures.

The overall prevalence of skin cutaneous events related to PPE was calculated by a random effect meta-analysis weighted by the study sample size. Forest plots were constructed to summarize the prevalence estimates and their 95% CIs. These figures present measures of heterogeneity across studies (Cochrane Q statistic, noted the I2 statistic). Microsoft Excel version 2016, Redmond, Washington, The USA. was used to run this data[112].

5. RESULTS

5.1. Skin barrier function in healthy individuals in different anatomical regions.

Skin is one of the most important organs of the body as it protects us against external stressor and maintain a suitable environment for life. Knowing skin properties and characteristics in healthy individuals at each anatomic region could help clinicians to better understand how skin barrier is disrupted in cutaneous diseases.

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CUTANEOUS HOMEOSTASIS AND EPIDERMAL BARRIER FUNCTION IN A YOUNG HEALTHY CAUCASIAN POPULATION

Abstract

Background. Transepidermal water loss (TEWL), stratum corneum hydration (SCH), and skin surface pH are indicators of skin barrier integrity. There is scant evidence on normative data for cutaneous homeostasis parameters in healthy individuals.

Material and methods. A cross-sectional study was conducted in healthy volunteers aged 20 to 40 years. TEWL, SCH, pH, erythema, and melanin were measured on cheek, volar forearm, and palm.

Results. The study included 87 healthy volunteers (34 males). The lowest TEWL was on the volar forearm (9.69±2.94 $g{\cdot}m^{-2}{\cdot}h^{-1}$) and the highest on palm (49.32±14.55 $g{\cdot}m^{-2}{\cdot}h^{-1}$). Erythema was higher on cheek than on palm or volar forearm (413.51 AU vs. 259.98 AU vs. 252.02 AU). The lowest melanin index was on palm (92.72±41.70 AU). pH levels were similar among locations. The erythema index was significantly higher in males *versus* females at all locations. Linear regression analysis adjusted for age and SCH revealed an increase of 0.45±0.18 $g{\cdot}m^{-2}{\cdot}h^{-1}$ TEWL on cheek and of 0.32±0.10 $g{\cdot}m^{-2}{\cdot}h^{-1}$ TEWL on forearm for each one-year increase in age.

Conclusion. We contribute normative data for individuals aged 20-40 years across three anatomical locations and propose a predictive model for TEWL on cheek and forearm as a function of age and SCH.

Keywords: skin barrier function, cutaneous homeostasis, biophysical parameters, anatomical sites, gender, age

1. Introduction

Skin is the largest organ of the human body and accomplishes multiple defensive and regulatory functions[1]. The barrier function of skin resides in the epidermis, especially in the stratum corneum[2]. This epidermal barrier maintains cutaneous homeostasis and protects the body against numerous external stressors, including chemical, environmental, and physical stress, such as ultraviolet (UV) radiation[3,4]. The regulation of cutaneous homeostasis remains poorly understood, and knowledge of the patterns of homeostatic parameters that regulate healthy skin is important to support clinical decision-making in patients with cutaneous diseases[5].

Transepidermal water and retained water make up the water content of skin. Transepidermal water from circulating blood migrates through the dermis into the epidermis, eventually evaporating on the skin surface, and it plays an essential role in the supply of nutrients to the epidermis, which is devoid of blood vessels. Retained water in the stratum corneum is localized within corneocytes between lipid bilayers, and it maintains the mechanical properties of the cornified layer, increases the plasticity of the epidermis, and enhances the hydrophilic properties of keratin[6]. Transepidermal water loss (TEWL), i.e., the diffusion of condensed water through the stratum corneum, is a key characteristic of the skin barrier[7]. Greater TEWL is often associated with skin barrier impairments and has been observed in some skin diseases, including atopic dermatitis and psoriasis[8]. Stratum corneum hydration (SCH), i.e., the water content of the stratum corneum, is another important parameter, and a lower value is frequently associated with skin barrier dysfunction. In addition, an elevated TEWL value in a disturbed skin barrier is frequently correlated with a reduced SCH value[9]. The skin surface pH is also considered in the assessment of epidermal functions, as acidic pH of the stratum corneum is considered to present an antimicrobial barrier preventing colonization[10]. Thus,

neutralization of the stratum corneum produces abnormalities in its function, with aberrant permeability barrier homeostasis and decreased stratum corneum integrity and cohesion[11]. Conversely, barrier disruption and injury to the stratum corneum was found to increase its pH from baseline levels of 5.0–5.5 up to 7.0[12]. Acidic pH is essential to preserve metabolic and enzymatic activity, maintain the structure of lipids, and defend against microorganisms[13].

Melanin and erythema are useful to assess the integrity of the epidermal barrier, which also has a photoprotective function. Skin pigmentation and light absorption by chromophores (urocanic acid and melanin) protect against UV light radiation. Melanin is formed in melanocytic melanosomes and is transferred to the keratinocytes, migrating with the desquamation cycle. There is a higher density of melanocytes on the face and genitals. However, differences in pigmentation among anatomic areas are not related to their density but rather to the proportion of mature melanosomes and their distribution and activity, which is influenced by endocrine factors, radiation, and the pH[14]. Erythema results from the exposure of skin to irritants such as chemical substances, cleansers, allergens, or UV, among others[15]. An integrated and a multiparametric approach is needed to evaluate the full range of biophysical functions of the epidermal barrier[16].

Despite their importance for the accurate evaluation and treatment of skin conditions, few normative data are available on cutaneous homeostasis parameters in healthy individuals[8,17,18]. Therefore, the objectives of this study were: 1) to develop normative data for skin erythema, melanin, pH, SCH, and TEWL; 2) to identify differences in these variables among different anatomic locations; and 3) to explore factors that may modify these values.

2. Material and methods

Design and study population

A cross-sectional study was undertaken, recruiting participants from among students at the School of Medicine of Granada University (Spain) from March through April 2019. Inclusion criteria were: age between 20-40 years, absence of concomitant disease, and no receipt of medication. No application of topical products was allowed during the 12 hours before measurements.

Study variables

Main variables of interest

Five biophysical parameters were measured at three locations: cheek, volar forearm, and palm. All participants underwent an adaptation period of at least 20 minutes before the measurements were taken. All these measurements were taken at identical sites following the same order: SCH (in arbitrary units [AU]), using a CM 825Corneometer®; TEWL ($g \cdot m^{-2} \cdot h^{-1}$), using a TM 300 Tewameter®; pH value, using a 905 skin pH meter®; and erythema and melanin indices (in AU), using an MX 18 Mexameter®. These epidermal barrier function parameters were measured with a Multi Probe Adapter (MPA, Courage + Khazaka electronic GmbH, Germany). All variables were measured ten times, using the average value for the analysis. All measurements were taken in the same room at a mean room temperature of 23±1ºC and ambient air humidity of 45% (range, 40–50%).

Other variables of interest

Data were gathered in a clinical interview on the participants' sex, age, smoking/alcohol habits, family history of cutaneous disease, personal history of atopy or other cutaneous disease, skincare habits (moisturizing or suntan lotion use), and hours of

sun exposure during the previous week. Two age groups were considered in the analysis: ≤23 years and > 23 years.

Statistical analysis

In a descriptive analysis, continuous variables were expressed as means ± standard deviation (SD) and qualitative variables as absolute and relative frequency distributions. The Student's t-test for independent samples or Student's t-test for paired samples, as appropriate, was used for comparisons of continuous variables. The chi-square test or Fisher's exact test, as appropriate, were used for qualitative data. The Pearson correlation coefficient was calculated to test for possible correlations between continuous variables. Linear regression models were constructed for predictive analysis.

Statistical significance was defined by a two-tailed $p<0.05$. SPSS version 24.0 (SPSS Inc, Chicago, IL) was used for statistical analyses.

Ethics

All participants signed their informed consent to participation in the study, which was approved by the ethics committee of Granada University. All measurements were non-invasive, and the confidentiality of participant data was strictly preserved.

3. Results

The study included 87 healthy individuals (34 men and 53 women) with a mean age of 22.72 (3.06 SD) years. Demographic characteristics of the participants are displayed in Table 1.

Table 2 exhibits the difference in parameters among the anatomic locations tested. The lowest TEWL was on the volar forearm (9.69 (2.94 SD) $g \cdot m^{-2} \cdot h^{-1}$) and the highest on the palm (49.32 (14.55 SD) $g \cdot m^{-2} \cdot h^{-1}$). The SCH value was lowest on the volar forearm (43.46 (10.74 SD) AU), and lower on the cheek (52.23 (13.18 SD) AU) than on the palm (60.06 (22.88 SD) AU), p<0.001. Erythema was higher on the cheek than on the palm or volar forearm (413.51 (78.06 SD) AU vs. 259.98 (60.64 SD) AU vs. 252.02 (50.59 SD) AU), and the lowest melanin index was on the palm (92.72 AU (41.70 SD). pH was lower on the palm than on the cheek and the volar forearm (5.58 (0.37 SD) vs 5.72 (0.29 SD) vs 5.74 (0.31 SD)).

TEWL values on the cheek (14.46 (3.70 SD) $g \cdot m^{-2} \cdot h^{-1}$ vs. 16.91 (7.80 SD) $g \cdot m^{-2} \cdot h^{-1}$, p=0.049) and volar forearm (9.23 (4.02 SD) $g \cdot m^{-2} \cdot h^{-1}$ vs. 10.82 (4.02 SD) $g \cdot m^{-2} \cdot h^{-1}$, p=0.022) were higher in the over-23-year-olds (Table 3). Results of linear regression analysis adjusted for age and SCH showed that each one-year increase in age was associated with an increase in TEWL of 0.45 $g \cdot m^{-2} \cdot h^{-1}$ (SD 0.18) on the cheek and 0.32 (SD 0.10) $g \cdot m^{-2} \cdot h^{-1}$ on the palm (table 5).

Comparison between the sexes (table 4) revealed higher melanin levels on the cheek of males (p=0.04) and higher erythema values at all locations in males than in females. Linear regression analysis showed that, in comparison to the females, erythema values for males were 81.56 (SD 14.81) AU higher on the cheek, 27.66 (SD 9.34) AU higher on the volar forearm, and 35.91 (SD 12.83) AU higher on the palm.

A positive correlation was observed between age and TEWL values on cheek (r=0.272, p=0.011) and volar forearm (r=0.349, p=0.001). Figure 1a-g depicts correlations between biophysical parameters at each location. On the cheek we found a negative correlation between TEWL and SCH values (r=-0.259, p=0.015, Figure 1a), a positive correlation between melanin and erythema (r=0.229; p=0.033, Figure 1b) and a negative correlation between pH and erythema (r=-0.224, p=0,037, Figure 1c). On the volar forearm, the sole correlation was between SCH and erythema values (r=0.48, p<0.001, Figure 1d). On the palm we found a negative correlation between melanin and TEWL (r=-0.211, p=0.05, Figure 1e), between pH and TEWL (r=-0.52, p<0.001, Figure 1f) and between pH and SCH (r=-0.406, p<0.001, Figure 1g).

4. Discussion

The skin barrier plays a crucial protective role against water loss and penetration of pathogens from the external environment. This study of healthy individuals revealed differences in TEWL, SCH, erythema, melanin and pH among three anatomic sites (cheek, volar forearm and palm). This fact might be explained by the variations in the amount of sebaceous glands, lipids and natural moisturizing factor, in the size of corneocytes, in exogenous compounds on skin surface and occlusion[19-21].

TEWL is a key characteristic of skin barrier function and may have predictive value for the development of atopic dermatitis and psoriasis[22]. However, no consensus has been reached on the definition of "normal" TEWL. According to this study, TEWL values in healthy individuals widely differ among anatomic locations, which has been attributed to differences in the number of corneocyte cell layers, and in the size and turnover rates of corneocytes[20]. TEWL values were higher on the cheek than on the volar forearm, consistent with previous reports[21,23]. This might be related to the smaller corneocytes, fewer cell layers, faster cell turnover, and greater vascularization in facial areas[19,24]. The quantity and composition of intercellular lipid bilayers might also affect inside-out water diffusion, and the greater density of sebaceous glands on the face than on the forearm would also be related to the higher TEWL on facial areas[25]. The highest TEWL value was observed on the palms, attributable to its thicker stratum corneum, higher exposure to friction and damage, and greater density of eccrine sweat glands[26]. Our findings are in agreement with the results of a recent systematic review, which found the highest TEWL values to be on the palm, followed by the face and forearm[8].

The lowest SCH value was on the volar forearm. The higher SCH on the cheek reflects the thinner stratum corneum of facial skin, which has smaller corneocyte layers in comparison to limbs, offering an adequately hydrated skin surface but a relatively poor

barrier function[19]. Higher SCH values on the cheek than on the forearm may be influenced by the greater ease of measuring water content in the thinner skin of the face, given that hydration gradually increases at deeper layers[21]. The highest SCH values were found on the palm, which may be explained by its higher density of eccrine sweat glands[26].

Both an increase in TEWL values and a decrease in SCH values are associated with skin disease[7], nevertheless, to the best of our knowledge, the correlation between these parameters have been only showed on the cheek[9], in agreement with our report. This could be due to regional anatomical differences in sweat gland activity, skin temperature, thickness, and corneocyte size and maturity[27].

Nedelec et al[18] described melanin and erythema parameters as determinants of skin health. We found higher levels of erythema and melanin on the cheek than on the forearm and the palm, which may be due to the increased blood circulation in this sun-exposed area[26,28]. As expected, the lowest melanin value was on the palm of the hand, which contains low melanocytes or melanin[29]. Our finding of virtually no change in pH values among locations is in agreement with previous studies[10,26].

The negative correlation found between melanin and pH on the cheek may be due to the more acidic melanocytic dendrites on type IV–V *versus* type I-II skin. These transfer more melanosomes to the stratum corneum, and melanosome secretion contributes to the more acidic pH of type IV–V skin[30], providing darkly-pigmented skin with a superior permeability barrier function[31].

Adjusted linear regression analysis revealed that a one-year increase in age was associated with an increase in TEWL of 0.45 $g{\cdot}m^{-2}{\cdot}h^{-1}$ on the cheek and 0.32 $g{\cdot}m^{-2}{\cdot}h^{-1}$ on the volar forearm. The relationship between age and TEWL has been controversial[8,32-34]. Although the rate of intrinsic skin aging does not differ among body areas[32], some locations are more exposed to UV radiation, cold dry weather, and pollution, among other

extrinsic factors. Hence, the relationship between age and TEWL may vary among anatomic sites and different age ranges. We propose, to our best knowledge for the first time, a model to predict TEWL on the volar forearm and on the cheek as a function of the SCH value and age within an age range of 20 to 40 years. This fact may help clinicians to make more emphasis on skin care recommendations for patients who are more likely to suffer epidermal damage with age.

In comparison to the females, the males had higher erythema values at all three locations and a higher melanin index on the cheek, similar to previously published findings and attributed to the greater exposure of males to outdoor activities[18,23]. Nevertheless, this difference might have been influenced by a volunteer bias, given that the majority of participants were female. Further limitations of our study include the relatively small sample size and the cross-sectional design.

In conclusion, this study of individuals with healthy skin describes differences in homeostasis among anatomic locations (cheek, volar forearm, and palm) and indicates the influence of sex and age on TEWL, SCH, melanin, erythema and pH values. These findings are useful for comparisons with pathological skin features. We propose a model to predict TEWL as a function of SCH value and age. The development of standardized biophysical profiles of healthy human skin and increased knowledge of modifying factors will enhance our understanding of cutaneous diseases and improve clinical decision-making.

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7. Tables

Table 1. Characteristics of the sample.

	Study population (n=87)	Age<23 (n=62)	Age>=23 (n=25)
Age	22.72 (3.06 SD)	62 (71.26%)	25 (28.74%)
Sex **- Male** **- Female**	 34 (39.1%) 53 (60.9%)	 25 (40.3%) 37 (59.7%)	 16 (64.0%) 9 (36.0%)
Smoking habit (yes)	10 (11.5%)	7 (11.3%)	3 (12.0%)
Alcoholic habit (yes)	54 (62.1%)	39 (62.9%)	15 (60%)
Solar exposure (hours)	7.86 (5.79 SD)	7.87 (5.88 SD)	7.88 (5.87SD)
Family history of atopy	25 (28.7%)	17 (27.4%)	8 (32.0%)
Skincare **- Moisturizing use (yes)** **- Sun lotion use (yes)**	 26 (29.9%) 7 (8.0%)	 19 (30.6%) 4 (6.5%)	 7 (28.0%) 3 (12.0%)

SD, standard deviation

Table 2. Biophysical skin parameters by anatomical location in the study population.

	Study population (n=87)					
	Cheek	**Volar forearm**	**Palm**	p*	p**	p***
TEWL ($g \cdot m^{-2} \cdot h^{-1}$)	15.16 (5.28 SD)	9.69 (2.94 SD)	49.32 (14.55 SD)	<0.001	<0.001	<0.001
SCH (AU)	52.23 (13.18 SD)	43.46 (10.74 SD)	60.06 (22.88 SD)	<0.001	<0.001	<0.001
Erythema (AU)	413.51 (78.06 SD)	252.02 (50.29 SD)	259.98 (60.64 SD)	<0.001	0.181	<0.001
Melanin (AU)	147.63 (33.23 SD)	151.07 (36.30 SD)	92.72 (41.70 SD)	0.412	<0.001	<0.001
pH	5.72 (0.29 SD)	5.74 (0.31 SD)	5.58 (0.37 SD)	0.492	<0.001	<0.001

AU, arbitrary units; SD, standard deviation; SCH, stratum corneum hydration; TEWL, transepidermal water loss.

*p value after using Student T test for paired samples when comparing the values of the corresponding skin parameter between face and arm

** p value after using Student T test for paired samples when comparing the values of the corresponding skin parameter between face and palm

*** p value after using Student T test for paired samples when comparing the values of the corresponding skin parameter between face and palm

Table 3. Biophysical skin parameters stratified by age.

	Cheek			Volar forearm			Palm		
	Age<23 (n=62)	**Age>=23 (n=25)**	**p-value***	**Age<23 (n=62)**	**Age>=23 (n=25)**	**p-value***	**Age<23 (n=62)**	**Age>=23 (n=25)**	**p-value***
TEWL ($g \cdot m^{-2} \cdot h^{-1}$)	14.46 (3.70 SD)	16.91 (7.8 SD)	0.049*	9.23 (4.02 SD)	10.82 (4.02 SD)	0.022*	49.85 (15.48 SD)	48.03 (12.11 SD)	0.6
SCH (AU)	51.80 (13.53 SD)	53.30 (12.47 SD)	0.634	43.08 (10.32 SD)	44.37 (11.90 SD)	0.617	61.94 (22.43 SD)	55.40 (23.80 SD)	0.230
Erythema (AU)	415.83 (75.21 SD)	407.76 (86.08 SD)	0.665	257.80 (48.48 SD)	237.71 (52.81 SD)	0.092	264.61 (60.22 SD)	248.51 (61.38 SD)	0.265
Melanin (AU)	146.31 (32.93 SD)	150.90 (34.42 SD)	0.563	153.98 (37.74 SD)	143.85 (32.03 SD)	0.572	92.76 (37.90 SD)	92.62 (50.80 SD)	0.241
pH	5.72 (0.91 SD)	5.74 (0.31 SD)	0.778	5.74 (0.31 SD)	5.76 (0.34 SD)	0.791	5.54 (0.35 SD)	5.66 (0.41 SD)	0.176

AU, arbitrary units; SD, standard deviation; SCH, stratum corneum hydration; TEWL, transepidermal water loss.

*p value after using Student T test for independent samples

Table 4. Biophysical skin parameters stratified by gender.

	Cheek			Volar foream			Palm		
	Male (n=34)	**Female (n=53)**	**p-value***	**Male (n=34)**	**Female (n=53)**	**p-value***	**Male (n=34)**	**Female (n=53)**	**p-value***
TEWL ($g \cdot m^{-2} \cdot h^{-1}$)	9.06 (6.35 SD)	7.09 (5.31 SD)	0.154	10.21 (3.77 SD)	9.35 (2.23 SD)	0.223	49.84 (12.82 SD)	48.99 (15.66 SD)	0.792
SCH (AU)	49.62 (13.33 SD)	53.90 (12.93 SD)	0.141	43.38 (11.21 SD)	43.51 (10.54 SD)	0.958	61.88 (21.16 SD)	58.90 (24.05 SD)	0.556
Erythema (AU)	463.20 (72.66 SD)	381.64 (63.87 SD)	<0.001*	270.17 (48.01 SD)	240.39 (48.65 SD)	0.006*	281.86 (62.23 SD)	245.95 (55.79 SD)	0.006*
Melanin (AU)	156.75 (32.00 SD)	141.79 (32.97 SD)	0.04*	153.06 (36.22 SD)	149.79 (36.64 SD)	0.684	95.46 (47.84 SD)	90.96 (37.62 SD)	0.626
pH	5.68 (0.33 SD)	5.75 (0.27 SD)	0.295	5.71 (0.23 SD)	5.77 (0.35 SD)	0.385	5.55 (0.31 SD)	5.59 (0.40 SD)	0.602

AU, arbitrary units; SD, standard deviation; SCH, stratum corneum hydration; TEWL, transepidermal water loss.

*p value after using Student T test for independent samples

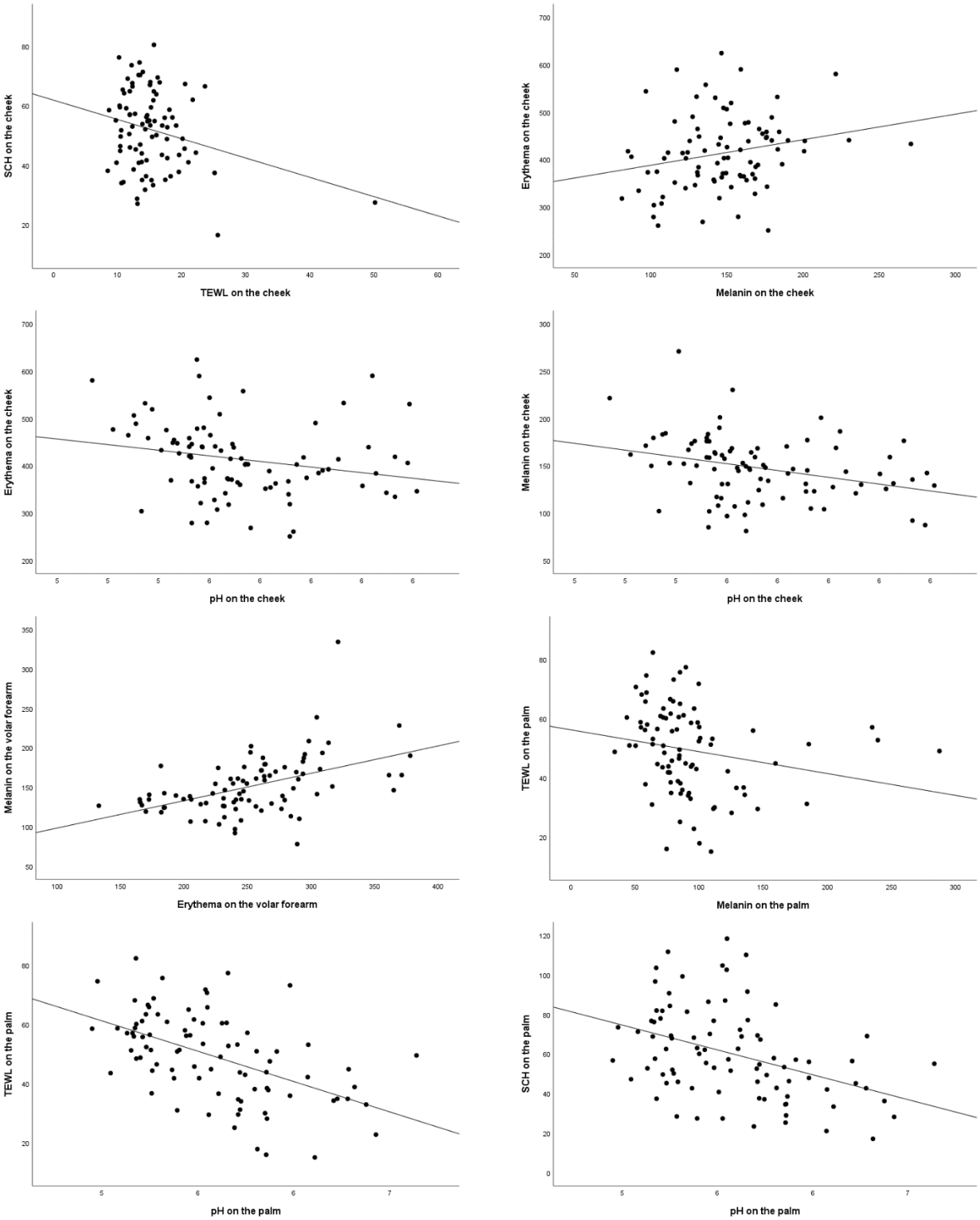
Table 5. Linear regression model to predict TEWL on the face and on the arm from age.

Dependent variable	Independent variables	Coefficient	Standard Deviation	p*
TEWL on the cheek	Constant	10.012	4.557	
	Age	0.462	0.175	0.010
	SCH on the cheek	-0.102	0.041	0.013
TEWL on the volar forearm	Constant	0.541	2.41	
	Age	0.317	0.097	0.002
	SCH on the arm	0.045	0.028	0.111
TEWL on the palm	Constant	25.12	9.891	
	Age	-0.008	0.400	0.984
	SCH on the palm	0.406	0.053	<0.001

SCH, stratum corneum hydration; TEWL, transepidermal water loss.

*p value after using a linear regression analysis to predict TEWL on the face an on the arm after adjusting by the age and SCH on the face and on the arm respectively.

Figure 1. Correlation between biophysical skin parameters at the same skin area. a) TEWL and SCH on the cheek (r=-0.259, p=0.015), b) Melanin and erythema on the cheek (r=0.229; p=0.033), c) pH and erythema on the cheek (r=-0.224, p=0,037), d) Erythema an melanin on the volar forearm (r=0.48, p<0.001), e) Melanin and TEWL on the palm (r=-0.211, p=0.05), f) pH and TEWL on the palm (r=-0.52, p<0.001), g) pH and SCH on the palm (r=-0.406, p<0.001).



5.2. Skin barrier function in patients with psoriasis and atopic dermatitis.

There is a continuous increase in the number of available therapies for psoriasis and atopic dermatitis. Nevertheless, it is not known the most effective treatment for each patient and, currently, there are no tool to assess objectively disease severity and clinical outcomes. Skin barrier dysfunction in patients with psoriasis and atopic dermatitis severity could help clinicians to solve these problems.

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Article

Skin Barrier Function in Psoriasis and Atopic Dermatitis: Transepidermal Water Loss and Temperature as Useful Tools to Assess Disease Severity

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Abstract: Multiple diagnostic tools are used to evaluate psoriasis and atopic dermatitis (AD) severity, but most of them are based on subjective components. Transepidermal water loss (TEWL) and temperature are skin barrier function parameters that can be objectively measured and could help clinicians to evaluate disease severity accurately. Thus, the aims of this study are: (1) to compare skin barrier function between healthy skin, psoriatic skin and AD skin; and (2) to assess if skin barrier function parameters could predict disease severity. A cross-sectional study was designed, and epidermal barrier function parameters were measured. The study included 314 participants: 157 healthy individuals, 92 psoriatic patients, and 65 atopic dermatitis patients. TEWL was significantly higher, while stratum corneum hydration (SCH) (8.71 vs. 38.43 vs. 44.39 Arbitrary Units (AU)) was lower at psoriatic plaques than at uninvolved psoriatic skin and healthy controls. Patients with both TEWL > 13.85 $g \cdot m^{-2}h^{-1}$ and temperature > 30.85 °C presented a moderate/severe psoriasis (psoriasis area severity index (PASI) ≥ 7), with a specificity of 76.3%. TEWL (28.68 vs. 13.15 vs. 11.60 $g \cdot m^{-2}h^{-1}$) and temperature were significantly higher, while SCH (25.20 vs. 40.95 vs. 50.73 AU) was lower at AD eczematous lesions than uninvolved AD skin and healthy controls. Patients with a temperature > 31.75 °C presented a moderate/severe AD (SCORing Atopic Dermatitis (SCORAD) ≥ 37) with a sensitivity of 81.8%. In conclusion, temperature and TEWL values may help clinicians to determine disease severity and select patients who need intensive treatment.

Keywords: atopic dermatitis; homeostasis; psoriasis; skin barrier; transepidermal water loss

1. Introduction

The skin is the largest organ of the human body, and accomplishes multiple defensive and regulatory functions [1]. The barrier function of skin resides in the epidermis, mainly in the stratum corneum [2]. This epidermal barrier maintains cutaneous homeostasis and protects the body against numerous external stressors [3]. Assessment of epidermal barrier function usually involves measurements of transepidermal water loss (TEWL) [4], stratum corneum hydration (SCH) [5], skin surface pH [6], temperature [7], elasticity [8], melanin [9], and erythema index [10].

Psoriasis and atopic dermatitis (AD) are cutaneous inflammatory diseases resulting from the interaction between environmental and genetic factors that may alter epidermal barrier function [11]. Hyper-proliferation and defective keratinocyte differentiation in psoriasis [12] and decreased filaggrin expression [13] may impair epidermal barrier function. There are scarce reports regarding barrier function characteristics in psoriasis and atopic dermatitis [14,15]. Nevertheless, the assessment of skin homeostasis and epidermal barrier function in these diseases could evaluate qualitative and quantitative skin alterations of lesioned and non-lesioned skin, and help to understand the com-plex and still incomplete etiopathogenesis of these diseases [15].

Moreover, multiple diagnostic tools have been used to evaluate severity in patients with psoriasis and AD [16,17]. The psoriasis area severity index (PASI) is the most widely used scale for assessing psoriasis severity [18]. This score quantifies extent (the percentage of involvement of the four anatomical regions: head, trunk, and upper and lower extremities) and intensity of the psoriatic plaques (evaluating erythema, desquamation, and induration separately for the four anatomical regions) [19]. The SCORing Atopic Dermatitis (SCORAD) is the most common in-dex used to assess AD severity [20]. It consists of the evaluation of the extent of the disorder, the intensity

(composed of six items: erythema, oedema/papules, effect of scratching, oozing/crust formation, lichenification, and dryness) and subjective symptoms (itch, sleeplessness) [21]. In therapeutics and outcome research, it is important to measure psoriasis and AD severity, but all of these scales have a subjective component that could lead to a high intra- and inter-observer variability [22,23]. In that way, the measurement of skin homeostasis and epidermal barrier function in psoriatic and AD patients could help clinicians to assess the disease severity objectively [24].

Thus, the objectives of this study are 1) to compare cutane-ous homeostasis and skin barrier function between healthy skin, psoriatic skin, and AD skin; and 2) to assess if skin homeostasis and skin barrier function could predict disease severity.

2. Materials and Methods

2.1. Design

A cross-sectional study was undertaken to assess skin ho-meostasis differences between healthy skin; involved and unin-volved skin in psoriatic patients; and involved and uninvolved skin in AD patients.

2.2. Study Population

Participants were recruited from October 2019 to February 2020 in the Dermatology Service of the Hospital Universitario Virgen de las Nieves in Granada.

- Inclusion Criteria:
    - Healthy volunteers were people who attended the Derma-tology Service for common conditions, such as melanocytic nevi or seborrheic keratoses, and did not have previous personal or family history of any inflammatory skin disease.
    - Patients with psoriasis were patients with an established clinical diagnosis of mild to severe plaque-type psoriasis [25] and had a psoriasis plaque on their elbows.
    - Patients with AD were patients with established clinical di-agnosis of mild to severe AD [26] and had an eczematous lesion on their volar forearms.
- Exclusion Criteria:
    - Psoriasis patients currently having non-plaque forms of psoriasis, e.g., erythrodermic, guttate, or pustular psoriasis, or a drug-induced form of psoriasis.
    - Healthy volunteers who had previous personal history of any inflammatory skin disease.

- Clinical infection on the measured area.
- History of cancer, including skin cancer.
- Subjects with intense sun exposure during the study.
- Not signing the informed consent form.

2.3. Study Variables

Main variables of interest

Homeostasis parameters related to epidermal barrier func-tion were measured. SCH (in arbitrary units, using Corneometer® CM 825, Mirocaya, Bilbao, Spain), TEWL (in g·m−2h−1, using Tewameter® TM 300, Mirocaya, Bilbao, Spain), pH (using Skin-pH-Meter® PH 905, Mirocaya, Bilbao, Spain), erythema and melanin index (in arbitrary units, using Mexameter® MX 18, Mirocaya, Bilbao, Spain), skin temperature (in °C, using Skin-Thermometer ST 500, Mirocaya, Bilbao, Spain), and elastic-ity parameters (including R2 value, measured in %, using Cut-ometer® Dual MPA 580, Mirocaya, Bilbao, Spain) were measured by a Multi Probe Adapter (MPA, Courage + Khazaka electronic GmbH, Mirocaya, Bilbao, Spain). Elasticity parameters were measured four times and the other variables were measured ten times, using their average for analysis. All of these measurements were taken following the same order. All measurements were taken in the same room at a mean room temperature of 23 ± 1 °C and ambient air humidity of 45% (range, 40–50%). All partici-pants underwent an adaptation period of at least 20 min before the measurements were taken. No systemic or topical treatments was allowed three hours before the measurements were taken.

These variables were measured at two body sites in psoriatic patients (on a psoriatic plaque and on an uninvolved skin area at the elbow), at two body sites in AD patients (on an eczematous lesion and on an uninvolved skin area at volar forearm), at

one body site in healthy volunteers (on the elbow in controls for pso-riasis or on the volar forearm in controls for atopic dermatitis).

Other variables of interest

Data were gathered in a clinical interview on the partici-pants' sex, age, smoking/alcohol habits, family history of cuta-neous disease, personal history of cutaneous disease, skincare habits (moisturizing or suntan lotion use), and hours of sun ex-posure during the previous week. Psoriasis severity was assessed by the PASI and body surface area (BSA), and AD severity was assessed by SCORAD.

2.4. Outcome Measures

Primary outcome measures:

- To assess differences in TEWL, SCH, and temperature values between healthy skin, psoriatic skin, and AD skin.
- To evaluate TEWL and temperature values' ability to dis-criminate mild psoriasis versus moderate/severe psoriasis.
- To evaluate TEWL and temperature values' ability to dis-criminate mild AD versus moderate/severe AD.

Secondary outcome measures:

- To assess differences in other homeostasis parameters be-tween healthy skin, psoriatic skin, and AD skin: erythema, melanin, pH, and elasticity.
- To assess differences in homeostasis parameters between mild psoriasis and moderate/severe psoriasis: TEWL, SCH, temperature, erythema, melanin, pH, and elasticity.

- To assess differences in homeostasis parameters between mild AD and moderate/severe AD: TEWL, SCH, tempera-ture, erythema, melanin, pH, and elasticity.

2.5. Statistical Analysis

In a descriptive analysis, continuous variables were ex-pressed as means ± standard deviations (SDs) and qualitative variables as absolute and relative frequency distributions. The Student's t-test for independent samples or Student's t-test for paired samples, as appropriate, was used for comparisons of continuous variables. The Pearson correlation coefficient was calculated to test for possible correlations between continuous variables. Psoriasis and AD severity, assessed by PASI and SCORAD respectively, were analyzed to establish cut-off points using receiver operating characteristic (ROC) curves for the val-ues of temperature, TEWL, and SCH. The results of ROC curves were used to calculate sensitivity and specificity for various cri-teria together. Statistical significance was defined by a two-tailed $p < 0.05$. SPSS version 24.0 (SPSS Inc, Chicago, IL, USA) was used for statistical analyzes.

3. Results

The study included 314 participants, consisting of 92 patients with psoriasis and their 92 controls and 65 atopic dermatitis patients and their 65 controls. Table 1 shows the characteristics of the sample

Table 1. Characteristics of the sample. This table shows sociodemographic features in psoriatic patients, atopic dermatitis patients, and healthy participants.

Sociodemographic features.	Psoriatic Patients (*n* = 92)	Healthy Participants assessed on the Elbow (*n* = 92)	Atopic Dermatitis Patients (*n* = 65)	Healthy Participants assessed on the Volar Forearm (*n* = 65)
Age (years)	48.63 (15.70)	42.06 (18.59)	28.14 (19.59)	35.96 (19.03)
Sex (%)				
Female	46 (50%)	57 (62%)	42 (64.6%)	48 (73.8%)
Male	46 (50%)	35 (38%)	23 (35.4%)	17 (26.2%)
Smoking habit (yes)	31 (33.7%)	12 (13%)	7 (10.8%)	6 (9.23%)
Alcohol habit (yes)	29 (31.5%)	29 (31.5%)	15 (23.1%)	10 (15.4%)
Family history of psoriasis/atopic dermatitis (yes)	43 (46.7%)	12 (13%)	32 (49.2%)	7 (10.8%)
Emollients use (yes)	51 (55.4%)	35 (38%)	51 (78.5%)	28 (43.1%)
Treatment				
Topical treatment	49 (53.26%)		39 (60%)	
Systemic treatment	23 (25%)		26 (40%)	
Biologic drugs	20 (21.7%)		0	

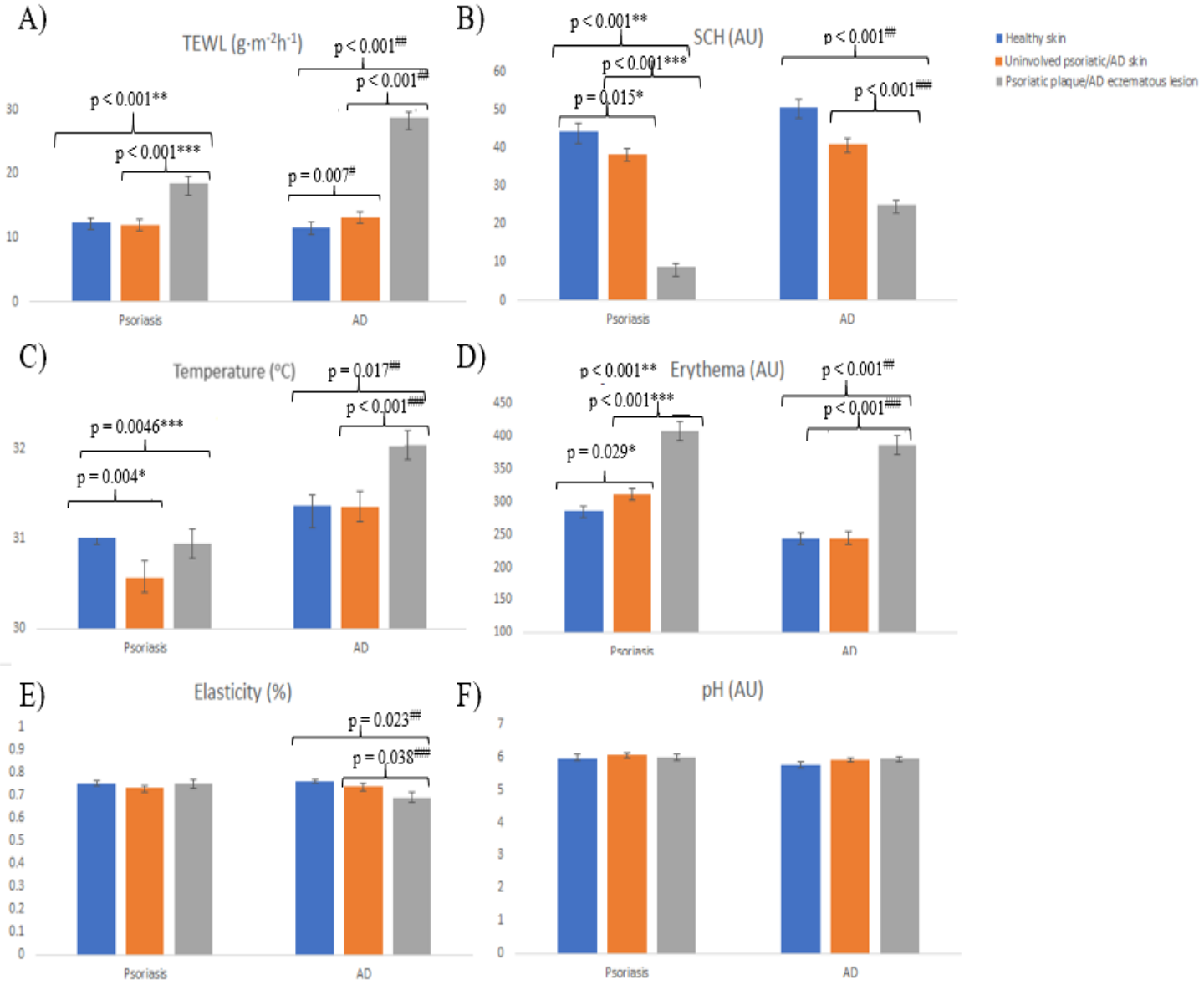
Data are expressed as relative (absolute) frequencies and means (standard deviations (SDs)).

3.1. Skin Homeostasis in Psoriatic Patients

Skin barrier function parameters between healthy, involved, and uninvolved skin in psoriatic patients were compared (Figure 1, Table S1). TEWL was significantly higher at psoriatic plaques (18.45 $g \cdot m^{-2} \cdot h^{-1}$) than at uninvolved psoriatic skin (12.06 $g \cdot m^{-2} \cdot h^{-1}$) and healthy skin (12.34 $g \cdot m^{-2} \cdot h^{-1}$), while no differences were found between uninvolved psoriatic skin and healthy skin. SCH was significantly lower at psoriatic plaques than uninvolved psoriatic skin and healthy skin (8.71 vs. 38.43 vs. 44.39 AU). Temperature was higher at psoriatic plaques than at uninvolved psoriatic skin (30.95 vs. 30.57 °C, $p = 0.046$). The erythema index was significantly higher at psoriatic plaques than at uninvolved psoriatic skin and healthy controls (408.44 vs. 311.56 vs. 285.91 AU). No differences in pH or elasticity were found.

Figure 1. Homeostasis parameters between psoriatic patients and healthy participants and homeostasis parameters between atopic dermatitis patients and healthy participants. A) Transepidermal Water Loss (TEWL) between psoriatic patients and healthy participants and TEWL between atopic dermatitis patients and healthy participants. B) Stratum corneum hydration (SCH) between psoriatic patients and healthy participants and SCH between atopic dermatitis patients and healthy participants. C) Temperature between psoriatic patients and healthy participants and temperature between atopic dermatitis patients and healthy participants. D) Erythema between psoriatic patients and healthy participants and erythema between atopic dermatitis patients and healthy participants. E) Elasticity between psoriatic patients and healthy participants and elasticity between atopic dermatitis patients and healthy participants. F) pH between psoriatic patients and healthy participants and pH between atopic dermatitis patients and healthy participants.

This figure shows TEWL, SCH, temperature, erythema, elasticity, and pH in psoriatic patients, AD patients, and healthy individuals. The differences between healthy skin, uninvolved psoriatic skin, and psoriatic plaque are observed in the left side of each parameter. The differences between healthy skin, uninvolved AD skin, and AD eczematous lesioned skin are found in the right side of each parameter.



AD, atopic dermatitis, AU, arbitrary units, SCH, stratum corneum hydration, TEWL, Transepidermal Water Loss.
*p value after using Student's t test for independent samples to compare homeostasis parameters between healthy skin and uninvolved psoriatic skin.
**p value after using Student's t test for independent samples to compare homeostasis parameters between healthy skin and psoriatic plaque.

***p value after using Student's t test for paired samples to compare homeostasis parameters between uninvolved psoriatic skin and psoriatic plaque.
#p value after using Student's t test for independent samples to compare homeostasis parameters between healthy skin and uninvolved AD skin.
##p value after using Student's t test for independent samples to compare homeostasis parameters between healthy skin and eczematous lesion.
###p value after using Student's t test for paired samples to compare homeostasis parameters between AD skin and eczematous lesion.

The mean PASI was 6.57 (4.82), so patients were divided into two groups: PASI < 7 and PASI ≥ 7 (Table 2). There were no differences in age, sex, or treatment distribution between groups. Regarding current treatment, 27.1% (16/59) patients with PASI < 7 and 21.2% (7/33) patients with PASI ≥ 7 were receiving systemic treatment without differences between groups (p = 0.835); 20.3% (12/59) patients with PASI < 7 and 24.2% (8/33) patients with PASI ≥ 7 were receiving biologics, without differences between groups (p = 0.941).

SCH was significantly lower in patients with PASI ≥ 7 than in patients with PASI < 7 on psoriatic plaques (4.78 vs. 10.91 AU, p < 0.001). Temperature was higher in patients with PASI ≥ 7 than in patients with PASI < 7 on psoriatic plaques (31.56 vs. 30.62 °C, p = 0.005). Moreover, it was observed that patients with PASI ≥ 7 had nearly significantly higher TEWL on psoriatic plaques than patients with PASI < 7 (20.75 vs. 17.16 $g \cdot m^{-2}h^{-1}$, p = 0.109). There was a negative correlation between SCH on the plaque and PASI (r = −0.292, p = 0.005), and a nearly significant positive correlation between temperature on the plaque and PASI (r = 0.187, p = 0.074).

Table 2. Homeostasis parameters in psoriatic patients depending on disease severity. This table shows differences in TEWL, SCH, temperature, erythema, melanin, pH, and elasticity between patients with mild psoriasis (PASI < 7) and patients with moderate/severe psoriasis (PASI ≥ 7).

Skin homeostasis parameters	Psoriatic Patients with PASI < 7 (n = 59)		Psoriatic Patients with PASI ≥ 7 (n = 33)		p value	p value
Title	Uninvolved Psoriatic Skin	Psoriatic Plaques	Uninvolved Psoriatic Skin	Psoriatic Plaques	p *	p **
TEWL ($g \cdot m^{-2} \cdot h^{-1}$)	12.18 (7.52)	17.16 (9.58)	11.86 (8.78)	20.75 (11.22)	0.855	0.109
SCH (AU)	37.76 (13.13)	10.91 (9.76)	39.63 (14.69)	4.78 (5.24)	0.531	< 0.001 **
Temperature (°C)	30.51 (2.00)	30.62 (1.65)	30.66 (1.09)	31.56 (1.13)	0.639	0.005 **
Erythema (AU)	311.78 (73.15)	404.37 (73.76)	311.34 (69.90)	412.79 (67.91)	0.981	0.648
Melanin (AU)	246.49 (81.63)	193.65 (69.98)	230.05 (75.64)	188.36 (69.30)	0.422	0.770
pH	6.01 (0.64)	6.06 (1.01)	6.12 (0.56)	5.90 (0.87)	0.422	0.468
Elasticity (%)	0.74 (0.13)	0.77 (0.20)	0.69 (0.15)	0.72 (0.17)	0.110	0.251

AU, arbitrary units; PASI, psoriasis area and severity index; SCH, stratum corneum hydration; TEWL, transepidermal water loss; * p-value after using Student's t-test for independent samples to compare homeostasis parameters between uninvolved psoriatic skin in psoriatic patients with PASI < 7 and uninvolved psoriatic skin in psoriatic patients with PASI ≥ 7; ** p-value after using Student's t-test for independent samples to compare homeostasis parameters between psoriatic plaques in psoriatic patients with PASI < 7 and psoriatic plaques in psoriatic patients with PASI ≥ 7.

As patients with moderate/severe psoriasis (PASI ≥ 7) exhibited higher temperature values on psoriatic plaques, an ROC curve was generated to determine an optimum cut-off value for temperature that allowed to suspect risk of moderate/severe psoriasis (area under the curve = 0.68, p = 0.004). A value for temperature exceeding 30.85 °C indicates, with a sensitivity of 72.7% and a specificity of 55.9%, that a patient had moder-ate/severe psoriasis. TEWL was also higher in psoriatic patients with moderate/severe PASI; thus, when generating the ROC curve to establish an optimum cut-off point for suspicion of moderate/severe psoriasis (area under the curve = 0.636, p = 0.031), it was noted that a TEWL value higher than 13.85 $g \cdot m^{-2} \cdot h^{-1}$ indicated that a patient had moderate/severe psoriasis, with a sensitivity of 81.8% and a specificity of 50.8%. SCH was lower in patients with high PASI, so a third ROC curve was generated to establish an optimum cut-off point for this parameter to identify possible patients with a risk of moderate/severe psoriasis (area under the curve = 0.285, p = 0.001). A value of SCH lower than 2.07 indicated, with a sensitivity of 60.6% and a specificity of 15.3%, that a patient had moderate/severe psoriasis. Moreover, it was observed that patients with

both temperature > 30.85 and TEWL > 13.85 presented moderate/severe psoriasis, with a sensitivity of 60.6% and a specificity of 76.3% (Table 3).

Table 3. Odds ratios for main parameters analyzed in the study to predict moderate/severe psoriasis (PASI ≥ 7). Sensitivity and specificity values to predict moderate/severe psoriasis based on skin homeostasis parameters, cut-off values, and odds ratios.

Skin homeostasis parameters	Cut-off value	Sensitivity	Specificity	OR	*p*
Temperature (°C)	30.85	72.7%	55.9%	3.390.010 *	
TEWL (g·m^{-2}h^{-1})	13.85	81.8%	50.8%	4.660.003 *	
SCH (AU)	2.07	39.4%	84.7%	0.280.011 *	
Two criteria (temperature > 30.85 + TEWL > 13.85)	-	60.6%	76.3%	4.950.001 *	

AU, arbitrary units; OR, odds ratio; PASI, psoriasis area and severity index; SCH, stratum corneum hydration; TEWL, transepidermal water loss. *p value after using a logistic regression to evaluate the association between disease severity (independent variable), as a categoric variable (PASI<7 or PASI ≥ 7) and each skin homeostasis parameter cut-off point (dependent variable), considered as a categoric variable (lower o equal than the cut-off point o higher than the cut-off point).

3.2. Skin Homeostasis in Atopic Dermatitis Patients

Skin barrier function parameters between healthy, involved, and uninvolved skin in AD patients were compared (Figure 1, Table S2). TEWL was significantly higher at AD eczematous lesions than at uninvolved AD skin and healthy skin (28.68 vs. 13.15 vs. 11.60 g·m^{-2}·h^{-1}). SCH was significantly lower at AD eczematous lesions than at uninvolved AD skin and healthy skin (20.20 vs. 40.95 vs. 50.73 AU). Temperature was significantly higher at AD eczematous lesions than at uninvolved AD skin and healthy skin (32.05 vs. 31.35 vs. 31.37 °C), while no differences were found between uninvolved AD skin and healthy skin. The erythema index was significantly higher at AD eczematous lesions than healthy skin (387.21 vs. 244.44 AU). No differences in pH were found. Elasticity was significantly lower at AD eczematous lesions than healthy skin (69% vs. 74% vs. 76%), while no differences were found between uninvolved AD skin and healthy skin.

The mean SCORAD was 36.96 (21.65), so patients were divided into two groups: SCORAD < 37 and SOCRAD ≥ 37 (Table 4). There were no differences in age, sex, or treatment distribution between groups. Regarding current treatment, 30.8% (8/26)

patients with SCORAD < 37 and 52.9% (18/34) were receiving systemic treatment without differences between groups (p = 0.132). No patient was being treated with biologics.

SCH was significantly lower in patients with SCORAD ≥ 37 than in patients with SCORAD < 37 both at uninvolved AD skin (34.78 vs. 47.10 AU, p = 0.003) and AD eczematous lesion (19.90 vs. 30.68 AU, p = 0.044). Temperature was higher in patients with SCORAD ≥ 37 than in patients with SCORAD < 37 at AD eczematous lesion (32.45 vs. 31.74, p = 0.015). Moreover, it was observed that patients with SOCRAD ≥ 37 had nearly significantly higher TEWL at the AD eczematous lesion than patients with SCORAD < 37 (31.67 vs. 26.33 $g \cdot m^{-2} \cdot h^{-1}$, p = 0.161). No differences in pH or melanin were found. Elasticity was significantly lower in patients with SCORAD ≥ 37 than in patients with SCORAD < 37, both at uninvolved AD skin (67% vs. 79%, p = 0.003) and AD eczematous lesion (63% vs. 75%, p = 0.01). Furthermore, a positive correlation between temperature and SCORAD at the AD eczematous lesions (r = 0.39, p = 0.002) was found, and between TEWL and SCORAD, both at the AD eczematous lesions (r = 0.27, p = 0.036) and at uninvolved AD skin (r = 0.27, p = 0.038). A negative correlation between SCH and SCORAD both at the AD eczematous lesions (r = −0.364, p = 0.005) and at uninvolved AD skin (r = −0.519, p < 0.001) was observed. Moreover, a negative correlation between elasticity and SCORAD, both at the AD eczematous lesions (r = −0.421, p = 0.003) and at uninvolved AD skin (r = −0.542, p < 0.001) was found.

Table 4. Homeostasis parameters in atopic dermatitis patients depending on disease severity. This table shows differences in TEWL, SCH, temperature, erythema, melanin, pH, and elasticity between patients with mild AD (SCORAD < 37) and patients with moderate/severe (SCORADI ≥ 37).

Skin homeostasis parameters.	AD Patients with SCORAD < 37 (*n* = 26)		AD Patients with SCORAD ≥ 37 (*n* = 34)		*p* value	*p* value
Title	Uninvolved AD Skin	AD Eczematous Lesion	Uninvolved AD Skin	AD Eczematous Lesion	*p* *	*p* **
TEWL (g·m^{-2}h^{-1})	10.88 (8.04)	26.33 (15.34)	13.75 (6.62)	31.67 (13.74)	0.135	0.161
SCH (AU)	47.10 (17.01)	30.68 (24.23)	34.78 (13.55)	19.90 (11.40)	0.003 *	0.044 **
Temperature (°C)	31.30 (1.04)	31.74 (1.00)	31.35 (1.46)	32.45 (1.15)	0.891	0.015 **
Erythema (AU)	201.05 (17.30)	351.78 (102.64)	254.93 (78.78)	395.71 (77.71)	0.004 *	0.361
Melanin (AU)	168.91 (37.39)	1990.04 (23.33)	212.55 (82.57)	215.24 (88.88)	0.221	0.298
pH	5.79 (0.62)	5.87 (0.61)	6.04 (0.41)	6.03 (0.47)	0.97	0.274
Elasticity (%)	0.79 (0.11)	0.75 (0.12)	0.67 (0.16)	0.63 (0.20)	0.003 *	0.01 **

AD, atopic dermatitis; AU, arbitrary units; PASI, psoriasis area and severity index; SCH, stratum corneum hydration; TEWL, transepidermal water loss; * p-value after using Student's t-test for independent samples to compare homeostasis parameters between uninvolved AD skin in AD patients with SCORAD < 37 and uninvolved AD skin in AD patients with SCORAD ≥ 37; ** p-value after using Student's t-test for independent samples to compare homeostasis parameters between AD eczematous lesion in AD patients with SCORAD < 37 and AD eczematous lesion in AD patients with SCORAD ≥ 37.

As patients with moderate/severe AD (SCORAD ≥ 37) exhibited higher temperature values at AD eczematous lesions, an ROC curve was generated to determine an optimum cut-off value for temperature that allowed to determine the risk of moderate/severe AD (area under the curve = 0.71, p = 0.006). A value for temperature exceeding 31.75 °C indicated, with a sensitivity of 81.8% and a specificity of 57.7%, that a patient had moderate/severe AD. TEWL was also higher in AD patients with moderate/severe SCORAD; thus, when generating the ROC curve to establish an optimum cut-off point for suspicion of moderate/severe AD (area under the curve = 0.633, p = 0.078), it was noted that a TEWL value higher than 23.19 g·m^{-2}·h^{-1} indicated that a patient had moderate/severe AD, with a sensitivity of 73.5% and a specificity of 53.8%. SCH was lower in patients with high SCORAD, so a third ROC curve was generated to establish an optimum cut-off point for this parameter to identify possible patients with a risk of moderate/severe AD (area under the curve = 0.367, p = 0.083). A value of SCH lower than 14.54 AU indicated, with a sensitivity of 71.9% and a specificity of 23.1%, that a pa-tient had moderate/severe AD. Moreover, it was observed that patients with both temperature > 31.75 °C and TEWL > 23.19 g·m−2·h−1 presented a moderate/severe AD, with a sensitivity of 69.2% and a specificity of 61.8% (Table 5).

Table 5. Odds ratios for main parameters analyzed in the study to predict moderate/severe AD (SCORAD > 37). Sensitivity and specificity values to predic moderate/severe AD based on skin homeostasis parameters, cut-off values, and odds ratio.

Skin homeostasis parameters	Cut-off Value	Sensitivity	Specificity	OR	*p*
Temperature (°C)	31.75	81.8%	57.7%	6.14	0.003 *
TEWL (g·m^{-2}h^{-1})	23.19	73.5%	53.8%	3.24	0.034 *
SCH (AU)	14.54	71.9%	23.1%	0.77	0.663
Two criteria (temperature > 31.75 + TEWL > 23.19)	-	69.2%	61.8%	3.64	0.19

AU, arbitrary units; OR, odds ratio; SCH, stratum corneum hydration; SCORAD, SCORing Atopic Dermatitis; TEWL, transepidermal water loss. *p value after using a logistic regression to evaluate the association between disease severity (independent variable), as a categoric variable (SCORAD < 37 or SCORAD ≥ 37) and each skin homeostasis parameter cut-off point (dependent variable), considered as a categoric variable (lower o equal than the cut-off point o higher than the cut-off point).

3.3. Skin Homeostasis Analysis Between Psoriatic Patients and AD Patients

It was observed that temperature was higher in AD patients than in psoriatic patients both at uninvolved skin (31.35 vs. 30.56 °C, p = 0.001) and involved skin (32.05 vs. 30.95, p < 0.001). Moreover, TEWL was higher at eczematous lesions than at psoriatic plaques (28.69 vs. 18.48 g·m−2·h−1, p < 0.001). Erythema was lower at eczematous lesions than at psoriatic plaques (244.50 vs. 311.56, p < 0.001). No differences in pH or elasticity were found.

4. Discussion

Skin homeostasis analysis showed differences between healthy skin, psoriatic skin, and AD skin. In psoriatic patients, SCH was lower at psoriatic plaques than uninvolved psoriatic skin and healthy controls. Psoriatic plaques showed higher TEWL, temperature, and erythema values than uninvolved psoriatic skin. Temperature and TEWL at psoriatic plaques could help to identify moderate/severe psoriatic patients. In AD patients, TEWL was higher at eczematous lesions than at uninvolved AD skin and healthy controls, while SCH was lower. Eczematous lesions showed higher temperature than uninvolved AD skin. Moreover, AD patients with a more severe disease showed higher temperature, higher TEWL, and lower SCH at their eczematous lesions. Temperature and TEWL at eczematous lesions in AD patients could help to identify AD moderate/severe patients.

This report shows that the whole epidermal barrier is affected in psoriatic patients, not only at psoriatic plaques. Some homeostasis parameters have previously been evaluated in psoriatic patients. Other research showed higher TEWL at psoriatic plaques than at uninvolved psoriatic skin and healthy controls [27,28]. Nevertheless, differences in TEWL values between un-involved psoriatic skin and healthy controls are controversial [27,28]. Lower SCH values have been found at psoriatic plaques than at uninvolved psoriatic skin and healthy controls, in agreement with our results [15,27]. The differences in TEWL and SCH between psoriatic plaques and uninvolved skin in the same patient could be explained by a decrease in AQP3 expression in plaques and perilesional skin [29]. Controversial results have been reported for pH values. Cannavo et al. found lower pH values for psoriatic skin [15], while Delfino et al. reported no change [30]. Temperature and erythema were also higher at psoriatic skin, explained by its inflammatory pathogenesis [31]. There is a need for reliable assessment of psoriasis

severity [32] and, to our knowledge, there is no information regarding a cutaneous homeostasis parameter to assess psoriasis severity. We observed that a value for temperature on psoriatic plaques higher than 30.85 °C indicates, with a sensitivity of 72.7%, that psoriasis is moderate/severe, and that a value for TEWL higher than 13.85 g·m−2·h−1 indicates, with a sensitivity of 81.8%, that psoriasis is moderate/severe. This may help clinicians to objectively measure psoriasis severity.

Furthermore, this study shows that the whole epidermal barrier is affected in AD patients. TEWL is the most studied parameter in AD patients. Like previous reports, this study shows that TEWL is higher at eczematous AD lesions than at uninvolved AD lesions and healthy skin [33–35]. The increased TEWL values reveal an epidermal barrier dysfunction that could be ex-plain by filaggrin mutations [14]. Jungersted et al. also showed that erythema was increases at AD lesions compared to healthy control skin, while SCH was lower and pH was similar at both locations in 49 participants [14]. Moreover, other previous re-ports, evaluating a smaller number of participants, showed that SCH was higher in healthy controls than at uninvolved AD skin and at eczematous lesions [36]. In agreement with our results, this report shows that the skin barrier function is degraded in AD patients, which is specifically expressed in lesioned skin [36]. This could be explained by a filaggrin deficiency, as this protein is a major constituent of the stratum corneum and contributes to keratin filament aggregation [37]. Temperature and erythema were also higher at eczematous lesions than at uninvolved AD skin and healthy skin, showing inflammatory changes in this disease [38]. To our knowledge, only one previous report has evaluated elasticity parameters in AD patients [39]. Like our results, they observed a more decreased elasticity at AD eczematous lesions than at uninvolved AD skin in 22 patients, without including a healthy control group. Differences in elasticity

may reveal that collagen or elastin, the main proteins responsible for skin elasticity [40], are other proteins altered in AD patients.

There is scarce information regarding cutaneous homeostasis parameters and AD severity. Correlations between skin hydration and SCORAD [22,41], and between TEWL and SCORAD [42], have been previously observed. Moreover, it has been shown that TEWL values at non-involved AD skin predicts the development of AD [43,44]. Nevertheless, cut-off points have not been established to assess disease severity. We observed that a value for temperature on the eczematous lesion higher than 31.75 °C indicates, with a sensitivity of 81.8%, that AD is moderate/severe, and that a value for TEWL higher than 23.19 g·m−2·h−1 indicates, with a sensitivity of 73.5%, that AD is moderate/severe. This research could help clinicians to select AD patients that need to be treated intensively. Moreover, the skin barrier function measurement could also help to resolve the current need for ac-curate and reproducible scoring systems for the grading of AD [16].

Limitations of this study include the lack of follow-up due to its cross-sectional design, and that patients with different ongoing treatments were included, which might modify epidermal barrier function. Nevertheless, there were no differences in systemic or biologic treatment distribution between severity groups, neither in psoriasis nor in AD.

5. Conclusions

In conclusion, the skin barrier is impaired in psoriasis and AD. Temperature and TEWL values may help clinicians to de-terminate disease severity and select patients who need an in-tensive treatment.

Supplementary Materials: The following are available online at www.mdpi.com/xxx/s1. Table S1. Homeostasis parameters between pso-riatic patients and healthy participants. Table S2. Homeostasis parameters between atopic dermatitis patients and healthy participants.

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Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data presented in this study are avail-able on request from the corresponding author.

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Supplementary Material

Table S1. Homeostasis parameters between psoriatic patients and healthy participants.

Skin homeostasis parameters	Healthy skin (n = 92)	Uninvolved psoriatic skin (n = 92)	Psoriatic plaque (n = 92)	p*	p**	p***
TEWL ($g \cdot m^{-2}h \cdot^{-1}$)	12.34 (7.77)	12.06 (7.95)	18.45 (10.28)	0.811	<0.001**	<0.001***
SCH (AU)	44.39 (18.91)	38.43 (13.66)	8.71 (8.90)	0.015*	<0.001**	<0.001***
Temperature (ºC)	31.18 (1.05)	30.57 (1.73)	30.95 (1.55)	0.004*	0.244	0.046***
Erythema (AU)	285.91 (55.23)	311.56 (70.99)	408.44 (70.52)	0.029*	<0.001**	<0.001***
Melanin (AU)	180.19 (46.24)	238.54 (78.57)	191.10 (8.92)	<0.001*	0.312	<0.001***
pH	5.97 (0.74)	6.05 (0.62)	6.01 (0.96)	0.457	0.791	0.687
Elasticity (%)	0.75 (0.11)	0.73 (0.14)	0.75 (0.19)	0.205	0.953	0.246

AU, arbitrary units; SCH, Stratum Corneum Hydration; TEWL, Transepidermal Water Loss. * p value after using Student's t test for independent samples to compare homeostasis parameters between healthy skin and uninvolved psoriatic skin. ** p value after using Student's t test for independent samples to compare homeostasis parameters between healthy skin and psoriatic plaque. *** p value after using Student's t test for paired samples to compare homeostasis parameters between uninvolved psoriatic skin and psoriatic plaque.

Table S2. Homeostasis parameters between atopic dermatitis patients and healthy participants.

Skin homeostasis parameters	Healthy skin (n = 65)	Uninvolved AD skin (n = 65)	AD eczematous lesion (n = 65)	p*	p**	p***
TEWL ($g \cdot m^{-2}h \cdot^{-1}$)	11.60 (7.78)	13.15 (7.92)	28.68 (14.28)	0.296	<0.001**	<0.001***
SCH (AU)	50.73 (21.78)	40.95 (16.03)	25.20 (18.28)	0.007*	<0.001**	<0.001***
Temperature (ºC)	31.37 (1.71)	31.35 (1.27)	32.05 (1.30)	0.956	0.017**	<0.001***
Erythema (AU)	244.44 (43.92)	244.50 (74.05)	387.21 (83.06)	0.997	<0.001**	<0.001***
Melanin (AU)	165.30 (30.83)	204.10 (77.42)	210.37 (98.37)	0.017*	0.023**	0.557
pH	5.75 (0.72)	5.91 (0.54)	5.94 (0.53)	0.207	0.112	0.442
Elasticity (%)	0.76 (0.10)	0.74 (0.15)	0.69 (0.17)	0.319	0.023**	0.038***

AD, atopic dermatitis; AU, arbitrary units; SCH, Stratum Corneum Hydration; TEWL, Transepidermal Water Loss. *p value after using Student's t test for independent samples to compare homeostasis parameters between healthy skin and uninvolved AD skin. ** p value after using Student's t test for independent samples to compare homeostasis parameters between healthy skin and AD eczematous lesion. *** p value after using Student's t test for paired samples to compare homeostasis parameters between uninvolved AD skin and AD eczematous lesion.

5.3. The impact of phototherapy on skin barrier.

Phototherapy is an effective treatment for psoriasis. Its beneficial effect is explained by the inhibition of epidermal hyperproliferation and an immunomodulatory effect, likely modifying skin barrier function. Assessing changes in skin barrier with phototherapy may increase the knowledge about how this treatment works and develop further treatments directly acting against skin barrier disruption.

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Epidermal barrier changes in patients with psoriasis: the role of phototherapy

Keywords: Homeostasis, Phototherapy, Psoriasis, Skin Physiology, Transepidermal Water Loss

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Abstract

Background. Some skin diseases may modify epidermal barrier function. Psoriasis is a chronic multi-systemic inflammatory disease that affects the epidermal barrier. Phototherapy is an option for treating psoriasis, but little is known about how epidermal barrier function is modified by phototherapy in psoriatic patients.

Objectives: 1) To compare skin homeostasis between involved and uninvolved skin in psoriatic patients with healthy controls 2) To evaluate changes in the epidermal barrier function in psoriatic patients treated with phototherapy.

Methods: Sixty patients with plaque-type psoriasis and sixty gender and age-matched healthy controls were enrolled. Temperature, transepidermal water loss (TEWL), stratum corneum hydration (SCH), pH, elasticity, erythema and melanin index were measured using non-invasive tools in the healthy control and involved and uninvolved psoriatic skin before and after phototherapy.

Results: Healthy controls had lower TEWL and erythema index and higher SCH than psoriatic patients, both at uninvolved psoriatic skin and psoriasis plaques. TEWL was higher at psoriasis plaques than at uninvolved skin (19.20 vs. 11.57g/h/m2; $p<0.001$). Following phototherapy, a decreasing trend was observed for TEWL, of 1.03 (SD 0.75) and 0.97 (SD 0.81)g/h/m^2 for uninvolved and involved skin respectively. SCH was significantly lower at psoriatic plaques than at uninvolved skin (7.32 vs. 36.62Arbitrary Units (AU); $p<0.001$). SCH increased by 1.15AU (SD 0.26) on psoriatic plaques after the phototherapy session ($p<0.001$).

Conclusion: Psoriatic plaques showed epidermal barrier dysfunction compared to uninvolved skin and healthy controls. Phototherapy may improve epidermal barrier function in psoriatic patients. SCH increased after a phototherapy session on the psoriatic plaques.

Summary statement

There is scarce information about how epidermal barrier function is modified by phototherapy in psoriatic patients. This study enrolled sixty patients with plaque-type psoriasis and sixty gender and age-matched healthy controls. Healthy controls had lower transepidermal water loss (TEWL) and erythema index and higher stratum corneum hydration (SCH) than psoriatic patients. Following only one phototherapy session, SCH increased by 1.15 AU (SD 0.26) on psoriatic plaques after the phototherapy session ($p<0.001$). Phototherapy may improve epidermal barrier function in psoriatic patients.

1. Introduction

The skin is the largest organ of the human body and accomplishes multiple defensive and regulatory functions[1]. Skin barrier function mainly resides in the epidermis and particularly in the stratum corneum[2]. The epidermal barrier is important for maintaining skin homeostasis and protecting the human body against many external stressors, including chemical stress, environmental conditions and physical stress[3,4]. Assessment of the epidermal barrier usually involves measurements of Transepidermal Water Loss (TEWL)[5]. Higher TEWL is often associated with skin barrier impairments[6]. Stratum corneum hydration (SCH) and skin surface pH are also considered to be important parameters for assessing the epidermal function[7,8]. Other parameters used to asses epidermal barrier function are temperature, elasticity and erythema index[9-12].

Psoriasis is a chronic multi-systemic inflammatory disease with predominant skin involvement that results from deregulation between epidermal keratinocytes and cells of both innate and acquired immunity[13]. It affects between 0.5 and 3% of the population[14]. Multiple diagnostic tools have been used to evaluate severity in patients with psoriasis: the Psoriasis Area and Severity Index (PASI), the Body Surface Area covered by psoriasis (BSA), and the Dermatology Life Quality Index (DLQI)[15-18], subjective measures which could lead to a high intra- and interobserver variability[19]. Epidermal barrier function has not been considered in detail regarding psoriasis pathophysiology although the possible interplay between pro-inflammatory cytokines and barrier integrity has been shown in

other inflammatory dermatological disorders[20]. Furthermore, hyperproliferation and defective keratinocyte differentiation may impair epidermal barrier function[21].

Phototherapy is a treatment option for patients with psoriasis and an effective first-line therapy for generalized plaque psoriasis[22]. 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[23]. The beneficial effect on psoriasis lesions is explained by the inhibition of epidermal hyperproliferation and its immunomodulatory effect[24]. To date, only two studies have evaluated the changes in epidermal barrier function following phototherapy, showing an improvement in TEWL[25] and SCH[26].

The aims of this study are: 1) To compare skin barrier function between normal skin (healthy controls) with involved and uninvolved skin in patients with psoriasis 2) To evaluate changes in epidermal barrier function in psoriatic patients after phototherapy.

2. Material and methods

Design

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

B) A prospective observational study on patients with psoriasis to assess changes in skin barrier function following a phototherapy session.

Study population

Participants were recruited from January to May 2019 in the Dermatology Service of the Hospital Universitario Virgen de las Nieves in Granada. Cases were patients with established clinical diagnosis of moderate-to-severe plaque-type psoriasis who were chosen using clinical criteria to attend phototherapy treatment with NB-UVB. Controls were healthy volunteers gender- and age-matched (±3 years) with cases. These volunteers were people who attended the Dermatology Service for common conditions such as melanocytic nevi or seborrheic keratoses, and did not have previous personal or family history of any inflammatory skin disease.

Study variables

Psoriasis severity was assessed by the psoriasis area and severity index (PASI) before inclusion in the study. Every study patient was also evaluated with the dermatology life quality index (DLQI). Gender, age, age at diagnosis, psoriasis family history, co-

morbidities, smoking habit, other inflammatory disorders, previous treatments, use of emollients, distribution of lesions and disease duration were gathered by means of clinical interview. Information about the previous number of phototherapy sessions, session dose and total cumulative dose was also collected.

Main variables of interest

Homeostasis parameters related to epidermal barrier function were measured. SCH (in arbitrary units, using Corneometer® CM 825), TEWL (in $g/h/m^2$, using Tewameter® TM 300), pH (using Skin-pH-Meter® PH 905), erythema and melanin index (in arbitrary units, using Mexameter® MX 18), skin temperature (in ºC, using Skin-Thermometer ST 500) and elasticity parameters (including R2 value, measured in %, using Cutometer® Dual MPA 580) were measured by a Multi Probe Adapter (MPA, Courage + Khazaka electronic GmbH, Germany). Elasticity parameters were measured four times and the other variables were measured ten times, using their average for analysis. Participants were not allowed to use any treatment topical or systemic at least 24 hours before skin homeostasis parameter were measured. These variables were measured at two body sites in patients: on a psoriatic plaque and on an uninvolved skin area at the elbow. Measurements were taken both before and after one NB-UVB phototherapy session. Control measurements were taken only once at the elbow. Measurements were taken in the same room and ambient air temperature was measured

with the TFA® Lab Thermometer IP65 LT-101. The average ambient air temperature at the time of the study was 22±1ºC.

Statistical analysis

Descriptive statistics were used to present the sample characteristics. Continuous data was expressed as the mean ± standard deviation. The absolute and relative frequency distributions were estimated for qualitative variables. The Shapiro-Wilk test was used to check the normality of data distribution. Linear regression models were constructed to compare continuous data between healthy skin and psoriatic patients. The student's t-test for paired samples was used to compare homeostasis parameters before phototherapy. The effect of phototherapy by time (before, after) and skin involvement (uninvolved skin, psoriatic plaque), adjusted by total cumulative dose, was analysed using repeated measures ANOVA (RM-ANOVA) with post hoc Bonferroni correction. A p-value of <0.05 was considered statistically significant. Statistical Analyses were performed using the SPSS package (SPSS for Windows, Version 24.0 Chicago: SPSS Inc.).

Ethics

This study was approved by the ethics committee of Hospital Universitario Virgen de las Nieves. The nature of the study was explained to all the participants, who agreed to participate by verbal and written consent. All measurements were non-invasive and patient data was kept confidential.

3. Results

A total of 120 subjects, consisting of 60 psoriatic patients and 60 healthy controls were included in the study. Table 1 summarizes the general characteristics of the sample.

Skin homeostasis analysis between psoriatic patients and healthy controls

Skin barrier function parameters between healthy controls and involved and uninvolved skin in psoriatic patients before phototherapy were compared (table 2). Temperature was higher at psoriatic plaques than at uninvolved psoriatic skin (31.07 vs 30.27ºC, p <0.001). TEWL was significantly higher at psoriatic plaques than uninvolved psoriatic skin and healthy controls (19.20 vs 11.57 vs 11.53 $g/h/m^2$). SCH was significantly lower at psoriatic plaques than uninvolved psoriatic skin and healthy controls (7.32 vs 36.62 vs 39.69 AU). The erythema index was significantly higher at psoriatic plaques than uninvolved psoriatic skin and healthy controls (408.44 vs 311.56 vs 285.91 AU) and the melanin index was significant higher at uninvolved psoriatic skin than psoriatic plaques and healthy controls (238.54 vs 191.10 vs 180.19 AU). No differences in pH or elasticity were found.

Skin homeostasis changes in patients with psoriasis after phototherapy

Homeostasis parameters changed after phototherapy session (table 3). Temperature was higher at psoriatic plaques than at uninvolved skin (31.35 vs 30.71ºC, p<0.001). Temperature increased by 0.81ºC (0.18 SD) at uninvolved skin (p=0.001) and

0.64ºC (0.17 SD) at psoriatic plaques (p=0.003) after phototherapy. No differences in pH or elasticity were found.

TEWL was also higher at psoriatic plaques than at uninvolved skin (18.23 vs 10.54 g/h/m^2, p<0.001). A decreasing trend was observed at both locations after the phototherapy session. It decreased by 1.03 (0.75 SD) g/h/m^2 at uninvolved skin (p=0.172) and 0.97 (0.81 SD) g/h/m^2 at psoriatic plaques (p=0.235).

SCH was lower at psoriatic plaques than at uninvolved skin (9.61 vs 36.50 AU, p<0.001). The phototherapy session had different effects on patients' SCH values depending on the skin involvement. SCH increased by 1.15 (0.26 SD) AU at psoriatic plaques (p<0.001) while no effect was reported for uninvolved skin (p=0.887).

Erythema and melanin index were higher at psoriatic plaques than uninvolved skin. The erythema increased by 9.63 (3.64 SD) AU at psoriatic plaques (p=0.007) while no effect was observed at uninvolved skin (p=0.713).

Figure 1 summarizes the changes after phototherapy at uninvolved skin and psoriatic plaques.

4. Discussion

Skin homeostasis analysis showed differences between control skin, uninvolved skin and plaques in psoriasis patients. Erythema was higher at psoriatic plaques than uninvolved psoriatic skin and healthy controls. Psoriatic plaques showed higher TEWL values and lower SCH values than uninvolved psoriatic skin. After phototherapy, increased SCH, temperature and erythema index levels at psoriatic plaques were observed. Phototherapy may improve epidermal barrier function in psoriatic patients.

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 controls[27,28]. Nevertheless, differences in TEWL values between uninvolved psoriatic skin and healthy controls are controversial. Including similar participants number, while Nikam et al. found higher TEWL on psoriatic skin[27], Takahashi et al did not report any differences[28], in agreement with our results. Lower SCH values have been found at psoriatic plaques than at uninvolved psoriatic skin and healthy controls, with no differences between uninvolved psoriatic skin and healthy controls, in agreement with our results[28,29]. The differences in TEWL and SCH between psoriatic plaques and uninvolved skin in the same patient could be explained by a decrease in AQP3 expression in plaques and perilesional skin[30].

Controversial results have been reported for pH values. Cannavo et al. found lower pH values for psoriatic skin[29] while Delfino et al reported no change[31]. Changes in elasticity have been only evaluated by Choi et al. who found lower values for psoriatic patients assessed by R7[32], the ratio of elastic recovery to total deformation, a less reliable parameter for measuring elasticity than the one we used (R2, overall elasticity)[33]. Temperature and erythema were also higher in psoriatic skin, explained by its inflammatory pathogenesis[34].

There is scarce research on the role of phototherapy in epidermal barrier function. Our results show improvement in epidermal barrier function following phototherapy. It has previously been reported that phototherapy decreases TEWL and increases SCH[25,26]. Brazzelli et al. have already examined changes in SCH and TEWL levels between pre- and post-treatment with eight sessions of phototherapy and active topical vitamin D3 ointment in psoriasis showing the recovery of epidermal hydration and TEWL level before the clinical improvement of the lesion[25]. Darlenski et al. have reported clinical improvement in psoriatic plaques with fourteen sessions of NB-UVB therapy, shown by a decreased PASI and reflected by an increase in SCH and a decrease in TEWL[26]. This study also showed an increased SCH at the psoriatic plaque after only one phototherapy session. So, in agreement with Brazzelli et al., the improved SCH at involved skin might precede the clinical improvement[25]. The decreased SCH might be explained by the phototherapy effect on the inhibition of epidermal hyperproliferation[24,25].

Temperature, erythema and melanin index increased after the phototherapy session, in accordance with previous reports[36-38]. Nevertheless, no information has been found regarding different effects depending on the skin involvement. This might highlight a local effect on psoriasis plaques[39-40]. Elasticity and pH did not change after phototherapy, with no previous information found to contrast these results.

This study was subject to several limitations: the limited follow-up period considered and the variation of the homeostasis parameter depending on external conditions. Nevertheless, in order to increase outcome reliability, all participants were measured in the same room and the ambient conditions were measured. Although the aim of the study was to assess epidermal barrier function and skin homeostasis parameter before and after one single treatment and only in psoriatic patients, to increase more knowledge regarding the role of phototherapy in epidermal barrier function and to distinguish with treatment effects and effects of improving condition, further prospective researches should be done in other inflammatory skin disease and using more treatment's options.

This study highlights the role of non-invasive, objective and easily performed measurements to evaluate barrier function. Psoriatic patients have higher TEWL and lower SCH values, both at psoriasis plaques and uninvolved skin, than healthy control skin. For the first time, to the best of our knowledge, we report changes in epidermal barrier function after one phototherapy session. SCH on psoriatic plaques improved after phototherapy which might be related to clinical efficacy on psoriatic patients under

phototherapy. The assessment of the cutaneous homeostasis parameters might help us to gain a better understanding of the role of phototherapy in the improvement of psoriatic patients.

5. References

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6. Tables

Table 1. Characteristics of the sample

	All participants (n=120)	Controls (n=60)	Psoriatic patients (n=60)	p*
Age (years)	46.51 (±16.71)	46.08 (±16.83)	46.93 (±16.72)	0.78
Sex (%)				1.00
-Female	68 (56.67%)	34 (56.67 %)	34 (56.67 %)	
-Male	52 (43.33%)	26 (43.33 %)	26 (43.33 %)	
Smoking habit				0.008*
- Non-smoker	68 (56.57%)	42 (70.00%)	26 (43.33%)	
- Ex-smoker	28 (23.33%)	10 (16.67%)	14 (23.33%)	
- Smoker	24 (20.00%)	8 (13.33%)	20 (33.33 %)	
Alcohol habit (yes)	38 (31.67%)	19 (31.67%)	19 (31.67%)	1.00
Family history of psoriasis (yes)	26 (21.67%)	0	26 (43.33%)	.
Emollients use (yes)	68 (56.67%)	23 (38.33%)	45 (75.00%)	<0.001*
Measurements discomfort (yes)	3 (2.50%)	1 (3.33%)	2 (6.70 %)	1.00
DLQI			7.90 (5.98)	
PASI			8.13 (5.04)	
BSA			12.65 (9.32)	
Previous treatments				
- Topical corticosteroids			60 (100%)	
- Acitretin, methotrexate or cyclosporine			11 (18.33%)	
- Biologic drugs			5 (8.33%)	
Concomitant treatments				
- Topical corticosteroids			26 (43.33%)	
- Acitretin			4 (6.67%)	
- Biologic drugs			1 (1.67%)	
Number of previous sessions of NB-UVB phototherapy			74.70 (6.91)	
Session dose (Jules)			0.70 (0.48)	
Total cumulative dose (Jules)			106.76 (56.37)	
Session time (second)			178.35 (21.63)	

BSA, Body Surface Area; DLQI, Dermatology Life Quality Index; NB-UVB, Narrow-Band Ultraviolet B; PASI, Psoriasis Area and Severity Index.

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

Table 2. Homeostasis parameters at controls versus uninvolved psoriatic skin and psoriatic plaque before phototherapy.

	Control	Uninvolved psoriatic skin before phototherapy	Psoriatic plaque before phototherapy	p*	p**	p***
pH	6.22	6.17	6.14	0.315	0.267	0.755
Temperature (ºC)	31.06	30.27	31.07	0.009*	0.614	<0.001***
Elasticity (%)	0.73	0.70	0.73	0.053	0.323	0.334
TEWL ($g/h/m^2$)	11.53	11.57	19.20	0.551	<0.001**	<0.001***
SCH (AU)	39.69	36.62	7.32	0.397	<0.001**	<0.001***
Erythema (AU)	285.91	311.56	408.44	0.104	<0.001**	<0.001***
Melanin (AU)	180.19	238.54	191.10	<0.001*	0.255	<0.001***

AU, arbitrary units; SCH, Stratum Corneum Hydration; TEWL, Transepidermal Water Loss

***p value after using a linear regression model adjusted by smoking habit and emollients use to compare homeostasis parameters between control and uninvolved psoriatic skin before phototherapy.**
****p value after using a linear regression model adjusted by smoking habit and emollients use to compare homeostasis parameters between control and psoriatic plaque before phototherapy.**
***** p value after using Student's t test for paired samples to compare homeostasis parameters between uninvolved psoriatic skin and psoriatic plaque before phototherapy.**

Table 3. Homeostasis parameters at controls versus uninvolved psoriatic skin and psoriatic plaque after phototherapy.

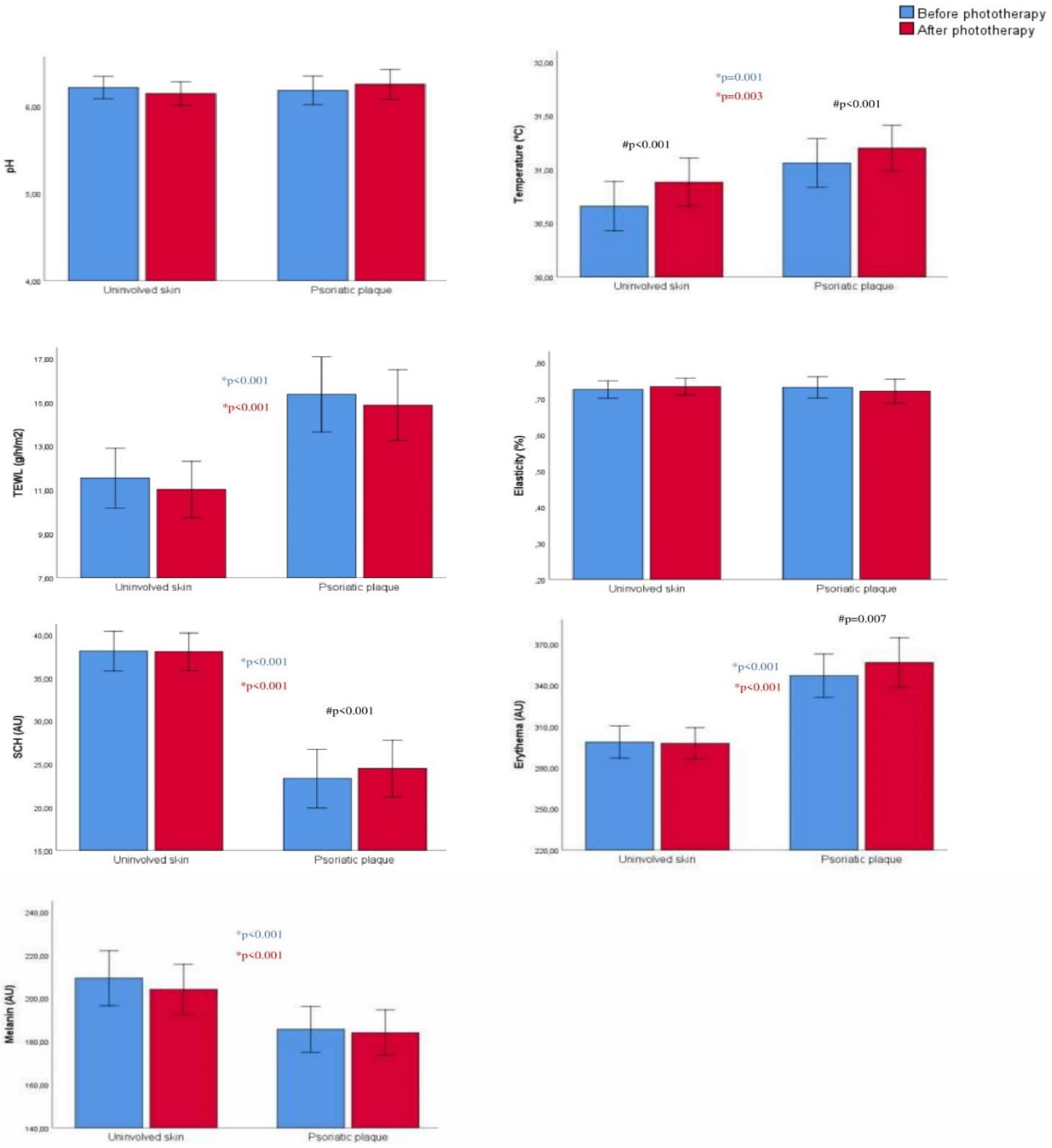
	Uninvolved psoriatic skin after phototherapy	**Psoriatic plaque after phototherapy**	Mean difference at uninvolved skin after vs before phototherapy	Mean difference at psoriatic plaque after vs before phototherapy	p*	p**	p***
pH	6.03	6.29	-0.16 (SD 0.08)	0.16 (SD 0.16)	0.351	0.676	0.204
Temperature (ºC)	30.71	31.35	0.45 (SD 0.14)	0.28 (SD 0.09)	<0.001*	0.001**	0.003***
Elasticity (%)	0.73	0.72	0.02 (SD 0.01)	-0.02 (SD 0.03)	0.323	0.236	0.491
TEWL ($g/h/m^2$)	10.54	18.23	-1.03 (SD 0.75)	-0.97 (SD 0.81)	<0.001*	0.172	0.235
SCH (AU)	36.50	9.61	-0.06 (SD 0.44)	1.15 (SD 0.26)	<0.001*	0.888	<0.001***
Erythema (AU)	309.63	427.69	-0.97 (SD 2.61)	9.63 (SD 3.64)	<0.001*	0.713	0.007***
Melanin (AU)	228.20	188.02	-10.35 (SD 5.05)	-3.08 (SD 2.76)	<0.001*	0.095	0.269

AU, arbitrary units; SCH, Stratum Corneum Hydration; TEWL, Transepidermal Water Loss

***p value after using RM-ANOVA, post hoc Bonferroni correction, adjusted by total cumulative dose to compare homeostasis parameters between uninvolved psoriatic skin and psoriatic plaque after phototherapy**
****p value after using RM-ANOVA, post hoc Bonferroni correction, adjusted by total cumulative dose to compare homeostasis parameters before and after the phototherapy session at uninvolved psoriatic skin.**
*****p value after using RM-ANOVA, post hoc Bonferroni correction, adjusted by total cumulative dose to compare homeostasis parameters before and after the phototherapy session at psoriatic plaque**

7. Figures

Figure 1. Homeostasis skin parameters on psoriatic patients on uninvolved psoriatic skin and psoriatic plaque before and after phototherapy.



*,# p < 0.05 by RM-ANOVA, post hoc Bonferroni correction, adjusted by total cumulative dose, to compare homeostasis parameters *comparing skin involvement and #comparing before and after phototherapy

5.4. Epidermal barrier function and cutaneous homeostasis as potentially predictive parameters of response to phototherapy.

Many medical appointments are needed to see a significant improvement in patients with psoriasis treated with phototherapy and today there are other therapeutic options faster and more effective than it. The cost-effectiveness of phototherapy could be implemented if clinicians could predict the clinical response in the first session. Skin barrier changes could help to select the most appropriated patient to be treated with phototherapy.

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Article

Erythema Increase Predicts Psoriasis Improvement after Phototherapy

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Abstract: Psoriasis is a major global health problem. There is a need to develop techniques to help physicians select the most appropriate cost-effective therapy for each patient. The main objectives of this study are (1) to evaluate changes in epidermal barrier function and skin homeostasis after phototherapy and (2) to explore potentially predictive values in epidermal barrier function and skin homeostasis to assess clinical improvement after fifteen sessions of phototherapy. A total of 76 subjects, 38 patients with plaque-type psoriasis and 38 gender- and age-matched healthy volunteers, were included in the study. Erythema, transepidermal water loss (TEWL), temperature, stratum corneum hydration (SCH), pH, sebum, and antioxidant capacity were measured before and after the first and fifteenth phototherapy session. Erythema (401.09 vs. 291.12 vs. 284.52 AU, $p < 0.001$) and TEWL (18.23 vs. 11.44 vs. 11.41 $g \cdot m^{-2} \cdot h^{-1}$, $p < 0.001$) were significantly higher at psoriatic plaques than in uninvolved psoriatic skin and healthy volunteers, respectively, while SCH was lower (9.71 vs. 44.64 vs. 40.00 AU, $p < 0.001$). After fifteen phototherapy sessions, TEWL (–5.19 $g \cdot m^{-2} \cdot h^{-1}$, $p = 0.016$) decreased while SCH (+7.01 AU, $p = 0.013$) and erythema (+30.82 AU, $p = 0.083$) increased at psoriatic plaques. An erythema increase exceeding 53.23 AU after the first phototherapy session, with a sensitivity of 71.4% and specificity of 84.2%, indicates that a patient may improve Psoriasis Area and Severity Index (PASI) by ≥3 points after fifteen phototherapy sessions. In conclusion, phototherapy improves epidermal barrier function in psoriatic patients and the erythema increase after one phototherapy session could help doctors select psoriasis patients who are more likely to respond to phototherapy.

Keywords: phototherapy; psoriasis; skin barrier; skin physiology; skin homeostasis

1. Introduction

Psoriasis is a chronic, recurrent, multisystemic inflammatory disease [1] caused by a combination of immunological imbalances, genetic associations, and environmental factors [2]. Its prevalence around the word has been estimated at between 0.51% and 11.43% [3]. Psoriasis is considered a major global health problem [4]. Although the skin manifestations are often the only recognized symptoms of psoriasis [5], this disease is associated with multiple comorbidities [6–9] and impacts the patient's quality of life [5,10]. Moreover, the economic burden of psoriasis is high, as in Europe the annual total cost per patient is EUR 6000–12,000 [11].

Multiple treatments are effective for psoriasis, including topical medicines, oral systemic prescriptions, phototherapy, and biologics [12]. Nevertheless, it is not known which type of patient would respond best to each treatment [13]. Moreover, tools to assess disease severity and treatment effectiveness are subjective [14]. Thus, there is a need to develop techniques to help physicians select the most appropriate cost-effective therapy for each patient [15].

Phototherapy is an effective, safe, and low-cost therapy for mild–moderate psoriasis, although many medical appointments are needed to see an improvement [16]. Several types of light and lasers have been developed to treat psoriasis, the narrowband ultraviolet light B (NB-UVB) being the most frequently used. NB-UVB wavelengths ranges from 311 to 313 nm. The starting dose is based on skin phototype or minimal erythema dose (MED), and two or three sessions per week are recommended [17]. Selecting the right patient profile for this treatment and accurately assessing disease severity would improve patient satisfaction and healthcare spending [13]. It would also be interesting to predict the response to assess home phototherapy effectiveness [18]. As the development of psoriasis plaques results from the deregulation of epidermal keratinocytes and immunity cells [19] and the phototherapy's beneficial effect on psoriasis lesions is explained by it blocking epidermal hyperproliferation and an immunomodulatory effect [20], objective changes in the epidermal barrier function may help to select the right psoriasis patients for phototherapy treatment and to assess disease improvement. Epidermal barrier dysfunction in psoriasis patients has previously been reported, assessed by an increase in transepidermal water loss (TEWL) and a decrease in stratum corneum hydration (SCH) [21,22]. To date, only three studies have evaluated the variations in epidermal barrier function following phototherapy, displaying an improvement in TEWL and SCH [23–25].

Thus, the aims of this study are (1) to compare epidermal barrier function and skin homeostasis of healthy volunteers, uninvolved psoriatic skin, and psoriatic plaques, (2) to assess changes in epidermal barrier function and skin homeostasis after one session of phototherapy, (3) to assess changes in epidermal barrier function and skin homeostasis after fifteen phototherapy sessions, and (4) to explore potentially predictive values in epidermal barrier function and skin homeostasis to assess clinical improvement after fifteen phototherapy sessions.

2. Materials and Methods

2.1. Design

A cross-sectional study was conducted to evaluate epidermal barrier function and skin homeostasis disparities between healthy skin, uninvolved psoriatic skin, and psoriatic plaques.

A prospective observational study was carried out on patients with psoriasis to assess epidermal barrier function and skin homeostasis following fifteen phototherapy sessions. Psoriatic patients were exposed to fifteen phototherapy sessions, while healthy volunteers were only reviewed after this period of time without being exposed to phototherapy.

2.2. Setting

This study was conducted between September 2019 and March 2020 in the Dermatology Department of the Hospital Universitario Virgen de las Nieves in Granada, Spain.

2.3. Study population

Inclusion Criteria:

- Patients with established clinical diagnosis of active moderate-to-severe plaque-type psoriasis (minimum Psoriasis Area and Severity Index (PASI) score of 4) [1] selected by clinical criteria to attend phototherapy treatment with UVB narrowband (NB-UVB) [16].
- Controls were healthy volunteers, gender- and age-matched (±3 years) with psoriasis patients. These volunteers were people who attended the Dermatology Department for trivial conditions such as melanocytic nevi or seborrheic keratoses. The same criteria were used to select the non-exposed group in the prospective study.

Exclusion Criteria:

- For psoriasis patients, currently having non-plaque forms of psoriasis.
- For healthy volunteers, having previous personal or family history of any inflammatory skin disease.
- Clinical infection on the treatment area.
- History of cancer or an immunocompromised disease.
- Not signing the informed consent form.

2.4. Follow-up and exposure

Exposed subjects were evaluated before and after receiving the first phototherapy session and before and after the 15th phototherapy session. The starting dose for NB-UVB therapy and the dosage schedule were based on skin phototype following the current guidelines [17]. The frequency was two or three times a week depending on the patient's availability. Non-exposed subjects were evaluated twice, on the same days as their exposed pair.

2.5. Variables

Clinical and sociodemographic variables.

Gender, age, smoking and alcohol habit, psoriasis family history, and use of emollients were gathered by means of clinical interview. Psoriasis severity was assessed by the PASI and the body surface area (BSA). Every study patient was also evaluated with the Dermatology Life Quality Index (DLQI). Information about disease duration, previous treatment, the previous number of phototherapy sessions, session dose, and total cumulative dose was also collected.

Epidermal barrier function variables.

Homeostasis parameters related to epidermal barrier function and skin homeostasis were measured. SCH (in arbitrary units, using Corneometer®CM825), TEWL (in $g \cdot m^{-2} \cdot h^{-1}$, using Tewameter®TM300), pH (using Skin-pH-Meter®PH905), erythema index (in arbitrary units, using Mexameter®MX18), sebum (in arbitrary units, usingSebumeter®SM815), and skin temperature (in °C, using Skin-ThermometerST500) were measured by a Multi Probe Adapter (MPA, Courage+Khazaka electronic GmbH, Köln, Germany). Total antioxidant capacity (TAC) was

measured using eBQC® electrochemical method (Bioquochem S.L. (BQCkit), Asturias, Spain), and expressed in microcoulombs. TAC is divided into two sections: fast antioxidants (Q1), which have a lower oxidation potential, and slow antioxidants (Q2) [26]. All variables were measured at a psoriatic plaque on the elbow and at an uninvolved skin area near the elbow in psoriatic patients, while healthy subjects were measured at a skin area on their elbows. All parameters were measured ten times for each area, using their average for analysis. The measurements were taken in the same room. The average ambient air temperature at the time of the study was 22 ± 1°C, and the average ambient air humidity was 45% ± 3%.

2.6. Statistical analysis

Descriptive statistics were used to present the sample characteristics. Continuous data were expressed as the mean ± standard deviation. The absolute and relative frequency distributions were estimated for qualitative variables. The Shapiro–Wilk test was used to check the normality of data distribution, and Levene's test was used to check the homogeneity of variance. Linear regression models were constructed to compare continuous data between healthy skin and psoriatic patients. To predict PASI improvement after fifteen phototherapy sessions, cut-off points were generated using ROC curves for the changes of erythema and SCH after the first phototherapy session. To produce these ROC curves, the sensitivities and specificities for changes of erythema and SCH values after the first phototherapy that predict an improvement in PASI of ≥3 after the fifteenth phototherapy session were tabulated and the graphical ROC curve was generated by plotting true positive rate (sensitivity) on the y-axis against false positive rate (1-specificity) on the x-axis for the various values tabulated. To select the optimal cut-off point, the point nearest to the top-left-most corner of the ROC curve was chosen, giving equal weight to the importance of sensitivity and specificity. A p-value of <0.05 was considered statistically significant. Statistical Analyses were performed using the SPSS package (SPSS for Windows, Version 24.0 Chicago: SPSS Inc.).

2.7. Ethics

This study was authorized by the ethics committee of Hospital Universitario Virgen de las Nieves. The nature of the study was explained to all participants, who agreed to participate through verbal and written consent. The measurements taken were noninvasive, and patient data were kept confidential. All experiments were done in accordance with relevant guidelines and regulations.

3. Results

3.1. Skin Homeostasis Parameters between Healthy Participants and Psoriatic Patients

The study included 76 participants, consisting of 38 psoriatic patients and 38 healthy participants, Table S1.

Differences in skin homeostasis parameters between healthy skin, uninvolved, and involved psoriatic skin before phototherapy were found, Table 1. Lower TEWL values were found in healthy skin compared with uninvolved psoriatic skin and psoriatic plaques (11.41 vs. 11.44 vs. 18.23 $g \cdot m^{-2} \cdot h^{-1}$, $p < 0.001$). Higher SCH values were observed in healthy skin compared with uninvolved psoriatic skin and psoriatic plaques (40.00 vs. 44.64 vs. 9.71 AU, $p < 0.001$). Lower temperature values were detected in uninvolved psoriatic skin than at psoriatic plaques (30.40 vs. 31.25 °C, $p < 0.001$). Lower erythema index was found in healthy skin than in uninvolved psoriatic skin and psoriatic plaques (284.52 vs. 291.12 vs. 401.09 AU, $p < 0.001$). Higher total antioxidant capacity was observed in uninvolved psoriatic skin than at psoriatic plaques (6.33 vs. 5.54 uC, $p = 0.014$). No differences were found in pH or sebum.

Table 1. Homeostasis parameters in healthy skin, uninvolved psoriatic skin, and involved psoriatic skin at baseline.

	Healthy skin at baseline (*n* = 38)	Uninvolved psoriatic skin at baseline (*n* = 38)	Psoriatic plaques at baseline (*n* = 38)	*P* *	*P* **	*P* ***
TEWL ($g \cdot m^{-2} h^{-1}$)	11.41 (6.63)	11.44 (8.11)	18.23 (9.46)	0.792	<0.001 **	<0.001 ***
SCH (AU)	40.00 (10.50)	44.64 (12.49)	9.71 (9.81)	0.073	<0.001 **	<0.001 ***
Temperature (°C)	30.92 (1.04)	30.40 (1.34)	31.25 (1.59)	0.080	0.280	<0.001 ***
Erythema (AU)	284.52 (55.54)	291.12 (75.43)	401.09 (64.51)	0.574	<0.001 **	<0.001 ***
pH	5.98 (0.63)	5.86 (0.64)	5.91 (0.47)	0.321	0.301	0.728
Sebum (AU)	27.91 (26.95)	26.97 (30.50)	30.14 (30.38)	0.957	0.056	0.386
Q1 (uC)	0.86 (0.2)	1.15 (0.46)	0.96 (0.45)	0.001*	0.176	0.001 ***
Q2 (uC)	4.30 (1.37)	5.20 (1.85)	4.57 (2.16)	0.028*	0.565	0.026 ***
QT (uC)	5.16 (1.53)	6.33 (2.26)	5.54 (2.53)	0.015*	0.474	0.014 ***

AU, arbitrary units; Q1, fast antioxidant capacity; Q2, slow antioxidant capacity; QT, total antioxidant capacity; SCH, stratum corneum hydration; TEWL, transepidermal water loss; uC, microcoulombs. The data are expressed as means (standard deviation). * *p*-value after using a linear regression model adjusted by emollient use to compare homeostasis parameters between healthy skin and uninvolved psoriatic skin at baseline. ** *p*-value after using a linear regression model adjusted by emollient use to compare homeostasis parameters between healthy skin and psoriatic plaques at baseline. *** *p*-value after using Student's t-test for paired samples to compare homeostasis parameters between uninvolved psoriatic skin and psoriatic plaques at baseline.

3.2. Differences in Skin Homeostasis Parameters after One Phototherapy Session

Skin homeostasis parameters were modified after one phototherapy session, Table 2. TEWL did not change at psoriatic plaques or in uninvolved skin after one phototherapy session. The effect of phototherapy on SCH values was different depending on the skin involvement. It was observed that SCH increased by 2.45 ± 0.72 AU ($p = 0.002$) at psoriatic plaques (but SCH was not modified in uninvolved skin ($p = 0.126$).

Temperature increased by 0.24 ± 0.10 °C at psoriatic plaques ($p = 0.016$). The erythema index increased by 31.42 ± 8.30 AU ($p < 0.001$) at psoriatic plaques, but no changes were observed in uninvolved skin.

Total antioxidant capacity was not modified at psoriatic plaques or in uninvolved skin after one phototherapy session. No differences in pH or sebum were observed.

Table 2. Homeostasis parameters for uninvolved psoriatic skin and psoriatic plaques after one phototherapy session.

	Uninvolved Psoriatic Skin after One Phototherapy Session (*n* = 38)	**Psoriatic Plaques after One PhoTotherapy Session (*n* = 38)**	**Mean Difference in Uninvolved Skin after vs. before Phototherap y**	**Mean Difference at Psoriatic Plaques after vs. before Phototherapy**	***P* ***	***P* ****	***P* *****
TEWL ($g \cdot m^{-2}h^{-1}$)	10.78 (8.84)	17.72 (8.46)	−0.66 (0.87)	−0.52 (0.94)	<0.001 *	0.45	0.568
SCH (AU)	42.78 (11.26)	12.16 (10.77)	−1.86 (1.19)	2.45 (0.72)	<0.001 *	0.126	0.002 ***
Temperature (°C)	30.54 (1.54)	31.49 (1.42)	0.14 (0.13)	0.24 (0.1)	<0.001 *	0.297	0.016 ***
Erythema (AU)	294.11 (78.14)	432.51 (81.91)	2.98 (6.19)	31.42 (8.30)	<0.001 *	0.633	0.001 ***
pH	5.84 (0.54)	6.04 (0.51)	−0.03 (0.11)	0.13 (0.18)	0.081	0.815	0.1
Sebum (AU)	30.21 (27.40)	27.71 (17.19)	0.97 (3.65)	−3.41 (3.84)	0.571	0.792	0.381
Q1 (uC)	1.09 (0.32)	0.93 (0.39)	−0.05 (0.07)	-0.03 (0.06)	0.010 *	0.42	0.66
Q2 (uC)	5.00 (1.31)	4.51 (1.57)	-0.18 (0.26)	-0.09 (0.24)	0.026 *	0.494	0.744
QT (uC)	6.09 (1.55)	5.44 (1.91)	-0.21 (0.32)	-0.11 (0.28)	0.013 *	0.505	0.703

AU, arbitrary units; Q1, fast antioxidant capacity; Q2, slow antioxidant capacity; QT, total antioxidant capacity; SCH, stratum corneum hydration; TEWL, transepidermal water loss; uC, microcoulombs. The data is expressed are means (standard deviation). * *p*-value after using Student's t-test for paired samples to compare homeostasis parameters between uninvolved psoriatic skin and psoriatic plaques after one phototherapy session. ** *p*-value after using Student's t-test for paired samples to compare homeostasis parameters in uninvolved psoriatic skin before and after one phototherapy session. *** *p*-value after using Student's t-test for paired samples to compare homeostasis parameters at psoriatic plaques before and after one phototherapy session.

3.3. Skin Homeostasis Changes after Follow-Up

The prospective study included 76 subjects, where 52 (68.42%) met the requirements (26 psoriatic patients and 26 healthy participants). The mean session dose at baseline was 0.46 (0.31) J. Homeostasis parameters changed after follow-up, Table 3. TEWL decreased by 3.50 ± 1.41 $g \cdot m^{-2} \cdot h^{-1}$ in uninvolved skin ($p = 0.021$) and by 5.19 ± 2.00 $g \cdot m^{-2} \cdot h^{-1}$ at psoriatic plaques ($p = 0.016$). No effect was observed in healthy non-exposed skin. SCH increased by 7.01 ± 2.63 AU at psoriatic plaque ($p = 0.013$), while no changes were observed in healthy skin.

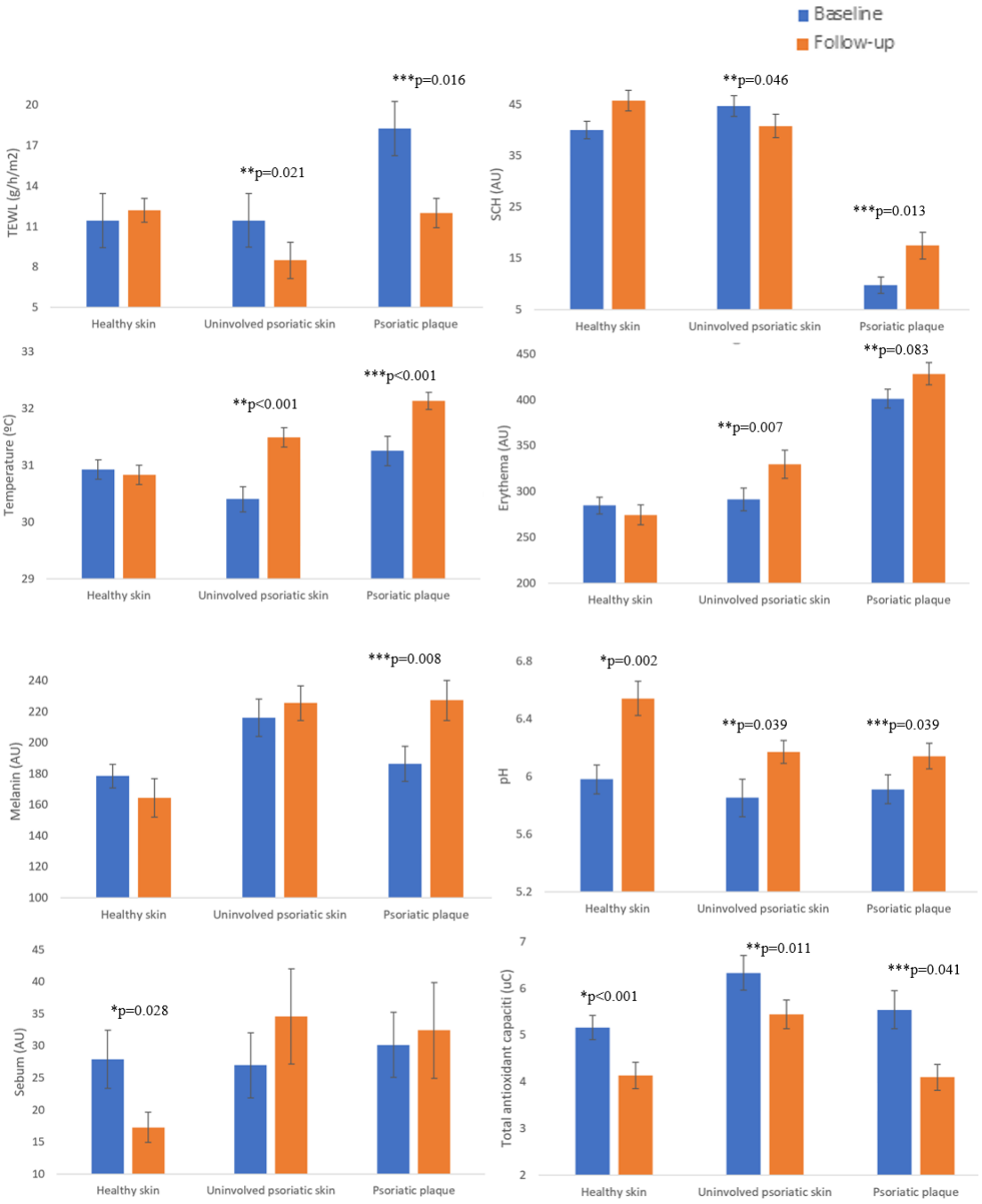
Table 3. Homeostasis parameters in healthy skin, uninvolved psoriatic skin, and psoriatic plaques after fifteen phototherapy sessions.

	Healthy skin after follow-up (n = 26)	**Uninvolved psoriatic skin after phototherapy (n = 26)**	**Psoriatic plaques after phototherapy (*n* = 26)**	**Mean difference in healthy skin after follow-up**	**Mean difference in uninvolved skin after vs. before phototherapy**	**Mean difference at psoriatic plaques after vs. before phototherapy**	*p* *	*p* **	*p* ***
TEWL ($g \cdot m^{-2}h^{-1}$)	12.18 (4.5)	8.48 (6.77)	11.98 (5.45)	0.30 (1.11)	−3.50 (1.41)	−5.19 (2.00)	0.786	0.021 **	0.016 ***
SCH (AU)	45.73 (10.13)	40.78 (11.70)	17.45 (13.41)	4.18 (1.96)	−6.10 (2.91)	7.01 (2.63)	0.53	0.046 **	0.013 ***
Temperature (°C)	30.93 (1.39)	31.49 (0.88)	32.13 (0.75)	−0.01 (0.25)	1.5 (0.26)	1.42 (0.28)	0.537	<0.00 1**	<0.001 ***
Erythema (AU)	274.13 (55.65)	329.57 (79.44)	428.15 (61.82)	−13.50 (6.78)	31.83 (17.06)	30.82 (17.06)	0.68	0.007*	0.083
pH	6.54 (0.59)	6.20 (0.28)	6.26 (0.36)	0.65 (0.18)	0.37 (0.16)	0.37 (0.16)	0.002*	0.039**	0.039***
Sebum (AU)	17.27 (11.90)	35.00 (39.18)	32.26 (38.78)	−10.38 (4.45)	12.83 (9.51)	7.17 (9.80)	0.028*	0.190	0.472
Q1 (uC)	0.72 (0.27)	0.87 (0.25)	0.85 (0.30)	−0.17 (0.04)	−0.39 (0.09)	−0.22 (0.11)	<0.001*	<0.001**	0.059
Q2 (uC)	3.39 (1.20)	4.32 (1.37)	4.07 (1.20)	−1.03 (0.26)	−1.24 (0.43)	−1.01 (0.49)	0.001*	0.009*	0.049*
QT (uC)	4.13 (1.42)	5.44 (1.57)	4.90 (1.43)	−1.18 (0.27)	−1.36 (0.49)	−1.23 (0.57)	<0.001*	0.011*	0.041*

AU, arbitrary units; Q1, fast antioxidant capacity; Q2, slow antioxidant capacity; QT, total antioxidant capacity; SCH, stratum corneum hydration; TEWL, transepidermal water loss; uC, microcoulombs. The data are expressed as means (standard deviation). * *p*-value after using Student's t-test for paired samples to compare homeostasis parameters in healthy skin before and after the follow-up. ** *p*-value after using Student's t-test for paired samples to compare homeostasis parameters in uninvolved psoriatic skin before and after fifteen phototherapy sessions. *** *p*-value after using Student's t-test for paired samples to compare homeostasis parameters at psoriatic plaques before and after fifteen phototherapy sessions.

Temperature increased after phototherapy by 1.5 ± 0.26 °C in uninvolved skin ($p < 0.001$) and by 1.42 ± 0.28 °C at psoriatic plaques ($p < 0.001$), while it did not change in healthy non-exposed skin. Erythema increased by 31.83 ± 17.06 AU in uninvolved skin ($p = 0.007$), and an almost significant increase of 30.82 ± 17.06 AU was also observed at psoriatic plaques ($p = 0.087$), Figure 1.

Figure 1. Homeostasis skin parameters in healthy skin, uninvolved psoriatic skin, and psoriatic plaques before and after follow-up. AU, arbitrary units; SCH, stratum corneum hydration; TEWL, transepidermal water loss; uC, microcoulombs. * *p*-value after using a linear regression model adjusted by emollient use to compare homeostasis parameters between control and uninvolved psoriatic skin before phototherapy. ** *p*-value after using a linear regression model adjusted by emollient use to compare homeostasis parameters between control and psoriatic plaques before phototherapy. *** *p*-value after using Student's t-test for paired samples to compare homeostasis parameters between uninvolved psoriatic skin and psoriatic plaques before phototherapy. Only *p*-values of <0.05 are shown.



3.4. Skin Homeostasis Predicts PASI Improvement

After follow-up, PASI decreased by 3.13 ± 3.13 points, so patients were placed in two groups: PASI reduction <3 and PASI reduction ≥3. Of the patients, 73.1% (19/26) were included in the first group and 26.9% (7/26) in the second. After the first phototherapy session, patients with a PASI improvement ≥3 showed a higher erythema increase (71.08 vs. 11.54 AU, $p = 0.011$), and an almost significant higher SCH increase (4.69 vs. 1.40; $p = 0.141$) and higher TEWL decrease (−4.97 vs. 0.86 $g \cdot m^{-2} \cdot h^{-1}$, $p = 0.199$).

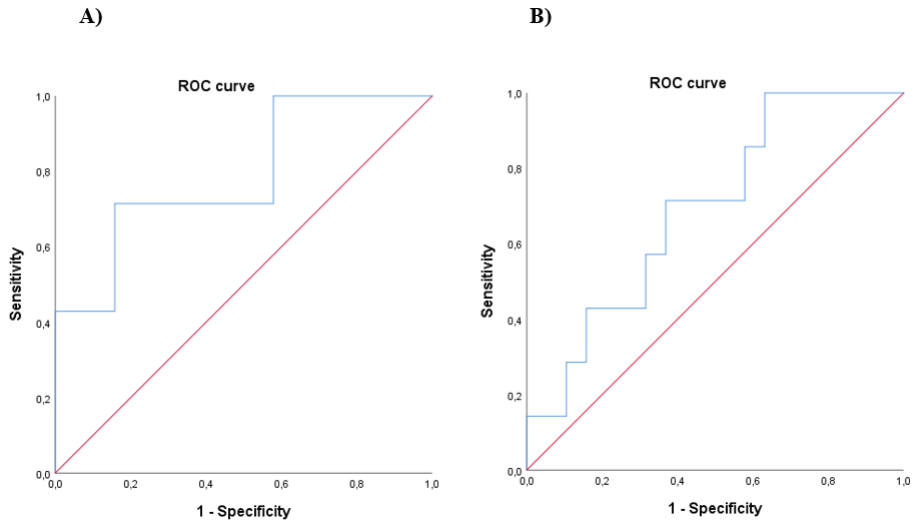
A ROC curve was generated to determine an optimum cut-off value for erythema increases after one phototherapy session, which allowed clinical improvement after 15 phototherapy sessions to be predicted (area under the curve = 0.789, $p = 0.026$) (Figure 2.A). A value for erythema increases exceeding 53.23 AU after the first phototherapy session, with a sensitivity of 71.4% and

specificity of 84.2%, indicates that a patient may improve PASI by ≥3 points after fifteen phototherapy sessions.

SCH increases were also higher in patients with PASI improvement ≥3. An ROC curve was generated to determine an optimum cut-off value for SCH increase after one phototherapy session, which allowed clinical improvement after 15 phototherapy sessions to be predicted (area under the curve = 0.692, p = 0.1402) (Figure 2B). A value for SCH increases exceeding 1.06 AU after the first phototherapy session, with a sensitivity of 71.4% and specificity of 63.8%, indicates that a patient may improve PASI by ≥3 points after fifteen phototherapy sessions.

After calculating the different cut-off levels, we evaluated whether combined values may also predict clinical improvement. Patients with erythema increase >53.23 AU and SCH increase >1.06 AU after the first phototherapy session may improve PASI by ≥3 after 15 phototherapy sessions, with a sensitivity of 57.1% and a specificity of 94.7% (Table S2).

Figure 2. Receiver operating characteristic (ROC) curve for the values of erythema increases after one phototherapy session. (**A**) A receiver operating characteristic (ROC) curve was created to determine the optimal cut-off value of erythema increases after one phototherapy session to predict PASI improvement in patients with psoriasis after fifteen phototherapy sessions (area under curve = 0.789, p = 0.026). An erythema increase exceeding 53.23 AU after the first phototherapy session had high probability of improving PASI by ≥3 points after fifteen phototherapy sessions (sensitivity = 71.4%; specificity = 84.2%). (**B**) A receiver operating characteristic (ROC) curve was created to determine the optimal cut-off value of stratum corneum hydration (SCH) increases after one phototherapy session to predict PASI improvement in patients with psoriasis after fifteen phototherapy sessions (area under curve = 0.692, p = 0.140). An SCH increase exceeding 1.06 AU after the first phototherapy session had high probability of improving PASI by ≥3 points after fifteen phototherapy sessions (sensitivity = 71.4%; specificity = 63.8%).



Area under the curve = 0.789, p = 0.026

Area under the curve = 0.692, p = 0.140

4. Discussion

Differences in skin homeostasis parameters between healthy skin, uninvolved psoriatic skin, and psoriatic plaques have been observed. After one phototherapy session, temperature, erythema, and SCH increased at psoriatic plaques. Moreover, after fifteen phototherapy sessions, decreased TEWL and increased SCH and temperature levels at psoriatic plaques were observed. Phototherapy could improve epidermal barrier function and skin homeostasis in psoriatic patients, and erythema increases after one phototherapy session could help clinicians select psoriasis patients with more probability of responding to phototherapy.

In agreement with previous reports, it has been observed that the whole epidermal barrier is affected in psoriatic patients, not only at psoriatic plaques [27]. Other research also found higher TEWL at psoriatic plaques than in uninvolved psoriatic skin and healthy controls [21,22,27] and lower SCH values at psoriatic plaques than in uninvolved psoriatic skin and healthy controls [21,27,28]. The differences in TEWL and SCH values between psoriatic plaques and uninvolved psoriatic skin may be explained by a low AQP3 expression in plaques [29]. Temperature and erythema were also higher at psoriatic skin, probably due to its inflammatory pathogenesis [30]. Moreover, TEWL and temperature at psoriatic plaques were noted as useful tools for evaluating psoriasis severity [27].

The role of phototherapy on epidermal barrier function and skin homeostasis is not well known. Our results found an improvement in epidermal barrier function and skin homeostasis after phototherapy. Recently, it has been observed that SCH decreased, and TEWL, erythema, and temperature increased at psoriatic plaques after only one phototherapy session [25]. Moreover, it was shown that phototherapy increased SCH and decreased TEWL after fourteen [24] and twenty-four [23] phototherapy sessions, without information regarding other skin homeostasis parameters. Our study found increased SCH at psoriatic plaques following only one phototherapy session and increased SCH and decreased TEWL at psoriatic plaques after fifteen phototherapy sessions. Moreover, in contrast with previous studies, we also included a non-exposed group with follow-up to prove that changes in SCH are not because of time. Changes in SCH might be due to the inhibition of epidermal hyperproliferation caused by phototherapy [20,31]. SCH and TEWL changes were greater at psoriatic plaques than in uninvolved psoriatic skin, which might underline a local effect on psoriasis plaques [32,33]. Temperature and erythema index rose after the phototherapy session, in agreement with previous reports [25,34–36]. Assessment of temperature and erythema increase may help clinicians optimize phototherapy to treat patients with an effective dosage without adverse events. The pH increased in healthy skin, uninvolved psoriatic skin, and psoriatic plaques, suggesting that time may have an effect on pH changes. Antioxidant capacity also decreased in healthy skin, uninvolved psoriatic skin, and psoriatic plaque. This fact might mean that the time have also an impact in antioxidant capacity or that the sticks used might lose their capacity to measure the antioxidant capacity along the time. There is little information regarding the effect of phototherapy on antioxidant capacity. Oxidative stress has been evaluated by measuring different parameters of a blood sample, with controversial results. Darlenski et al. found a slight decrease in the detoxifying activity of catalase without significant differences after phototherapy [24]. On the other hand, Pektas et al. observed total oxidant status and oxidative stress index increased after phototherapy [37]. Our results showed total antioxidant capacity decreases after phototherapy, in agreement with this research by Pektas.

Brazzelli et al. suggested that SCH improvement at psoriatic plaques might precede clinical improvement [23]. As far as we know, it is not known which parameters might predict clinical improvement in psoriatic patients treated with phototherapy. We observed that SCH changes after one phototherapy session might predict PASI improvement after fifteen phototherapy sessions. Moreover, a value for erythema increases exceeding 53.23 AU after the first phototherapy session, with a sensitivity of 71.4% and specificity of 84.2%, indicates that a patient may improve PASI by ≥3 points after fifteen phototherapy sessions. This research could help clinicians select psoriatic patients for phototherapy treatment. Therefore, patients who do not reach this value of erythema after the first session can be treated with another therapeutic alternative. Moreover, this research would also be interesting for selecting candidates for home

phototherapy, as patients who have an erythema increase exceeding 53.23 AU after the first phototherapy session may improve during treatment.

This study has some limitations. (1) The variation of the homeostasis parameters depending on external conditions. Nevertheless, to improve outcome reliability, all participants were measured by the same researcher in the same room and the ambient conditions were measured. (2) The loss of patients observed during follow-up as COVID-19 broke out during the follow-up period and the activity of dermatology practices was greatly reduced.

5. Conclusions

As far as we know, this is the first study to propose a cut-off point in erythema increases after one phototherapy session to select psoriasis patients with more likelihood of responding to fifteen phototherapy sessions. This could increase the treatment's cost-effectiveness and reduce indirect costs and hospital visits for patients with probable low response.

Supplementary Materials: The following are available online at www.mdpi.com/xxx/s1, Table S1. Characteristics of the participants included in the study. Table S2. Sensitivity and specificity in the prediction of clinical improvement after 15 phototherapy sessions based on the skin homeostasis changes after one phototherapy session.

Author Contributions: Conceptualization, T.M.-V. and S.A.S.; methodology, T.M.-V. and S.A.S.; software, A.M-.L. (Alejandro Molina-Leyva), A.B.E.; validation, T.M.-V., A.M.-L. (Antonio Martinez-Lopez) and S.A.S.; formal analysis, T.M.-V. and S.A.S.; investigation, T.M.-V. and S.A.S.; resources, S.A.S.; data curation, T.M.-V., A.S.S., and M.S.G.; writing—original draft preparation, T.M.-V., and S.A.S.; writing—review and editing, T.M.-V., E.J.M., and S.A.S.; visualization, T.M.V., A.M.L. (Alejandro Molina-Leyva), A.M.-L. (Antonio Martinez-Lopez) and S.A.S.; S.A.S.; project administration, S.A.S.; funding acquisition, S.A.S. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Ethics Committee of Hospital Universitario Virgen de las Nieves, Granada, Spain (protocol code V01 and date of approval 19/05/2019).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data presented in this study are available on request from the corresponding author.

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Conflicts of Interest: The authors declare no conflict of interest.

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Table S1. Characteristics of the participants included in the study.

	All participants at baseline (n=76)	Non-exposed participants at baseline (n=38)	Exposed participants at baseline (n=38)	All participants with follow-up (n=52)	Non-exposed participants with follow-up (n=26)	Exposed participants with follow-up (n=26)	p*	p**
Age (years)	43.03 (17.48)	44.92 (17.17)	45.13 (18.17)	44.77 (17.15)	45.00 (16.51)	44.54 (18.08)	0.959	0.85
Sex (%)								
-Female	40 (52.6%)	20 (52.60%)	20 (52.6%)	24 (46.2%)	12 (46.2%)	12 (46.2%)	1.00	1.00
-Male	36 (47.4%)	18 (47.40%)	18 (47.4%)	28 (53.8%)	14 (53.8%)	14 (53.8%)		
Phototype								
- II	6 (7.9%)	2 (5.3%)	4 (10.50%)				0.781	0.621
-III	66 (78.9%)	33 (86.8%)	30 (78.90%)					
-IV	7 (9.2%)	3 (7.9%)	4 (10.50%)					
Smoking habit								
- Non-smoker	62 (81.6%)	32 (84.20%)	30 (78.9%)	45 (86.5%)	23 (88.5%)	22 (84.6%)	0.554	1.00
- Smoker	14 (18.4%)	6 (15.80%)	8 (21.1%)	7 (13.5%)	3 (11.5%)	4 (15.3%)		
Alcohol habit (yes)	35 (46.1%)	17(44.70%)	18 (47.4%)	26 (46.2%)	12 (46.2%)	12 (46.2%)	0.818	1.00
Family history of psoriasis (yes)	18 (28.9%)	0 (0.00%)	18 (47.4%)	11 (21.2%)	0 (0.0%)	11 (42.3%)	<0.001*	<0.001**
Emollients use (yes)	41 (53.9%)	16 (42.10%)	25 (65.8%)	26 (50.0%)	9 (34.6%)	17 (65.4%)	0.038*	0.027**
DLQI **- Baseline** **- After 15 phototherapy sessions**			7.91 (6.61) -			6.92 (5.71) 4.88 (5.41)	-	-
PASI **- Baseline** **- After 15 phototherapy sessions**			8.55 (4.34) -			7.86 (4.44) 4.72 (4.00)	-	-
BSA **- Baseline** **- After 15 phototherapy sessions**			11.02 (8.54) -			10.19 (8.60) 6.35 (5.12)	-	-
Disease duration (years)			13.59 (11.46)			15.42 (11.22)	-	-
Previous treatments								
- Topical corticosteroids			28 (100.00%)			26 (100.00%)	-	-
- Systemic drugs			7 (18.40%)			6 (23.10%)		
- Biologic drugs			3 (7.89%)			3 (11.5%)		
Session dose (Joules) **- Baseline** **- After 15 phototherapy sessions**			0.42 (0.27) -			0.46 (0.31) 1.41 (0.16)	-	-
Session time (seconds) **- Baseline** **- 15th phototherapy sessions**			114.84 (82.00) -			127.48 (96.95) 366.62 (50.22)	-	-

BSA, Body Surface Area; DLQI, Dermatology Life Quality Index; NB-UVB, Narrow-Band Ultraviolet B; PASI, Psoriasis Area and Severity Index.

Data are expressed as relative (absolute) frequencies and means (standard deviation (SD). The Student's t test for independent samples or Welch's test, as appropriate, were used to compare continuous variables

and the chi-square test or Fisher's exact test, as appropriate, were applied to compare categoric data. Two-tailed $p<0.05$ was considered statistically significant in all tests.
*p value to compare non-exposed participant and exposed participants at baseline after using Student's t test for independent samples or Welch's test, as appropriate, to compare continuous variables; and the chi-square test or Fisher's exact test, as appropriate, to compare categoric data
**p value to compare non-exposed participant and exposed participants with follow-up after using Student's t test for independent samples or Welch's test, as appropriate, to compare continuous variables; and the chi-square test or Fisher's exact test, as appropriate, to compare categoric data.

5.5. The impact of gloves and masks on skin barrier.

The COVID-19 outbreak has increase the use of gloves and face masks. Moreover, mask wearing has become compulsory in many countries. The use of these equipment has been related to several skin disorders. There are several types of masks available and knowing which is the least aggressive for the skin could help to avoid skin lesions and develop new types of masks using skin-friendly materials.

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Impact of gloves and mask use on epidermal barrier function in health care workers

Short title: Gloves and mask impact on skin

Keywords: Contact Dermatitis; Dermatology; Health care workers; Hygiene; Occupational health practice

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Abstract

Background. Coronavirus Disease 2019 has rapidly spread all over the word. Protective equipment (PPE) including masks and gloves are needed to avoid transmission. Adverse skin reactions associated to PPE has been described, but there is no information regarding objective measures to assess skin impairment related to PPE.

Objectives. To evaluate the effect of using facial mask and nitrile gloves on epidermal barrier function and skin homeostasis.

Methods. A cross-sectional study was designed. Thirty-four Healthcare Workers (HCW) wearing nitrile gloves and a mask for two hours were included. Transepidermal Water Loss (TEWL), Stratum Corneum Hydration (SCH), erythema and temperature were measured.

Results. TEWL (31.11 vs 14.24 g/h/m^2), temperature (33.29 vs 32.57ºC) and erythema were significantly higher at the area covered by the gloves compared to non-covered area. TEWL (22.82 vs 13.69 g/h/m^2), temperature and erythema (411.43 vs 335.52 AU) were significantly increased at the area covered by the mask while SCH was lower. TEWL was higher at the area covered by a surgical mask than at a filtering respirator mask coded filtering facepiece 2 (FFP2) (27.09 vs 18.02 g/h/m^2 p=0.034).

Conclusion. Skin homeostasis and epidermal barrier function may be impaired by gloves and mask use. High quality PPE should be provided and adequate skin prevention measures should be implemented to reduce epidermal barrier damage.

1. Introduction

In December 2019, a new virus initially called "Novel Coronavirus 2019-nCoV" and later renamed to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), rapidly emerged in Wuhan, Hubei Province, China, and quickly spread lengthwise China and other countries around the world. At the time of this writing, the total number of cases worldwide exceeded 20 million people, affecting 188 countries, with more than 730,000 deaths[1]. Spain has been one of the most affected countries with more than 320,000 cases and 28,000 deaths[1].

To stop the spread of the outbreak, thousands of health care workers (HCW) have been working tirelessly taking care of infected and suspected patients. This effort has made HCW have a high risk of infection, specially while providing care to COVID-19 patients with inappropriate personal protective equipment (PPE)[2]. In fact, during SARS pandemic in 2003, HCW made up 21% of global cases[3]. To date, more than 50,000 HCW have been infected in Spain, up to 20% of Italian HCW have developed Coronavirus Disease 2019 (COVID-19) and an early report in a single-center case series in Wuhan found that 29% of hospitalized patients were HCW[4,5].

HCW should protect themselves from the virus by performing adequate hand washing and wearing adequate PPE, including medical masks, goggles or face shields, plastic gowns and gloves. The long-term working sessions and the daily use of the PPE can lead into physical and psychological disturbances among HCW[6], such as headache or exacerbation of their pre-existing disorder[7]. In fact, the prevalence of PPE-related skin injuries has been estimated between 42.8% and 74%[8,9]. Facial masks, goggles and face shields can lead to erosion, abrasion, maceration and ecchymosis in the cheeks, forehead and nasal bridge[10]. Moreover, a recent study reported an overall 21% of work absenteeism due to these facial lesions[11]. The frequent use of hand washing alcoholic or

chlorine-based disinfectants could also cause skin injuries, leading to desquamation and even irritative or allergic contact dermatitis 10 and the prolonged use of gloves could cause irritant and allergic contact dermatitis, glove-related hand urticaria[12], pompholyx or secondary infections[10].

The skin 44amagee associated to PPE could be evaluated objectively by the measurement of some parameters. Assessment of epidermal barrier function usually involves measurements of Transepidermal water loss (TEWL)[13], the quantity of condensed water that diffuses across a fixed area of stratum corneum to the skin surface per unit time[14]. Higher TEWL is often associated with skin barrier impairments[15]. Stratum corneum hydration (SCH) is another important parameter[16], and a lower value is frequently associated with skin barrier dysfunction[17]. Erythema and temperature may also influence epidermal barrier function and skin homeostasis[18,19].

Although many PPE-related skin injuries have been described in literature, to date, the impairment of the skin barrier has not been measured by objective methods. So, the aim of this study is to evaluate the effect of using facial mask and nitrile gloves on epidermal barrier function and skin homeostasis.

2. Material and methods

A cross-sectional study was designed. It was conducted between April 2020 and May 2020 in the Dermatology Department of the Hospital Universitario Virgen de las Nieves in Granada, Spain. Healthy HCW, males or females over 18 years, volunteers who were wearing for at least two hours nitrile gloves and a mask (a surgical mask or a filtering respirator mask coded filtering facepiece 2 (FFP2)) were included in the study. The exclusion criteria of the study population were: 1) not having previous personal history of any inflammatory skin disease (psoriasis, atopic dermatitis, hidradenitis suppurativa, acne or seborrheic dermatitis); 2) clinical infection on the measured area; 3) history of allergy or; 4) not signing the informed consent form.

Information regarding gender, age, occupational category, kind of mask and gloves wearing were gathered during the clinical interview. Homeostasis parameters related to epidermal barrier function were measured. Transepidermal Water Loss (TEWL) (in g/h/m^2, using Tewameter® TM 300), stratum corneum hydration (SCH) (in arbitrary units, using Corneometer® CM 825), erythema (in arbitrary units, using Mexameter® MX 18), and skin temperature (in ºC, using Skin-Thermometer ST 500) were measured by a Multi Probe Adapter (MPA, Courage + Khazaka electronic GmbH, Germany). All variables were measured at least two hours (ranging from 2 to 3 hours) after the participant was wearing the gloves and the mask into their shift varying days of their work schedule. All participants did not change the mask during this period while gloves change was allowed if needed. The new gloves should be immediately put on without using any products on the hands and arms. Measurements were taken at four anatomic areas: at the distal right volar forearm covered by the glove and in another area 2 cm far from not covered (Figure 1); at the right cheek covered by the mask and in another area 2 cm far from not covered. All parameters were measured ten times at each

area, using their average for analysis. Measurements were taken in the same room and ambient air temperature was measured with the TFA® Lab Thermometer IP65 LT-101. The average ambient air temperature at the time of the study was 22±1ºC and the average ambient air humidity was 45±3%.

Descriptive statistics were used to present the sample characteristics. Continuous data was expressed as the mean ± standard deviation. The absolute and relative frequency distributions were estimated for qualitative variables. The Shapiro-Wilk test was used to check the normality of data distribution. The Student's t-test for paired samples or the Wilcoxon test were used to compare homeostasis parameters between areas. The Student's t-test for independent samples or the Mann-Whitney test were applied when necessary to compare independent continuous data. Cohen's d was calculated to assess effect size, using the standard deviation of the baseline measure. A p-value of <0.05 was considered statistically significant. Statistical Analyses were performed using the SPSS package (SPSS for Windows, Version 24.0 Chicago: SPSS Inc.).

This study was approved by the ethics committee of Hospital Universitario Virgen de las Nieves (Epidermal barrier function and skin homeostasis project). The nature of the study was explained to all the participants, who agreed to participate. All measurements were non-invasive and patient data was kept confidential.

3. Results

Thirty-four participants, 61.76% (21/34) females and 38.24% (13/34) males, were included in the study. The mean age was 44.97 (11.97 SD) years, 46.33 (11.33 SD) for females and 42.77 (13.08 SD) for males. 47.06% (16/34) were doctors, 26.47% (9/34) were nurses and 26.47% (9/34) were miscellaneous HCWs, including nurses' assistant and cleaners.

Skin homeostasis analysis between areas covered and non-covered by gloves

Epidermal barrier function parameters between the distal volar forearm covered and non-covered by the nitrile gloves were compared (Table 1). TEWL was higher at the gloves-covered area (31.11 vs 14.24 g/h/m^2, $p<0.001$, $d=0.92$). SCH was also increased at the area covered (43.26 vs 58.28 AU, $p<0.001$, $d=0.88$). Moreover, temperature (33.29 vs 32.57ºC, $p<0.001$, $d=0.84$) and erythema (243.97 vs 215.55 AU, $p<0.001$, $d=0.65$) were also higher at the area covered by the gloves when compared to non-covered area.

Skin homeostasis analysis between areas covered and non-covered by mask

Homeostasis parameters were also different in the areas covered and non-covered by a mask (Table 2). TEWL was significantly higher on the area covered by the mask (22.82 vs 13.69 g/h/m^2, $p<0.001$, $d=0.73$) while SCH was lower (53.87 vs 59.50 AU, $p=0.058$, $d=0.37$). Temperature (33.19 vs 32.54ºC, $p<0.001$, $d=0.80$) and erythema (411.43 vs 335.52 AU, $p<0.001$, $d=0.88$) were both increased at the area covered by the mask.

The ®nfluence of mask type on skin homeostasis

Differences in homeostasis parameters were found depending on the type of mask (Table 3). SCH was lower at the surgical mask-covered area (49.70 vs 58.56 AU, p=0.092, d=0.53) when compared to FFP2 mask-covered. No difference in temperature was found (33.25 vs 33.13ºC, p=0.674, d=0.14).

TEWL was significantly higher at the area covered by a surgical mask than at the FFP2 one (27.09 vs 18.02 g/h/m^2, p=0.034, d=0.59). Moreover, surgical mask had a higher power in increasing TEWL (p=0.026), Table 4. While the cheek covered by surgical mask increased 12.54 (SD 2.14) g/h/m^2 compared to non-covered area, the FFP2 area covered was only 5.28 (2.27) g/h/m^2 higher than the non-covered.

The influence of age and sex on skin homeostasis covered areas

To evaluate the impact of age in skin homeostasis covered areas, participants were grouped in individuals ≤ 45 years and > 45 year (Table 5). It was observed that mask impact was similar between age groups. Nevertheless, it was found that the gloves have a different impact depending on the age. The older group had higher temperature increase between cover and non-covered area than the young group (0.93 vs 0.53ºC, d=0.85, p=0.013). Moreover, the erythema increase in gloves-covered areas was also higher in the older group (43.00 vs 15.47 AU, d=0.98, p=0.036). A positive correlation between age and temperature increase (r=0.34, p=0.051) was found. No differences between sexes were found.

4. Discussion

This study shows that epidermal barrier function and skin homeostasis may be impaired by gloves and mask. An increased TEWL, temperature and erythema in the area covered by gloves and an increased TEWL, temperature and erythema and a decreased SCH in the area covered by masks was observed. Moreover, surgical masks are more harmful for skin than FFP2 mask, showing higher TEWL in areas covered by surgical masks. Epidermal barrier function integrity is important to prevent SARS-CoV-2 infection as previous reports have shown[11,20].

Hands are the most common site affected by PPE-related adverse skin reactions during COVID-19 outbreak[9]. This is due to excessive hand washing, hydro alcoholic solutions and gloves use[21]. Medical gloves are mostly made of different polymers such as latex and nitrile[12], being the nitrile one the preferred during the COVID-19 pandemic because of its high protection and durability[22]. Many adverse skin reactions have been described associated to its use, such as irritant contact dermatitis, allergic contact dermatitis, and contact urticaria[12]. Gloves use often causes skin maceration presenting as softening, whitening, wrinkling of the skin, and sometimes, skin peeling[23]. This study showed higher SCH values at the gloves covered area which may be explained in part by the increases sweat production in the covered area[13]. Nevertheless, the difference in TEWL between two near areas, gloves covered and non-covered, reflect a skin barrier damage related to gloves use. This may explain the increased cases of hand eczema, allergic contact dermatitis, secondary superficial fungal infection and pompholyx between HCW gloves users[23,24]. Previously, it has also been described higher TEWL values during 30 minutes of gloves use[25]. Nevertheless, the effects of glove occlusion is controversial in the literature[26]. This study also shows high erythema and temperature

at the area covered by gloves. This is in agreement with previous reports as erythema is the second most reported skin adverse sign between HCWs[27].

Moreover, the high erythema and temperature are markers of inflammation and increased skin permeability[28]. Although, SARS-CoV spreads mainly via the respiratory route, other possible pathways of infection have been proposed, including skin surface[20,29]. So the permeability increased by gloves, added to the abundantly presentation of angiotensin-converting enzyme 2, the cell receptor for SARS-CoV-2, in the basal layer of the epidermis and the blood vessels of the skin may increase the risk for being infected with SARS-CoV-2[20,19], while transepidermal transmission of this virus is still theoretical. Possible solutions to prevent PPE and hand hygiene-related injuries have been described such as increase protective skincare measures after washing hands or using gloves[30] and alcohol-based disinfectants solutions containing glycerin as moisturizer[21].

Cheeks are the second area most affected by PPE-related adverse skin reactions during COVID-19 outbreak 9. In fact, masks are the most common culprit agent among all PPE causing skin damage[27] leading to indentations, ecchymosis, maceration, abrasion and erosion[10]. This study observed high TEWL values at the mask covered area, revealing a skin impairment associated to mask use. This may explain some skin reactions associated with mask use such as allergic contact dermatitis or urticarial facial eruption[31]. In contrast to gloves, mask covered areas showed lower SCH values than non-covered. This may be explained because the lower density of eccrine sweat glands at the cheek[32]. Moreover, this study shows that mask covered area have high temperature and erythema than near non-covered areas, relating to increased permeability[28]. This could also explain the mask-induced itch[33] and may be a risk factor to get SARS-CoV-2 as frequent face touching may increase the exposure and entry of

SARS-CoV-2 infection[11]. Moreover, the increased temperature is also a contributor for developing acne and seborrheic dermatitis[31,34]. To the best of our knowledge, there is no previous information regarding epidermal barrier function and skin homeostasis with mask use.

This report also shows high TEWL increased at areas covered by surgical mask that at FFP-2 mask covered areas. This may mean that surgical masks are more harmful for skin barrier. FFP-2 masks have more filter efficiency[35], meaning they are more protective to avoid COVID-19 transmission[36]. Nevertheless, no differences in skin damage between different types of mask has been reported to date. A possible explanation to differences in TEWL values may be the different material they are made from[37].

This study also found higher increased in erythema and temperature at gloves covered areas in people over 45 years. It has been previously pointed out that these parameters may be associated to a high permeability[28]. Moreover, elderly people are more susceptible to skin damage[38] and more frequently experience itch[39], causing face touching and increasing the exposure to SARS-CoV-2. This is an important fact, as old people have a high risk of developing critical or mortal COVID-19 disease[40].

While, the normal values for homeostasis parameter are still controversial, our study shows similar values on the non-covered areas than previous report in healthy people. In our population, mean TEWL was 14.24 g/h/m^2 on the distal volar forearm and 13.69 g/h/m^2 on the cheek, in agreement with normal values in a meta-analysis (normal values ranging from 9.84 to 17.96 g/h/m^2 on the distal right volar forearm; and ranging from 12.92 to 14.91 g/h/m2 on the right cheek) [15]. SCH values were also similar to previous reports 41. Erythema values on non-covered areas were also within the

normal values on healthy skin: 215.55AU on the volar forearm (normal values 222.7-288.4AU) and 335.52AU on the cheek (normal values 294.2-409.4AU) [42].

Limitations of this study include the small sample size and the lack of follow-up to assess skin barrier disfunction along time. Moreover, the distal volar forearm may not be the area primarily affected by glove use, meaning that the effect by glove use may be underestimated in this study. This location was selected instead of the palm to increases similarities between skin properties in covered and non-covered areas. Nonetheless, this pioneering study provides insights into objective measures for gloves and mask skin damage during the COVID-19 outbreak.

Skin homeostasis and epidermal barrier function may be impaired by gloves and mask use. Surgical mask use is associated with higher TEWL values than FFP2 mask. While before COVID-19 pandemic, only HCWs wear gloves and mask during a limited period, now the whole population use them for long-period. High quality PPE should be provided and adequate skin prevention measures should be implemented to reduce epidermal barrier damage.

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6. Tables

Table 1. Homeostasis parameters at areas covered and non-covered by gloves.

	Distal forearm non-covered by gloves (n=34)	Distal forearm covered by gloves (n=34)	Cohen's d	p*
TEWL ($g/h/m^2$)	14.24 (9.84)	31.11 (18.34)	0.92	<0.001*
SCH (AU)	43.26 (12.31)	58.28 (17.08)	0.88	<0.001*
Temperature (ºC)	32.57 (0.81)	33.29 (0.86)	0.84	<0.001*
Erythema (AU)	215.55 (38.69)	243.97 (44.97)	0.65	<0.001*

AU, arbitrary units; SCH, Stratum Corneum Hydration; TEWL, Transepidermal Water Loss

* p value after using Stu'ent's t test for paired samples to compare homeostasis parameters between forearm covered and non-covered by gloves

Table 2. Homeostasis parameters at areas covered and non-covered by mask.

	Cheek non-covered by mask (n=34)	Cheek covered by mask (n=34)	Cohen's d	p*
TEWL ($g/h/m^2$)	13.69 (4.66)	22.82 (12.59)	0.73	<0.001*
SCH (AU)	59.50 (14.76)	53.87 (15.30)	0.37	0.058
Temperature (ºC)	32.54 (0.85)	33.19 (0.81)	0.80	<0.001*
Erythema (AU)	335.52 (80.50)	411.43 (86.20)	0.88	<0.001*

AU, arbitrary units; SCH, Stratum Corneum Hydration; TEWL, Transepidermal Water Loss

* p value after using Stu'ent's t test for paired samples to compare homeostasis parameters between forearm covered and non-covered by gloves

Table 3. Homeostasis parameters at areas covered by different types of masks.

	Surgical mask (n=18)	FFP2 mask (n= 16)	Cohen's	p*
TEWL ($g/h/m^2$)	27.09 (15.30)	18.02 (6.09)	0.59	0.034*
SCH (AU)	49.70 (16.73)	58.56 (12.39)	0.53	0.092
Temperature (ºC)	33.25 (0.86)	33.13 (0.78)	0.14	0.674
Erythema (AU)	429.85 (91.23)	390.70 (77.78)	0.43	0.190

AU, arbitrary units; SCH, Stratum Corneum Hydration; TEWL, Transepidermal Water Loss

* p value after using Stu'ent's t test for independent samples or Mann-Whitney test to compare homeostasis parameters between the cheek covered by a surgical mask or a FFP2 mask.

Table 4. Mean differences between covered and uncovered mask areas for homeostasis parameters.

	Surgical mask (n=18)	FFP2 mask (n= 16)	Cohen's	p*
TEWL ($g/h/m^2$)	12.54 (11.40)	5.28 (5.30)	0.64	0.026*
SCH (AU)	-8.99 (18.94)	-1.85 (13.37)	0.57	0.218
Temperature (ºC)	0.61 0.42)	0.69 (0.53)	0.19	0.615
Erythema (AU)	80.28 (65.06)	70.98 (46.95)	0.14	0.640

AU, arbitrary units; SCH, Stratum Corneum Hydration; TEWL, Transepidermal Water Loss

* p value after using Stu'ent's t test for independent samples or Mann-Whitney test to compare changes in mask covered and non-covered homeostasis parameters between the type of masks.

Table 5. Mean differences between covered and uncovered areas for homeostasis parameters between age groups.

	Gloves				Mask			
	Age ≤ 45 (n=18)	**Age > 45 (n= 16)**	**Cohen's**	**p***	**Age ≤ 45 (n=18)**	**Age > 45 (n= 16)**	**Cohen's**	**p****
TEWL ($g/h/m^2$)	**14.11 (11.61)**	**19.97 (15.46)**	**0.50**	**0.218**	**7.93 (5.96)**	**10.48 (12.70)**	**0.43**	**0.45**
SCH (AU)	**9.34 (9.14)**	**12.29 (19.66)**	**0.32**	**0.571**	**-6.92 (21.55)**	**-4.19 (9.13)**	**0.13**	**0.640**
Temperature (ºC)	**0.53 (0.47)**	**0.93 (0.39)**	**0.85**	**0.013***	**0.71 (0.32)**	**0.59 (0.60)**	**0.38**	**0.471**
Erythema (AU)	**15.47 (28.14)**	**43.00 (44.31)**	**0.98**	**0.036***	**70.42 (57.29)**	**82.08 (57.04)**	**0.20**	**0.557**

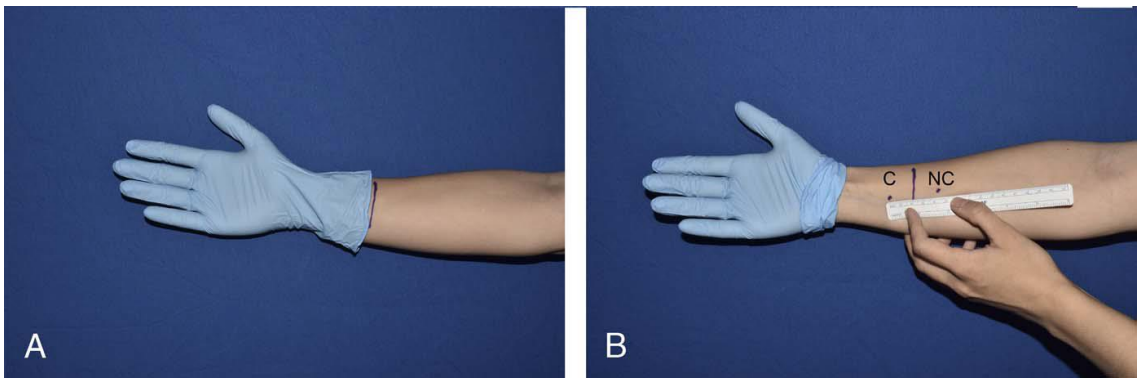
AU, arbitrary units; SCH, Stratum Corneum Hydration; TEWL, Transepidermal Water Loss

* p value after using Stu'ent's t test for independent samples or Mann-Whitney test to compare changes in gloves covered and non-covered homeostasis parameters between participants ≤ 45 years and > 45 years

** p value after using Stu'ent's t test for independent samples or Mann-Whitney test to compare changes in mask covered and non-covered homeostasis parameters between participants ≤ 45 years and > 45 years.

7. Figures

Figure 1. A) Area covered by gloves. B) Measurements' location on the right volar forearm; C: gloves covered area; NC: gloves non-covered area



5.6. Hand hygiene strategies: skin barrier dysfunction, effectiveness and tolerability.

The COVID-19 outbreak has also increase the public interest for hand hygiene products. Currently there are several hand hygiene products available, including soaps, alcohol-based hand sanitizers and disinfectant wipes, but there is scarce knowledge about which is the least aggressive for the skin, the most effective reducing microorganism or the most tolerable for the user.

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Assessment of hand hygiene strategies on skin barrier function during COVID-19 pandemic: a randomized clinical trial

Running title: Impact of hand hygiene on skin barrier

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Abstract

Introduction. COVID-19 has increased the frequency of hand washing. There is scarce evidence regarding the impact of different hand hygiene procedures on skin barrier function in clinical practice.

Objective. To compare the impact on skin barrier function of different hand hygiene measures in health care workers in daily practice.

Methods. A randomized controlled clinical trial was conducted. Participants were randomized to sanitize their hands with water and soap, alcohol-based hand sanitizers (ABHS) or disinfectant wipes during their 8-hour work-shift. Epidermal barrier functional parameters, like transepidermal water loss (TEWL), and the microbial load were assessed before and immediately after the workday. Tolerance and acceptability of each product were recorded after work.

Results. Sixty-two participants were included and 20, 21 and 21 were randomized respectively to use water and soap, ABHS and disinfectant wipes. After the 8-hour shift, TEWL increase was higher with disinfectant wipes than with soaps or ABHS (+5.45vs+3.87vs-1.46g·h^{-1}·m^{-2} respectively, *P*=.*023*). Bacteria and fungi colony-forming unit (CFU) count reduction was lower for water and soap group than for ABHS and disinfectant wipes. Disinfectant wipes were considered more difficult to use (*P*=.*013*) compared to water and soap and ABHS.

Conclusion. Daily hand hygiene with ABHS showed the lowest rates of skin barrier disruption and the highest reduction of CFU.

Keywords: Hand Sanitizers; Hand Disinfection; Hand Hygiene; COVID-19, Skin Barrier

1. Introduction

The frequency of hand washing and disinfection has increased during the coronavirus 2019 disease (COVID-19) pandemic[1] as it is believed that SARS-CoV-2 can also be transmitted by direct and indirect contact[2,3]. For the required proper hand hygiene procedure[4,5], currently there are several hand hygiene products available, such as soaps, alcohol-based hand sanitizers (ABHS) and disinfectant wipes[6]. ABHS reduce skin pathogens more efficiently[7,8] and, therefore, frequent application of ABHS containing at least 60% alcohol or, if unavailable, hand washing with soap and water for at least 30 seconds, are recommended[9,10]. Nevertheless, a frequent use of these products may induce dry hands and skin damage, resulting in irritant or allergic contact dermatitis[11]. Moreover, injured skin is a potential host for SARS-CoV-2[12].

Skin barrier impairment can be measured easily using objective parameters: namely transepidermal water loss (TEWL)[13,14], the quantity of condensed water that diffuses across a fixed area of stratum corneum to the environment[13] which increases with barrier impairments[15], stratum corneum hydration (SCH) [16], pH[17], temperature[18] and antioxidant capacity[19]. TEWL has been shown to increase with use of soaps[20] and to decrease with ABHS[21], but there is only one study comparing the impact of different hand hygiene products on skin barrier function in the clinical practice[22].

The main objective of this study is to compare the impact on skin barrier function of soaps, ABHS and disinfectant wipes in health care workers in daily practice.

2. Material and methods

2.1. Study design

An observer-blinded randomised comparative study following CONSORT guidelines (Supplementary Material) was designed and conducted between October 2020 and January 2021 in the Dermatology Department of the Hospital Universitario Virgen de las Nieves in Granada, Spain. Participants were health care workers (HCWs), aged 18-60 years, who were randomized in a 1:1:1 ratio (computerized randomization) to use for their hand hygiene between every patient, either washing with water and soap, applying and rubbing their hands with an ABHS or using disinfectant wipes for 20 seconds at least. Informative leaflets with rules for each procedure were delivered. Composition of each product is described in Supplementary Material. Intervention assignments were allocated by the study coordinator (SAS). The evaluator (TMV) was blinded to the assignments.

All participants were selected just at work arrival and included in the study after giving their written informed consent. After randomization, baseline measurements were taken at around 08:00 a.m. before participants had started their work shift, at least 30 minutes after any hand hygiene procedure. Participants were instructed how to use only the allocated hand hygiene procedure, record the frequency of its application and to avoid the use of protective gloves during the study and if gloves were worn, to take them off as soon as possible. After a full working day (around 03:00 p.m.), at least 5 minutes after the last hand hygiene procedure, microbiological samples were collected and, at least 30 min thereafter, skin barrier function parameters were measured.

Exclusion criteria were a previous personal history of any inflammatory skin disease, clinical infection of the area under evaluation, known or suspected incapacity to comply with the study protocol or no signature of the informed consent form.

2.2. Outcomes and measures

The primary outcome measure was skin barrier impairment, assessed by changes in TEWL and secondary outcome measures were changes in temperature, SCH, erythema, pH and antioxidant capacity[23], reduction of microbial load- assessed by changes in bacteria and fungi colony forming units (CFUs)-, and perceived differences in tolerability and acceptability[24] among the three hand hygiene procedures.

Skin homeostasis and epidermal barrier function parameters

Before and after a working day, measurements were performed on the dominant palm after resting at least for 30 minutes in a room with controlled ambient air temperature and humidity, which were measured with the TFA Lab Thermometer IP65 LT-101, Wertheim, Germany (average air temperature 22±1ºC; ambient air humidity of 45%±5%). We used Tewameter TM 300, Courage + Khazaka electronic GmbH, Bilbao, Spain for TEWL (in g·h-1·m-2), Corneometer CM 825, Courage + Khazaka electronic GmbH, Bilbao, Spain for SCH (in arbitrary units), Skin-pH-Meter PH 905, Courage + Khazaka electronic GmbH, Bilbao, Spain, for skin pH, Mexameter MX 18, Courage + Khazaka electronic GmbH, Bilbao, Spain for evaluating erythema index (in arbitrary units) and Skin-Thermometer ST 500, Courage + Khazaka electronic GmbH, Bilbao, Spain for skin temperature (in ºC) connected to a Multi Probe Adapter (MPA, Courage + Khazaka electronic GmbH, Bilbao, Spain). All parameters were measured ten times, and their average was used for analysis.

Total antioxidant capacity (TAC), both fast antioxidants (Q1), that have a lower oxidation potential, and slow antioxidants (Q2)[23], were measured using eBQC electrochemical method (Bioquochem S.L. (BQCkit), Asturias, Spain), and expressed in micro-coulombs. Briefly, a conductive hydrogel, designed for direct measurement of

the antioxidant capacity, is stuck to the skin surface and maintained in contact for five minutes and then peeled off and placed on the measurement area of the e-BQC strips[23].

Microbiological evaluation

At baseline and after the working day, microbiological samples were obtained by direct application of the 4 fingertips in a Petri dish with culture medium, either for bacteria (right hand) or fungi (left hand). For bacteria, smears were placed in Trypcase Soy 3P Irradiated Trypcase Soy Agar (TSA3), a non-selective method, between 28-32ºC for 72 hours and for fungi in Sabouraud Dextrose 3PTM Agar with irradiated neutralisers (SN3P) between 20-25ºC for 96 hours. The composition of each medium is described in Supplementary Material. The total number of CFU per plate were counted after 72 or 96 hours of incubation, and differences between baseline and end of the working day were used to assess the microbial load.

Tolerability and acceptability

Tolerability and acceptability of the hand hygiene procedures were assessed after the workday using the protocol proposed by the WHO that allowed both objective evaluation by an observer and subjective evaluation by the participants[24]. Briefly, on a seven-point Likert scale, participants assessed the product's: colour (unpleasant-pleasant), smell (unpleasant-pleasant), texture (sticky-non-sticky), irritation (very irritating-not irritating), drying effect (very much-not at all), ease of use (very difficult-very easy), speed of drying (very slow-very fast), application (unpleasant-pleasant), and overall evaluation (dissatisfied-satisfied). Likewise, on a seven-point scale, participants rated the skin condition of their hands: appearance (abnormal-normal); intactness (abnormal-normal); moisture content (abnormal-normal); sensation (abnormal-normal);

overall integrity of the skin (very altered-not altered). Skin condition was also assessed by the dermatologist evaluator, as follows: redness (0–3, no redness-very bright with oedema), scaling (0–3, no scaling-very pronounced desquamation), fissures (0–3, no fissure-extensive cracks with bleeding or seeping), visual scoring of skin scale (0, no observable scale or irritation of any kind; 1, occasional scale that is not necessarily uniformly distributed; 2, dry skin and/or redness; 3, very dry skin with whitish appearance, rough to touch, and/or redness, but without fissures; 4, cracked skin surface but without bleeding/seeping; 5, extensive cracking of skin surface with bleeding/seeping). All evaluations were carried out at baseline and after the working day using the hand-hygiene product.

Other variables

Sociodemographic data including sex, age, professional group (doctor, nurse, miscellaneous), work-related activities likely to cause skin damage and use of protective hand lotion/cream were recorded by a clinical interview. The phototype was assessed by a dermatologist using Fitzpatrick grading[25]. The frequency of hand hygiene procedures was self-reported by each participant.

2.3. Statistical analysis

Participants were evaluated according to their randomized group using intention-to-treat analysis. Descriptive statistics were used to present the sample characteristics. Continuous data was expressed as the mean±standard deviation. The absolute and relative frequency distributions were estimated for qualitative variables. The Shapiro-Wilk test was used to check the normality of data distribution and Levene's test to check the homogeneity of variance. One-way analysis of variance (ANOVA), post-hoc

Bonferroni correction, was used to compare quantitative variables between different hand hygiene procedure groups. The Student's t-test for paired samples was used to compare differences in parameters before and after using the hand hygiene product. A linear regression model was constructed to evaluate variables associated with TEWL change. Epidemiological and statistical criteria were used to model variable selection. The effect of each exploratory variable on the model and its significance were studied. If the variable improved the model fit and adequacy (based on the likelihood ratio criteria and the significance of the parameter), it was kept; otherwise, the variable was excluded. The model was checked for pairwise interaction between covariates. Potential confounding covariates were studied using a change of significance in the model's parameters or a change of 30% of its value. Statistical significance was defined by a two-tailed $P<.05$. Statistical analyses were performed using the SPSS package (SPSS for Windows, Version 24.0 Chicago: SPSS Inc.).

Accepting an alpha risk of 0.05 and a beta risk of 0.2 in a two-sided test, 20 subjects are necessary in each group to recognize as statistically significant a minimum difference of 6 units in TEWL between any pair of groups assuming that 3 groups exist. The common deviation is assumed to be 6. It has been anticipated a drop-out rate of 5%. G*Power 3.1.9.2., Heinrich-Heine-Universität Düsseldorf, was used to calculate the sample size.

2.4. Ethics

This study was approved by the ethics committee of Hospital Universitario Virgen de las Nieves the 8th September 2020 (HCHJ01 / 1489-N-20). The nature of the study was explained to all the participants, who agreed to participate by verbal and written consent. All measurements were non-invasive and subject data was kept confidential.

3. Results

3.1. Baseline demographic and clinical characteristics

Sixty-two HCWs were included in the study, 20 of them in the water and soap group, 21 in ABHS group and 21 in disinfectant wipes group (Figure S1). Only one subject did not finish the study. No significant differences in participants' demographic characteristics between groups were found, Table 1. The mean age was 38.32 (13.46) years and the female: male ratio was 1.48:1. Overall mean frequency of hand hygiene procedures was 8.52 (1.76) without differences between groups: 8.20 (1.32) times for water and soap, 8.43 (1.81) times for ABHS and 8.90 (2.07) times for disinfectant wipes. Only two participants used protective gloves during the study (one in AHBS group and another in water and soap group) and the stated duration of wearing was less than five minutes**.**

3.2. Skin barrier impairment

TEWL increased by 5.45 (2.15) $g \cdot h^{-1} \cdot m^{-2}$ in disinfectant wipes group and 3.87 (1.71) $g \cdot h^{-1} \cdot m^{-2}$ in water and soaps group while it was reduced by 1.46 (1.42) $g \cdot h^{-1} \cdot m^{-2}$ in the ABHS group with significant differences between groups (P=.020), (Table 2). Those using disinfectant wipes showed greater increases in TEWL values compared to those using ABHS (P=.023) but no statistically differences were observed between disinfectant wipes and soap or between soap and ABHS.

pH increased by 0.37 (0.12) in the water and soap group but remained unchanged in the ABHS group and disinfectant wipes group. There were differences in pH changes between the 3 groups (P=.014), but the difference was only statistically significant when comparing the groups with soap and disinfectant wipes (P=.014).

Temperature decreased significantly by 1.62 (0.48) ºC when using water and soap and by 1.73 (0.47) ºC when using ABHS. TAC decreased significantly in all groups, both fast antioxidants and slow antioxidants. Fast antioxidant capacity decreased by 0.45 uC in water and soap group, 0.25 uC in ABHS group and 0.25 uC in disinfectant wipes group; and slow antioxidant capacity decreased by 0.86 uC in water and soap group, 0.71 uC in ABHS group and 0.58 uC in disinfectant wipes group. TAC decreased by 1.31 uC when using water and soap, by 0.96 uC when using ABHS and by 0.86 uC when using disinfectant wipes. SCH and erythema did not change significantly in any group (Table 2).

A linear regression model was constructed to assess variables that could influence TEWL change (Table 3). After adjusting by type and number of the hand hygiene procedures in each work-shift, temperature change, sex and age, it was observed that water and soap (β=4.77, P=.05), disinfectant wipes (β=6.14, P=.016) and the temperature change (β=1.18, P=.015) were independently associated with TEWL change.

3.3. Reduction of microbial load

Percentage reduction in bacteria CFU count was lower in the water and soap group compared to those using ABHS or disinfectant wipes (65.7% vs 90.5% vs 87.44%, P=.002), Figure 1A. Moreover, percentage reduction in fungi CFU count was lower in the water and soap group than in those using ABHS and disinfectant wipes (41.4% vs 80.3% vs 82.8%, P=.017), Figure 1B. No significant differences in fungi and bacteria CFU count reduction were observed between ABHS and disinfectant wipes groups, Figure S2.

3.4. Tolerability and acceptability

Differences were found in subjective evaluation of water and soap, ABHS and disinfectant wipes regarding grading of colour (P=.046), drying effect (P=.032) and ease to use (P=.013), but not in other subjective parameters. The colour of disinfectant wipes was ranked lower than of ABHS (P=.047). Disinfection wipes received worse ratings for the drying effect than ABHS (P=.047). Disinfectant wipes were less easy to use than ABHS (P=.011) (Table 4). Regarding tolerability objective evaluation, differences in changes in redness (-0.05 vs. 0.76 vs. 0.95, P<.001) and changes in visual scoring of skin scale (-0.05 vs. 0.71 vs. 0.95, P<.001) were observed between water and soap, ABHS and disinfectant wipes respectively, whereas scaling or fissures were similar between groups. Changes in redness correlated with changes in erythema (r=0.38, P=.007). Water and soap produced less redness than ABHS (P<.001) and disinfectant wipes (P<.001) with no differences between ABHS and disinfectant wipes.

4. Discussion

This study evaluated the impact of different hand hygiene procedures on the skin of the hands after a shift of 8 hours in HCWs, which is difficult to compare with other studies which usually have this evaluation after longer periods and mostly in experimental settings, outside the regular work setting[26, 27]. In our study we noticed that already after a single working day there were important differences between the three procedures of hand sanitation in almost all the parameters we evaluated (TEWL, CFU and tolerability rates).

Disinfectant wipes showed the highest TEWL increase. Water and soap also led to increase of TEWL values, similarly to disinfectant wipes. ABHS showed the best results, as it was the only hand hygiene procedure that did not increase TEWL values, likely in relation to lower skin barrier impairment. Previous studies showed that TEWL is increased by soaps[20] and is decreased by ABHS[21] but it has been also stated that the skin barrier function is impaired by ABHS when applied on skin areas previously exposed to water immersion[28]. To our knowledge, the single previous study that assessed the impact of different hand hygiene procedures on skin barrier function in the clinical practice, evaluated the effects of soap and water vs. ABHS and showed no significant differences in TEWL changes[26]. Moreover, in experimental settings, with a lower participants number, ABHS caused less skin irritation and less skin barrier disruption than detergents[27, 29, 30]. ABHS and disinfectant wipes contain additional skin care substances, such as glycerin, a moisturizing agent which may replenish lipids and trap water, improving epidermal barrier[31]. Moreover, cleaning hands with soap and water removes skin lipids as they are rinsed off, whereas they remain on the skin when using ABHS30. Lipids may be also potentially wiped off when using disinfectant wipes[32] explaining their higher epidermal disruption compared to ABHS. Furthermore,

the type of hand hygiene product was found to be an independent predictor for change in TEWL after adjusting for other variables namely gender and age, whose influence on TEWL is controversial[32]. Other factors, including the number of hand hygiene procedures and skin temperatures, which may have an impact on TEWL[13], were similar in the three groups.

pH increase observed in the water and soap group may be explained by the alkaline pH of soap, or related to stratum corneum swelling, lipid rigidity and skin irritation[33]. TAC decreased in all groups, both fast antioxidants and slow antioxidants. TAC has been used as an inverse biomarker of oxidative stress, as it is an indicator of the sample ability to scavenge free radicals[23]. We used an electromechanical method to assess this parameter, that carries out a complete oxidation of the sample, considering individual peaks as the response of a specific antioxidant and obtaining the TAC measure through a mathematic algorithm. The total charge of antioxidants is divided in two sections: fast, including antioxidants with lower potential of oxidation, and slow, including antioxidants with higher potential of oxidation[23]. TAC predominantly measures chain breaking antioxidants, including uric acid and ascorbic acid, and exclude contribution of metal binding proteins[34]. TAC decreases when using all hand hygiene products may be due to the reduction in biological and chemical antioxidant substances, such as gallic acid equivalents or vitamin C equivalents[35], while the lack of differences between procedures could be explained because the increases oxidative damage to lipids and proteins is not being considered in this measure[34]. It would be interesting to use different measurements of individual antioxidants and markers of oxidative damage to accurately assess differences in antioxidant capacity between hand hygiene procedures[34, 36].

Regarding the antimicrobial power, water and soap showed the lowest reduction in bacterial and fungi CFU count. ABHS and disinfect wipes had similar CFU reduction rates and both higher than water and soap. ABHS kills microorganism by penetrating though their membrane and inducing cellular lysis while soaps only remove debris from the skin[31]. Therefore, ABHS and disinfectant wipes may be more effective in reducing live bacteria and fungi that are able to form colonies in culture (reduced CFU) than water and soap, as shown in our study. Most studies observed higher rates of microorganism decontamination with ABHS[37] compared to soaps, including in the everyday use[6, 31], which is also in agreement with in vitro studies[38]. In agreement, WHO guidelines on hand hygiene in health care recommends using ABHS instead of water and soap if hands are not visibly dirty[10]. Viruses are more difficult to study in vivo and there are scarce studies that compare the viral load reduction with different types of hand hygiene product. In vitro, both soaps and ABHS are effective in inactivating enveloped virus[39]. ABHS has also a high activity against non-enveloped viruses[10]. Regarding disinfectant wipes, previously it has been observed that they are non-inferior compared to water and soap[40] and less effective than ABHS[41] in reducing bacteria from the hands. These studies evaluated the antimicrobial power of the product after artificial contamination of the hands with Escherichia coli[40,41] while our study evaluated the effectiveness in removing usual microorganisms on the hand without any bacteria addition. The differences observed in the antimicrobial power between studies may depend on the predominant type of bacteria on the hand.

Hand hygiene products also must be tolerable and acceptable to the user[42]. The lowest rating of tolerability and acceptability in the present study was for disinfectant wipes, as they were considered as having the highest drying effect and being the least easy to use. Tolerability rates did not differ between ABHS and water and soap. Previous

studies showed that ABHS are well accepted and tolerated among HCWs[42], and during working hours they could be even more timesaving than water and soap[43]. There are no studies evaluating the tolerability of disinfectant wipes. In our study, the lowest rating of acceptability for disinfectant wipes might be explained by the fact that people are less used to employ them, and their application is more difficult and time-consuming than using a solution. Regarding tolerability objective evaluation, disinfectant wipes showed the highest rates for erythema increase, which might be explained by skin irritation.

This study has some limitations: 1) Only one type of hand hygiene product was tested in each participant; 2) The short follow-up, as the effect of the hand hygiene product was evaluated after one work shift. Nevertheless, the assessment of skin barrier function parameters after only one day allowed to evaluate the overall impact of the hand hygiene products, as other factors, such as emollients use, could bias this effect. 3) Bacterial and fungal CFU were not differentiated. Therefore, we were not able to determine what type of product was most effective in eliminating the different types of micro-organisms. 4) In contrast to most other studies, the palms and not the dorsum of the hands were selected for measuring the skin bioengineering parameters. The thicker stratum corneum of the palms may induce a distinct response to the hygiene procedures, but on the other hand, the dorsum of the hands might be more influenced by external factors14. 5) There was a risk that evaporation of wash water was measured when assessing the TEWL. However, the 30-minute adaptation period before TEWL measurements reduced this possible bias.

5. Conclusion

According to our findings, daily hand hygiene with ABHS showed the lowest rates of skin barrier impairment, the highest rates of CFU reduction and was considered the most convenient and easy method to use.

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Figure legend

Figure 1. Reduction of microbial load. A) Bacteria colony-forming unit count reduction. B) Fungi colony-forming unit count reduction.

Table legend

Table 1. Baseline demographic and clinical characteristics.

Table 2. Changes in skin homeostasis and epidermal barrier function parameters between groups.

Table 3. Analysis of the factors related to TEWL changes.

Table 4. Tolerability and acceptability of the hand hygiene products.

Supplementary Material

Figure S1. Participants flow chart.

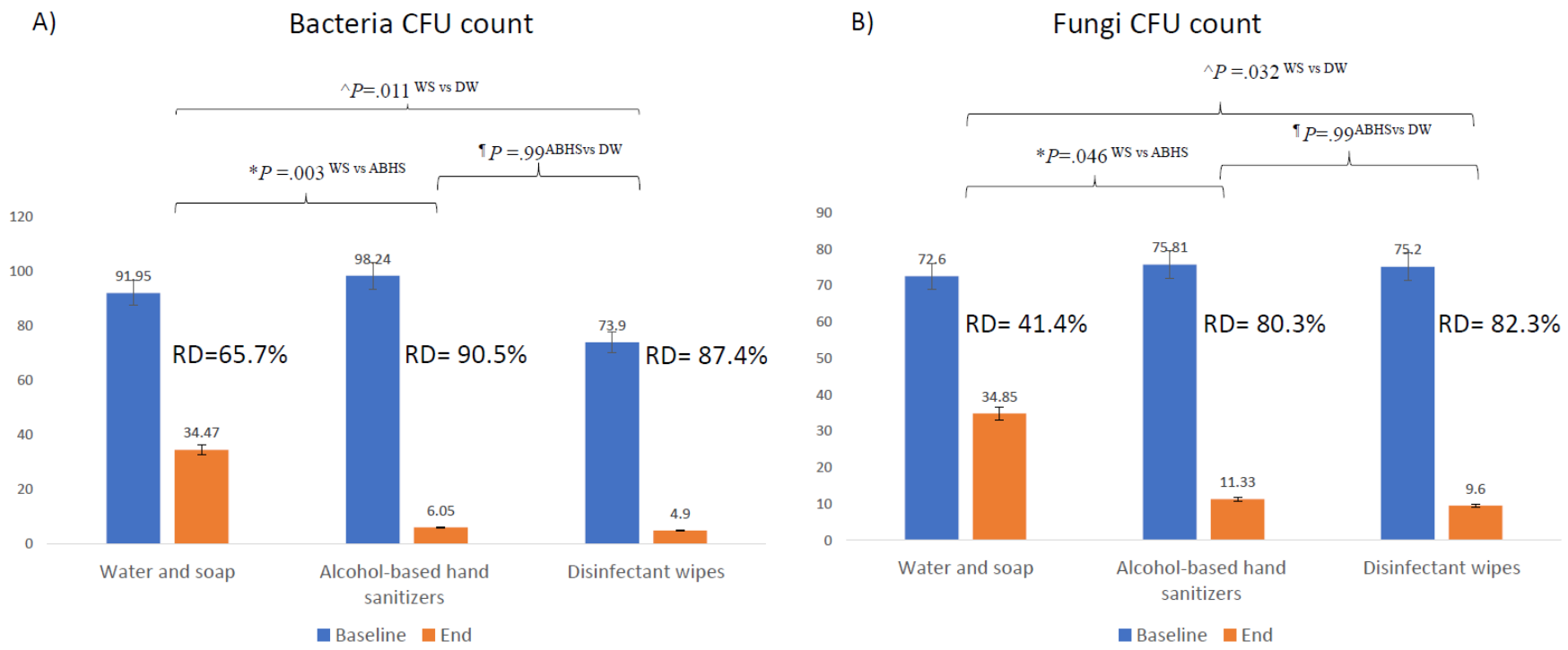
Figure S2. A) Bacteria colony-forming unit count before and after follow-up using each hand hygiene product, B) Fungi colony-forming unit count before and after follow-up using each hand hygiene product. These are the culture plates of one subject each from the respective group.

Composition of hand hygiene products and the medium used to culture microorganism.

Consort Checklist

 doi: 10.1111/cod.14034

Figure 1. Reduction of microbial load. A) Bacteria colony-forming unit count reduction. B) Fungi colony-forming unit count reduction.



Tables

Table 1. Baseline demographic characteristics.

Characteristic	All participants (n=62)	Water and soap (n=20)	Alcohol-based hand sanitizers (n=21)	Disinfectant wipes (n=21)	*P-value*
Age	38.32 (13.46)	39.20 (12.66)	36.43 (13.7)	39.38 (14.37)	.736*
Sex					
- Female	37 (59.7%)	13 (65%)	12 (57.1%)	12 (57.1%)	.840#
- Male	25 (40.3%)	7 (35%)	9 (42.9%)	9 (42.9%)	
Professional group					
- Doctors	34 (54.8%)	12 (60%)	11 (52.4%)	11 (52.4%)	.693#
- Nurses	6 (9.7%)	3 (15%)	1 (4.8%)	2 (9.5%)	
- Miscellaneous	22 (35.5%)	5 (25%)	9 (42.9%)	8 (38.1%)	
Phototype					
- II	4 (6.5%)	0	2 (9.5%)	2 (9.5%)	.394#
- III	57 (91.9%)	20 (100%)	18 (85.7%)	19 (90.5%)	
- IV	1 (1.6%)	0	1 (4.8%)	0	
Non- work-related activities likely to cause damage in skin (yes)	14 (22.6%)	5 (25%)	5 (23.8%)	4 (19%)	.889#
Use of protective hand lotion/cream					
- Several times/day	10 (16.1%)	4 (20%)	3 (14.3%)	3 (14.3%)	.831#
- Once/day	9 (14.5%)	3 (15%)	2 (9.5%)	4 (19%)	
- Sometimes	13 (21%)	5 (25%)	3 (14.3%)	5 (23.8%)	
- Rarely	7 (11.3%)	1 (5%)	3 (14.3%)	3 (14.3%)	
- Never	23 (37.1%)	7 (35%)	10 (47.6%)	6 (28.6%)	

Data are expressed as absolute (relative) frequencies or mean (standard deviation).

* *P-value* after using one-way independent ANOVA, to compare differences in continuous variables between different hand hygiene products (water and soap, alcohol-based sanitizer and disinfectant wipes).

#*P-value* after using chi-square test or Fisher's exact test, as appropriate, were applied to compare categoric data between different hand hygiene products (water and soap, alcohol-based sanitizer and disinfectant wipes).

Table 2. Changes in skin homeostasis and epidermal barrier function parameters.

Skin homeostasis parameters	**Water and soap (n=20)**				**Alcohol-based sanitizer (n=21)**				**Disinfectant wipes (n=21)**				***P-value#***
	Baseline (n=20)	End (n=20)	Change (n=20)	***P-value****	Baseline (n=21)	End (n=21)	Change (n=21)	***P-value****	Baseline (n=21)	End (n=20)	Change (n=20)	***P-value****	
TEWL ($g \cdot h^{-1} \cdot m^{-2}$)	24.41 (7.55)	28.29 (11.81)	+3.87 (1.71)	.035	22.93 (7.41)	21.48 (8.15)	-1.46 (1.42)	.316	23.09 (9.67)	28.75 (14.16)	+5.45 (2.15)	.020	.020^
SCH (AU)	44.14 (14.14)	40.85 (16.00)	-3.29 (2.03)	.122	46.60 (16.11)	43.26 (17.82)	-3.35 (1.99)	.109	44.33 (17.21)	45.20 (19-19)	+0.75 (2.43)	.760	.319
Temperature (ºC)	28.94 (2.31)	27.32 (2.48)	-1.62 (0.48)	.003	29.70 (2.31)	27.97 (2.40)	-1.73 (0.47)	.001	29.58 (2.53)	29.58 (2.37)	-0.65 (0.49)	.230	.549
Erythema (AU)	238.40 (40.85)	224.04 (39.40)	-14.35 (8.73)	.117	253.19 (55.47)	251.40 (52.93)	-1.78 (6.82)	.797	251.47 (39.04)	263.81 (48.18)	+ 9.85 (5.60)	.095	.068
pH	6.31 (0.48)	6.68 (0.45)	+0.37 (0.12)	.005	6.57 (0.60)	6.51 (0.54)	-0.07 (0.17)	.685	6.85 (0.53)	6.64 (0.39)	-0.24 (0.14)	.116	.014¶
Total antioxidant capacity (uC)	6.28 (1.51)	4.98 (1.15)	-1.31 (0.23)	<.001	6.82 (1.64)	5.86 (1.50)	-0.96 (0.42)	.033	6.64 (1.57)	5.75 (1.31)	-0.86 (0.29)	.009	.613
- Fast antioxidant capacity (uC)	0.99 (0.45)	0.54 (0.19)	-0.45 (0.10)	<.001	0.97 (0.51)	0.72 (0.25)	-0.25 (0.13)	.062	0.90 (0.39)	0.65 (0.18)	-0.25 (0.08)	.004	.302
- Slow antioxidant capacity (uC)	5.30 (1.23)	4.44 (1.00)	-0.86 (0.21)	.001	5.85 (1.30)	5.15 (1.29)	-0.71 (0.34)	.049	5.71 (1.25)	5.10 (1.19)	-0.58 (0.24)	.027	.762

Data are expressed as mean (standard deviation).

AU, arbitrary units; SCH, Stratum Corneum Hydration; TEWL, Transepidermal Water Loss, uC, Micro-coulombs.

**P-value* after using Student's t test for paired samples to compare parameters at baseline and after using the hand hygiene product.

#*P-value* after using one-way independent ANOVA, post-hoc Bonferroni correction, to compare changes in skin homeostasis parameters between different hand hygiene products (water and soap, alcohol-based sanitizer and disinfectant wipes).

^ post-hoc Bonferroni correction to compare changes in TEWL between soap and alcohol-based sanitizer (*P=.111*), between soap and disinfectant wipes (*P=1*), between alcohol-based sanitizer and disinfectant wipes (*P=.023*).

¶ post-hoc Bonferroni correction to compare changes in pH between soap and alcohol-based sanitizer (*P*=.106), between soap and disinfectant wipes (*P*=.014), between alcohol-based sanitizer and disinfectant wipes (*P=1*).

Table 3. Analysis of the factors related to Transepidermal Water Loss changes.

	Crude model			**Adjusted model**		
	β	**CI 95%**	***P-value****	**β**	**CI 95%**	***P-value#***
Water and soap vs ABHS	1.97	(-2.64, 6.59)	.395	4.77	(0, 9.55)	.050
Disinfectant wipes vs ABHS	4.30	(-0.20, 8.80)	.061	6.14	(1.20, 11.09)	.016
Temperature change	1.36	(0.14, 1.30)	.006	1.18	(0.24, 1.12)	.015
Number of times of handwashig	-0.74	(-1.98, 0.51)	.240	-0.80	(-1.97, 0.36)	.171
Sex (female)	2.44	(-1.95,6.82)	.270	2.73	(-1.39, 6.85)	.189
Age	0.095	(-0.07, 0.26)	.240	0.01	(-0.14, 0.17)	.873

ABHS, alcohol-based hand sanitizers, CI, Confidence Interval

Data are expressed as mean (standard deviation).

**P-value* after using a linear regression model to assess TEWL changes with one predictor. #*P-value* after using a linear regression model to assess TEWL changes adjusted by the type of hand hygiene product (creating two dummy variables to compare water and soap vs alcohol-based hand sanitizers (ABHS) and disinfectant wipes vs ABHS), temperature change, number of times of hand washing, sex and age. β coefficient and 95% confidence interval (CI 95%) are shown.

Table 4. Tolerability and acceptability of the hand hygiene products

	All participants (n=62)	**Water and soap (n=20)**	**Alcohol-based hand sanitizer (n=21)**	**Disinfectant wipes (n=21)**	***P-value#***
Subjective evaluation of the test product after using					
Color (unpleasant-pleasant)	6.24 (1.15)	6.35 (1.04)	6.62 (0.67)	5.76 (1.48)	.046
Smell (unpleasant-pleasant)	5.95 (1.27)	6.35 (0.88)	6.05 (1.24)	5.47 (1.50)	.080
Texture (very sticky- not sticky at all)	5.16 (2.17)	4.75 (2.45)	4.86 (2.06)	5.86 (1.90)	.194
Irritation (very irritation-not irritating)	5.89 (1.67)	5.80 (1.96)	6.33 (0.86)	5.52 (1.94)	.284
Drying effect (very much-not at all)	3.66 (2.07)	4.15 (2.06)	4.24 (1.92)	2.71 (1.82)	.032
Ease to use (very difficult-very easy)	5.95 (1.67)	6.10 (1.48)	6.62 (1.16)	5.14 (1.98)	.013
Speed of drying (very slow-very fast)	4.85 (1.87)	4.15 (2.06)	5.24 (1.67)	5.14 (1.77)	.121
Application (very unpleasant-very pleasant)	5.97 (1.47)	6 (1.52)	6.24 (1.26)	5.67 (1.62)	.457
Overall evaluation (dissatisfied-very satisfied)	5.84 (1.35)	5.85 (1.27)	6.24 (1.13)	5.43 (1.54)	.150
Subjective evaluation of skin condition after using the product					
Appearance (abnormal-normal)	5.95 (1.66)	5.80 (1.79)	6.38 (1.07)	5.67 (1.98)	.342
Intactness (abnormal-normal)	6.56 (0.98)	6.60 (0.94)	6.60 (1.14)	6.48 (0.87)	.898
Moisture content(abnormal-normal)	5.77 (1.73)	5.45 (2.09)	6.48 (0.81)	5.38 (1.88)	.71
Sensation (abnormal-normal)	6.31 (1.39)	6.10 (1.71)	6.86 (0.36)	5.95 (1.56)	.075
Overall integrity (very altered- perfect)	6.39 (1.00)	6.25 (1.07)	6.67 (0.58)	6.24 (1.22)	.292
Objective evaluation					
Change in Redness	0.56 (0.08)	-0.05 (0.05)	0.76 (0.12)	0.95 (0.12)	<.001
Change in Scaliness	0.10 (0.04)	0.05 (0.05)	0.20 (0.09)	0.05 (0.05)	.072
Change in Fissures	0 (0)	0 (0)	0 (0)	0 (0)	1
Change in Visual Scoring of Skin Scale	0.55 (0.64)	-0.05 (0.22)	0.71 (0.56)	0.95 (0.59)	<.001

Data are expressed as mean (standard deviation).

P-value after using one-way independent ANOVA to compare tolerability and acceptability between different hand hygiene products (water and soap, alcohol-based handrub and hydroalcoholic wipes)

Figure S1. Participants flow chart.

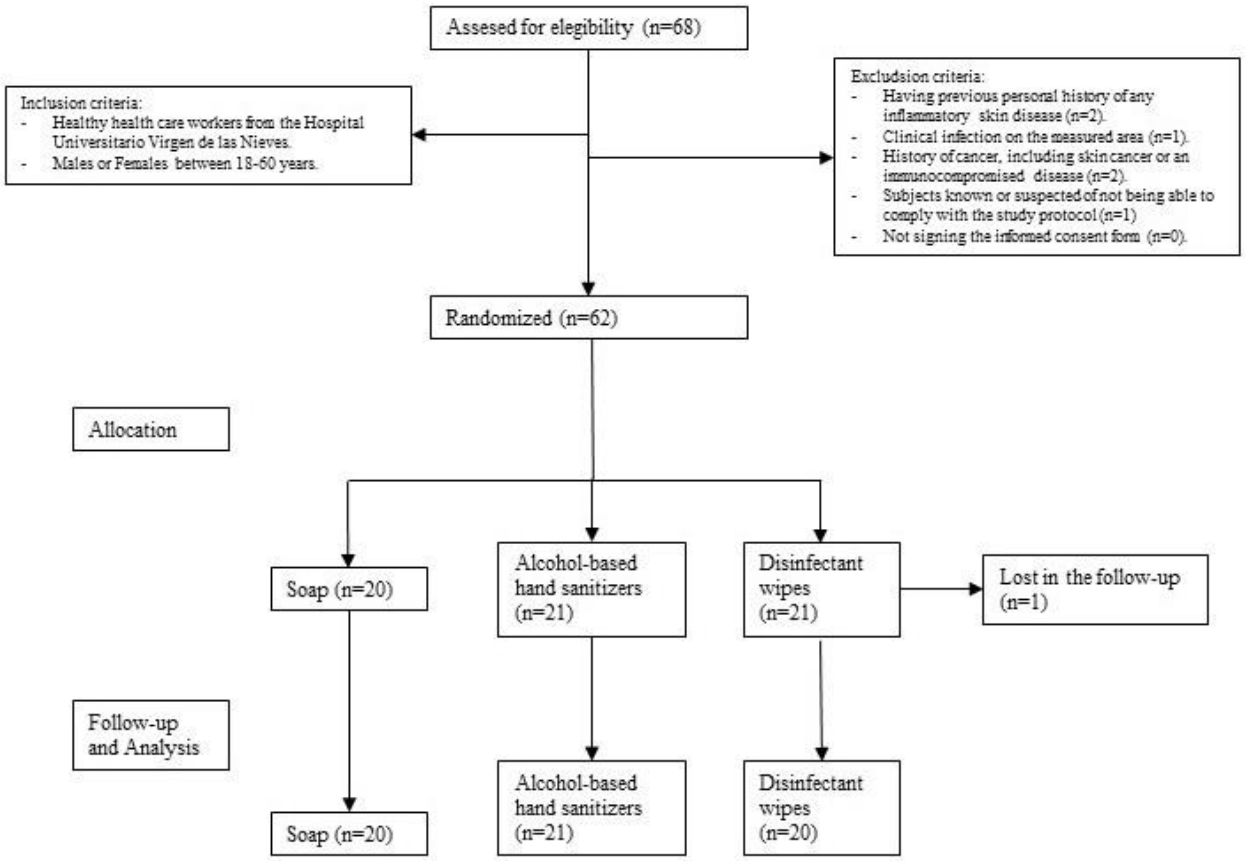
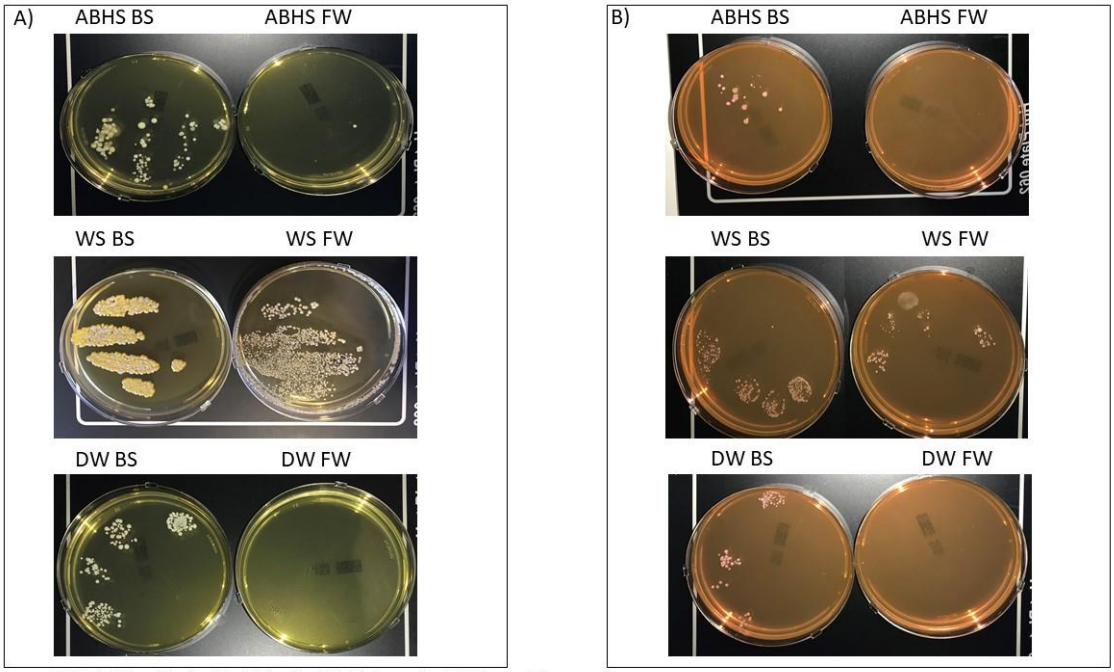


Figure S2. A) Bacteria colony-forming unit count before and after follow-up using each hand hygiene product, B) Fungi colony-forming unit count before and after follow-up using each hand hygiene product. These are the culture plates of one subject each from the respective group.



ABHS, alcohol-based hand sanitizers; BS, baseline; DW, disinfectant wipes; FW, follow-up; WS, water and soap

Composition of hand hygiene products and the medium used to culture microorganism

Composition of hand hygiene products

- Soap was composed of sodium laureth sulfate, sodium chloride, cocamide DEA, phenoxyethanol, cocamidopropyl betaine, glycol distearate, cocamide MEA, perfum, citric acid, water. *55201101-JU-GEL DERMOMANZANA, Tensigel NCB, CDI Vallès Productos y Sistema para la Higiene Profesional, JUSMER, Barcelona, Spain.*
- Alcohol based-hand sanitizer (ABHS) consisting of in 70% alcohol, 27.55% water, 2% triethanolamine, 0.25% acrylates, 0.2% glycerine. *Gel Higienizante de manos Hidroalcoholico MIXER, Mixer & Pack SL, Madrid, Spain.*
- Disinfectant wipes (DW) composed of 75% alcohol, 23.5% water, 1.5% glycerine. *Toallitas Hidroalcoholicas Deliplus, Ubesol Laboratorios Maverick, Valencia, Spain.*

Composition of the medium used to culture microorganism

- Trypcase Soy 3P Irradiated Trypcase Soy Agar (TSA3 composed of agar 15 g, casein enzyme peptone (bovine) 15 g, soybean enzyme peptone 5 g, sodium chloride 5 g and purified water 1 L.
- Sabouraud Dextrose 3PTM Agar with irradiated neutralisers (SN3P) composed of dextrose 40 g, agar 15 g, casein peptone (bovine) 5 g, meat peptone 5 g, L-histidine 1 g, soy lecithin 0,7 g, polysorbate 5 g, sodium thiosulphate, 0.05 g and purified water 1 L.

 doi: 10.1111/cod.14034

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	4
	2b	Specific objectives or hypotheses	5
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	5
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	5
Participants	4a	Eligibility criteria for participants	5
	4b	Settings and locations where the data were collected	5
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	6
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	6-7
	6b	Any changes to trial outcomes after the trial commenced, with reasons	7
Sample size	7a	How sample size was determined	7

 doi: 10.1111/cod.14034

	7b	When applicable, explanation of any interim analyses and stopping guidelines	7-8
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	6
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	6
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	6
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	6
	11b	If relevant, description of the similarity of interventions	6
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	9-10
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	10
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	11
	13b	For each group, losses and exclusions after randomisation, together with reasons	11
Recruitment	14a	Dates defining the periods of recruitment and follow-up	11
	14b	Why the trial ended or was stopped	11
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	11, Table 1

 doi: 10.1111/cod.14034

Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	11, Fugure S1
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	11-12
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	11-12
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	11-12
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	11
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	15
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	14-15
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	13-14
Other information			
Registration	23	Registration number and name of trial registry	-
Protocol	24	Where the full trial protocol can be accessed, if available	-
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	1

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org

5.7. Systematic review and meta-analysis regarding skin adverse events associated with personal protective equipment.

The need of using personal protective equipment has increased due to COVID-19 pandemic. Many researches have been published about skin side events related to them. Nevertheless, it is not clear what is the real prevalence of these skin adverse events, what type of side events are the most common or what are the risk factors for developing them.

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Title: Skin adverse events related to personal protective equipment: a systematic review and metanalysis.

Running head: Skin adverse events related to personal protective equipment.

Keywords: COVID-19, Personal Protective Equipment, Skin, Systematic Review.

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Figures: 0

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Abstract

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a global pandemic that has spread all over the word. To avoid the virus transmission, healthcare workers (HCWs) must wear adequate personal protective equipment (PPE). PPE is associated with several side events, including skin reactions. The objective of this study is to summarize the prevalence, type and risk factors for cutaneous adverse events related to PPE and prevention measures to avoid them. A systematic review and metanalysis was conducted using Medline, Scopus and Embase databases from conception to 21st January 2021. All types of epidemiological studies regarding skin adverse events related to PPE were included. The literature search identified 1,007 references, 35 of them met the eligible criteria and were included for analysis, representing 31,453 participants. The media of skin side events related to PPE was 75.13%. The rate of cutaneous adverse events related to mask was 57.71% and those associated with gloves and hand hygiene products was 49.16%. Most common skin adverse events were contact dermatitis, acne and itching. The most damaged anatomical regions were the nasal bridge, the cheeks and the hands. The duration of PPE wearing was the most common risk factor. Frequent hand washing, gloves and masks were the agents most frequently related to skin reactions. N95 respirators were the most harmful mask type for the skin. Hydrocolloid use prevented from developing skin adverse events related to masks. In conclusion, the rate of cutaneous adverse events related to PPE use is high. A longer duration of PPE wearing was the most common risk factor. Using hydrocolloid could prevent from skin injuries related to mask use.

1. Introduction

In December 2019, a novel virus, called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and causal agent of the Novel Coronavirus-2019 disease (COVID-19), emerged in Wuhan, China Popular Republic, and rapidly spread around the world. Currently, more than 90 million people have been infected, with up to 2 million of deaths worlwide[1].

To fight against the pandemic and avoid the virus transmission, healthcare workers (HCWs) must wear adequate personal protective equipment (PPE), including medical masks, goggles or face shields, plastic gowns and gloves, and perform frequent hand washing[2]. The long-term working sessions and the daily use of the PPE can lead to physical and psychological disturbances among HCWs[3, 4]. Moreover, several cutaneous adverse events have been related to PPE[5]. Nevertheless, the prevalence of skin cutaneous adverse events related to PPE range between different studies[6, 7], it is not known the type of material most likely to cause skin damage and there is scarce evidence regarding preventive measures to avoid adverse skin events related to PPE[8, 9].

The aims of this study are to summarize the prevalence, type and risk factors for cutaneous adverse events related to PPE and to evaluate preventive measures taken to avoid cutaneous adverse events related to PPE in HCWs and the general population.

2. Material and methods

2.1. Design

A systematic review and meta-analysis were conducted (Supplementary Material)

Research questions:

1) What is the prevalence of skin adverse events related to PPE?
2) Which are the most common skin adverse events associated with PPE and which are the most affected regions?
3) What are the risk factors for developing skin side events related to PPE?
4) What is the prevalence and what kind of side events are related to mask use?
5) What is the prevalence and what are kind of side events are related to gloves and hand washing?
6) What prevention measures could be taken to avoid skin adverse events related to PPE?

2.2. Search strategy

A literature search was performed using Medline, Scopus and Embase databases from conception to 21st January 2021, following PRISMA Guidelines (Supplementary Material). The following search algorithm was used: ((PERSONAL PROTECTIVE EQUIPMENT) OR GLOVES OR MASK OR FACEMASK OR (RESPIRATORY EQUIPMENT) OR (ALCOHOL-BASED HAND RUB) OR SOAP OR ALCOHOL) AND (SKIN OR CUTANEOUS OR DERMATOLOGY OR (SKIN REACTION) OR (SKIN ADVERSE EVENTS)) AND (COVID-19 OR (CORONAVIRUS DISEASE 2019)).

2.3. Inclusion and exclusion criteria

The search was limited to: (i) human data, (ii) *in vivo* studies, (iii) skin adverse events related to PPE, (iv) articles written in English. All types of epidemiological studies (clinical trials, cohort studies, case-control studies and cross-sectional studies) regarding skin adverse events related to PPE were included and analyzed. Reviews, guidelines, protocols, case series, case reports and conference abstracts were excluded.

2.4. Study selection

Two researchers (TMV and CCB) independently reviewed the titles and abstracts of the articles obtained in the first search to assess relevant studies. The full texts of all articles meeting the inclusion criteria were reviewed, and their bibliographic references were checked for additional sources. The articles considered relevant by both researchers were included in the analysis. Disagreements about inclusion or exclusion of articles were subjected to discussion until a consensus was reached. If not reached, resolution was achieved by discussion with a third researcher (AMLo).

2.5. Variables

The variables assessed were study design, rate and type of skin adverse events related to PPE, risk factors for developing skin manifestations, number of participants, author, country, age, sex, assessment tools, anatomical regions damaged, kind of preventive measures.

2.6. Statistical analysis

The overall prevalence of skin cutaneous events related to PPE was calculated by a random effect meta-analysis weighted by the study sample size. Forest plots were

constructed to summarize the prevalence estimates and their 95% CIs. These figures present measures of heterogeneity across studies (Cochrane Q statistic, noted the I2 statistic). Microsoft Excel version 2016, Redmond, Washington, The USA. was used to run this data[10].

3. Results

The literature search identified 1,007 references, 668 after removing duplicated papers. After reviewing the title and abstract, 136 records underwent full-text review. A total of 101 records were excluded because they did not investigate skin adverse events associated with PPE. Other reasons for exclusion along with the flow chart are shown in Figure S1. Finally, 35 studies, representing 31,453 participants, met the eligible criteria and were included and fully reviewed.

3.1. What is the prevalence of skin adverse events related general personal protective equipment?

The media of skin side events related to PPE was 75.13%, after conducting a random effect meta-analysis weighted by the study sample size, Figure S1. Thirteen studies explored cutaneous adverse events related to PPE[5-7, 11-20]. Seven studies evaluated the prevalence of skin side events related to PPE[5-7, 11-14]. All the reports were cross-sectional studies that evaluated the presence of skin side events with self-administered questionnaires. 1,912 out of 2,424 participants had skin side events, with high female: male ratio, and an age ranged from 20 to 65 years, Table 1.

3.2. Which are the most common skin adverse events associated with PPE and which are the most affected regions?

Contact dermatitis, acne and eczema were the most frequent disorders[19, 20]; itching and burning the most common symptoms[20]; and erythema and papules the most frequent signs[20]. The prevalence and the type of specific skin conditions related to PPE and the features of skin side events was also investigated[15-18], Table S1.

The most frequently damaged anatomical regions were the nasal bridge (67.22%), the cheeks (66.9%) and the hands (62.6%) [5, 12, 13]. Soap and water (56.4%), gloves (47.5%), sanitizers (38.6%) and masks (20.8%) were the most frequent culprit agents[20].

3.3. What are the risk factors for developing skin side events related to PPE?

Longer duration of PPE wearing was the risk factor most frequently associated with skin side events[5, 7, 12-14, 19, 20]. Other risk factors related to high rate of cutaneous adverse events were female sex[12], non-use of moisturizers[14], a previous history of dermatitis[16] or wearing a N95 mask compared to a surgical one[7].

3.4. What is the prevalence and what kind of side events are related to mask use?

The media prevalence of skin side events related to mask use was 57.17% after conducting a random effect meta-analysis weighted by the study sample size, Figure S2. Eleven studies evaluated the skin effects related to mask wearing[21-31]. Four studies analyzed the overall prevalence of skin side events related to mask wearing[21-24], Table 2. All of them were cross-sectional studies assessing the prevalence by questionnaires. 5,296 participants were included, 3,900 non-HCWs and 1,396 HCWs. 2,430 participants reported cutaneous adverse events related to mask use. The prevalence of skin side events related to mask use was higher in HCWs (63.14%) than in non-HCWs (42.38%) without statistically significant differences, Figure S4. Longer periods of mask wearing were a risk factor for skin adverse events[21, 32], while controversial results were found regarding the type of mask. Most reports observed that wearing a surgical mask was a risk factor for developing skin side events compared to other kind of mask[21, 23, 24]. Nevertheless,

Matusiak et al. showed that surgical mask was a protective factor for sweating and itch[32]. Acne and itching were the most common adverse events reported in these studies[21-23].

Moreover, two studies analyzed itching related to mask wearing[25, 26], Table 2. Itching was reported in 875 out of 4,644 participants. The worst intensity of itch using a numeric rating scale was moderate in most cases. Sensitive skin, atopic predispositions, facial dermatoses (such as acne or seborrheic dermatitis) and longer periods of mask use were risk factors for developing mask-related itching [25, 26]. The frequency of itching was also higher in people wearing a N95/FFP2 mask compared to other types of masks[25].

In addition, five studies evaluated skin barrier function impairment due to mask wearing[27-31], Table 3. Temperature[27, 28, 30, 31] and redness or erythema[28-30] were higher while stratum corneum hydration (SCH)[28-30] was lower on the mask covered area compared to the non-covered one. Controversial results were observed in other parameters. The effect in skin barrier function between surgical mask and N95 one has been evaluated in three studies[27, 29, 30]. Two studies showed higher transepidermal water loss (TEWL) values on the mask covered area compared to the non-covered[29, 30], while another two investigations did not report changes between both areas[28, 31]. Comparing different types of masks, it was observed that temperature increase were higher when using a N95 mask (1.2 vs 0.7 ºC)[28]. Nevertheless, greater TEWL increases were found when using a surgical mask (12.54 vs 5.28 $g \cdot h^{-1} \cdot m^{-2}$, p= 0.026)[30]. Other study did not report differences in skin homeostasis parameters between types of masks[30].

3.5. What is the prevalence and what kind of side events are related to gloves and hand washing?

The media prevalence of skin side events related to gloves and hand washing was 49.16% after conducting a random effect meta-analysis weighted by the study sample

size, Figure S5. Skin effects related to gloves use and hand washing were evaluated in nine studies[24, 30, 33-39], Table 4. Three studies evaluated the general prevalence of skin adverse events associated with gloves use and hand hygiene in 3,713 participants (3,283 non-HCWs and 430 HCWs)[24, 33, 34]. 1,475 participants reported skin side events. The prevalence of skin side events related to gloves and hand washing was higher in HCWs (68.16%) than in non-HCWs (36.88%), Figure S6.

One report also found that hand skin manifestations increased by 8.4% compared to the pre-pandemic period[34]. Most common adverse event were dryness, erythema, itching and fissures [24, 33, 34]. Female sex[34], working in unit with COVID-19 patients[34], hand washing more than 10 times/day[24], alcohol concentration >60%[24] and using gloves[24] were related to a higher rate of skin adverse event[34].

Furthermore, three studies evaluated the prevalence and risk factors of hand eczema in 7,079 participants (6,858 children and 221 HCWs) [35, 37, 38]. The prevalence of hand eczema in children was 38.3% (2,627/6,858) during the pandemic and it increased by 26.2% compared to the pre-pandemic period. The prevalence of hand eczema in HCWs was between 14.9%[37] and 50.5%[38] without differences between HCWs working in COVID-19 intensive care units and HCWs without frequently contact with COVID-19 patients[37]. People in the first group were surgeons and nurses from a single surgical center and participant in the second group were physicians and nurses from an intensive-care unit for COVID-19 patients. The median Hanc Eczema Severity Index was 24 (range 3-84)[38]. Female gender[35], previous history of atopic dermatitis[35] or hand eczema[38] and high frequency of hand washing[35, 38] were risk factors associated with hand eczema. Its most frequent morphology was erythematous-squamous (75.8%, 41/54) and the most common affected area was the hand dorsum (85.2%, 46/54)[38].

Contact urticaria was observed in 8.2% (32/390) HCWs and was associated with the number of working hours and previous history of dermatological diseases[36]. Irritant contact dermatitis was reported in 42.4% (4,496/6,273) children. Female gender and high frequency of hand washing was associated with high rate of irritant contact dermatits[33].

Only one study reported objective impairment in skin barrier function associated with nitrile gloves use. They showed higher TEWL (31.11 vs 14.24 $g \cdot h^{-1} \cdot m^{-2}$, $p < 0.001$), SCH (43.26 vs 58.28 AU, $p<0.001$), temperature (33.29°C vs 32.57°C, $p<0.001$) and erythema (243.97 vs 215.55 AU, $p<0.001$) at the area covered by gloves compared to the non-covered area[30].

3.6. What prevention measures could be taken to avoid skin adverse events related to PPE?

Hydrogel patch, small patches used in areas of pressure points of PPE, could be used to avoid skin injuries related to mask use. Four studies evaluated prevention measures for avoiding skin adverse events related to PPE[8, 40-42], Table 5. All of them were focused on preventing skin injuries related to mask use. Zhou et al. observed that hydrogel use decreased pain, itching and indentation both on cheeks and nasal bridge in 26 HCWs wearing N95 masks[40]. Moreover, Dong et al observed that the use of hydrogel patch on one side of the face reduced overall skin reaction rate (including indentation, redness and pain) compared to the other side without hydrogel in 19 front-line HCWs using N95 masks[42]. Dressing mask with extra-thin hydrocolloid was also compared to foam dressing in 88 HCWs without differences between groups in skin injuries[8]. Furthermore, it was also observed that the use of prophylactic dressing and nasal strip reduced skin injuries

by 2.5 times. Itching, erythema, papules, pustules and discomfort in breathing were also reduced, while satisfaction scores increased[41].

Moreover, it has been reported that the use of moisturizing hand cream might prevent from developing skin adverse events related to hand washing and gloves use, Table 4.

4. Discussion

In this systematic review we have observed that the prevalence of skin adverse events related to PPE is high. Contact dermatitis, acne, eczema and itching are the most common skin adverse events. Masks and gloves are the agent most frequently related to cutaneous side events. Longer duration of wearing PPE is the most frequent risk factor for developing cutaneous reactions. Prevention measures are focused on skin injuries related to mask use.

Three out four individuals could develop skin adverse events related to PPE. Nevertheless, this rate showed high variation between studies[5-7, 11-14]. Differences in participants (non-HCWs, HCWs in frequently contact with COVID-19 patients or HCWs not working in COVID-19 units) could explain these disparity[7]. Moreover, the prevalence of skin adverse events was mainly evaluated by self-administered questionnaires. High variability rate was also observed in skin side events associated with masks[21-24], and gloves and hand washing[24, 33, 34]. It was observed that the rate of skin side events related to both mask or gloves was almost double in HCWs and non-HCWs, what may be explained because HCWs needs to wear longer periods mask or gloves. This fact makes it necessary to establish preventive measures in HCWs to avoid adverse events.

Most common adverse events were contact dermatitis, dryness, acne and eczema pressure related symptoms and itching[13, 23, 33]. Contac dermatitis, dryness and itching were related to masks, gloves and hand-washing[24, 33]. Pressure related symptoms was mainly associated with mask wearing[7, 17]. Other conditions were also reported, such as acne and related disorders, urticaria[36], palmar hyperqueratosis[19] or pigmentation[21]. It has been proved that PPE use increase TEWL[30], what could explain their dryness effect. Furthermore, the temperature raise creates a favorable environment for the development of some microorganisms, such as *Propionibacterium acnes*, favoring acne development[43].

The face and the hands were the most frequently damaged regions[5, 12]. Hand eczema was a frequent condition on the hands[38]. Face was a common location for developing skin injuries related to mask wearing, mainly on the nasal bridge and the cheeks[7, 17, 44]. Acne was also frequent on mask-covered areas[21, 31].

Studies agreed that longer PPE use and frequent hand washing were the main risk factor to develop skin adverse events[5, 7, 12, 21, 35, 36, 38]. Having a previous history of atopy or hand eczema were also risk factors for developing hand problems[35, 36, 38]. A previous history of acne or seborrheic dermatitis and having an oily skin were risk for developing acne aggravated by masks[23]. Nevertheless, there is controversial information regarding other kind of risk factors, such as sex or the mask type. Researches showed that female sex was a risk factor for the overall rate of skin adverse events associated with PPE[12], skin adverse events related to mask use[23], irritant contact dermatitis[18, 39] and hand eczema[35]. The prevalence of contact dermatitis and occupational dermatosis was also higher in female sex[45, 46]. However, female sex was considered a protective factor for skin injuries related to PPE in another research[17]. Differences between sexes could be due to a greater rate of nurse, mainly women, that could use PPE longer than doctors, where the female:male ratio would be more homogeneous.

There are also controversial results concerning the type of mask. N95 respirators were a risk factor for the overall rate of skin adverse events related to PPE[13]. Warming and sweating were less frequent with surgical masks than with other types[32], while acne rate did not differ between different kind of masks[15]. Higher temperature, a marker of inflammation[47], was observed when using a N95 respirator compared to a surgical one. Moreover, surgical mask increased TEWL values more than FFP2[30], a parameter indicating epidermal dysfunction when it is high[48]. Regarding the available data, it could be concluded that mask type that most damaged the skin, in descending order, were: N95

respirators, surgical mask, FFP2 and cloth masks, Figure S7. These differences could be due to the type of material they are made of. When deciding to wear a kind of mask, it should also be kept in mind that they might provide different protection for COVID-19 transmission. Similar rates of virus infection have been reported between N95, surgical mask and FFP2 one, while cloth masks are not recommended as PPE[49].

Regarding prevention measures, only studies using hydrocolloid to prevent skin injuries have been reported[8, 40-42]. Moisturizers use also reduced skin adverse events related to PPE and frequent hand washing[50]. As longer PPE wearing is a common risk factor to develop skin side events[5, 7, 12, 35, 36], permitting several daily rest periods could reduce skin damage. It would be also important to wash the face with noncomedogenic cleanser to avoid acne development[51]. The frequent use of emollient creams and the use of alcohol-based hand rubs instead of frequent hand washing would be also advisable to decrease side events on the hand[52.] , although it should be also considered that the use of hydro-alcoholic gels could have deleterious effect on the skin, particularly if there is a history of a previous eczema. Furthermore, developing educational programs to teach people how to use PPE could be a recommendable measure to reduce the rate of skin side events.

Limitations. Most researches were cross-sectional studies, so their scientific evidence is limited. Most studies did not use validated questionnaires to assess skin cutaneous event. Furthermore, the absence of dermatological assessment makes it difficult to assess the real influence of previous history of acne, atopy or other dermatoses on the development of these adverse events. The population included vary between studies (HCWs, non-HCWs, students, children) and many selection biases may have affected these reports, as the samples came from hospital settings, schools or daycare. Moreover, the absence of patch testing during COVID-19 pandemic, did not allow to

really distinguish irritative hand eczema from allergic hand eczema related to glove chemicals, disinfectants, preservatives or fragrances from hand washing soaps.

Recommendations for futures studies. A more accurate rate of skin side events related to PPE could be obtained if participants were evaluated by a dermatologist and not only by self-administered questionaries. It would be also important that the studies included objective measure, such as TEWL, to evaluate precisely the epidermal dysfunction related to PPE. Further clinical trials should be carried out to compare different types of masks, gloves and hand washing products using objective parameters to find the lees-aggressive PPE.

In conclusion, the rate of cutaneous adverse events related to PPE use is very high, longer use periods was the most important risk factor for developing them. Most skin adverse events were mild, being dryness, pressure related symptoms and itching the most frequent. Frequent hand washing, gloves and mask use and are two important agents related with skin disorders. Hydrogel patches could be a protective measure against mask-related symptoms.

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Tables

Supplementary material

Table S1. Studies exploring specific adverse cutaneous events related to personal protective equipment.

Figure S1. Flow chart of the studies included.

Figure S2. Metanalysis of the prevalence of skin side events related to PPE.

Figure S3. Metanalysis of the prevalence of skin side events related to mask use.

Figure S4. Metanalysis of the prevalence of skin side events related to mask use between HCWs and non-HCWs.

Figure S5. Metanalysis of the prevalence of skin side events related to gloves and hand-hygiene products.

Figure S6. Metanalysis of the prevalence of skin side events related to gloves and hand-hygiene products between HCWs and non-HCWs.

Figure S7. Type of masks.

PRISMA guidelines check list.

Table 1. Studies regarding prevalence of skin adverse events related to personal protective equipment.

Study and site	Design	Participants	Age (years)	Sex (female: male ratio)	Assesment tools	Prevalence of skin side events	Most common adverse events	Anatomical regions most damaged	Risk factors
Yuan N et al. China.	Cross-sectional study	129 HCWs	NS	NS	Online self-administered questionnaire	94.6% (122/129)	Facial indentation, rash, dermatitis.	NS	NS
Swaminathan R et al. UK	Cross-sectional study	72 HCWs	NS	1.7:1	Online self-administer questionnaire	43.2% (31/72)	NS.	NS	NS
Pei S et al. China	Cross-sectional study	484 HCWs.	20-60	3.14:1	Online self-administer questionnaire	73.1% (354/484)	Pruritus, erythema, prurigo, blisters, rhagades, papule/oedema, exudation/crust, lichenification.	Face, hand, limbs, trunk.	High level of protection, higher working frequency, longer duration of wearing protective suits.*
Lin P et al. China	Cross-sectional study	376 HCWs	NS	3.5:1	Questionnaire	74.5% (280/376)	NS	Hands, cheeks, nasal bridge.	Female sex, working in hospitals with a more severe epidemic, working in inpatient wards, longer PPE wearing periods (> 6 hours). #
Lan J et al. China	Cross-sectional study	542 HCWs	20-56	3.8:1	Online self-administer questionnaire	97.0% (526/542)	Symptoms: Dryness/tightness, tenderness, itching, burning/pain. Signs: Desquamation, erythema, maceration, fissure, papule, erosion and ulcer, vesicle, wheal.	Nasal bridge, cheek, hands, forehead.	Wearing a N95 mask or goggles, longer PPE wearing periods (> 6 hours), frequent hand hygiene (> 10 times daily). #

Daye M et al. Turkey	Cross-sectional study	440 HCWs	33.5 (21.0-65.0)	1.5:1	Questionnaire	90.2% (397/440)	Dryness, itching, flaking, tingling, spalling, peeling, lichenification. .	NS	Not using moisturizers, previous history of allergies or skin disease, using mask with metal nose bridge and located especially on the nose. ¥
Battista RA et al. 2020. Italy	Cross-sectional study	381 participants. (185 HCWs, 31 people with high public contact job, 165 with low public exposure).	35.0 ± 11.7	2:1	Email / phone questionnaires	53.02% (202/381)	Itching, acne, skin rash, pressure related symptoms.	NS	Longer PPE wearing periods (> 6 hours), using a N95/FFP2 mask.#

HCWs, healthcare workers; L3PPE, Level 3 barrier protection personal protective equipment; NS, not specified; PPE, personal protective equipment.

Continuous data is expressed as media ± SD or median (interquartile range) and categorical data are presented as n or n/N (%).

*Non-defining statistical test

#Logistic regression analyses

¥Chi-square ($\chi 2$) test

Table 2. Studies regarding the prevalence of skin adverse events related to mask wearing

Study and site	Design	Participants	Age (years)	Sex (female:male ratio)	Type of masks	Assesment tools	Prevalence of skin adverse events	Main adverse events	Risk factors
General skin adverse events									
Techasatian L et al. Thailand	Cross-sectional study	833 participants. 357 HCWs (42.9%) and 476 non-HCWs (57.1%).	32 (IQR 25-41)	2.75:1	- 526 surgical masks (63.15%), - 292 cloth masks (35.05%), - 9 surgical masks covered by a piece of cloth (1.0%), - 6 N95 masks (0.72%).	Questionnaire	54.5% (454/833)	Acne, rashes, itch, pigmentation and pressure-related skin injuries.	Wearing a surgical mask compared to a cloth mask, longer periods of mask wearing (> 4 hours), masks-reuse. #
Matusiak, Ł et al. Poland	Cross-sectional study	876 HCWs	From 18 to 27	NS	NS	Online questionnaire	96.9% (849/876)	Warming/sweating, itch, skin irritation.	Not wearing a surgical mask compared to the other types of masks. #
Chaiyabutr C et al. Thailand	Cross-sectional study	1,231 non-HCWs	NS	2.81:1	- 1231 fabric masks (52.3%), - 552 surgical masks (44.8%), - N95 mask (2.8%, n=35).	Online self-administered questionnaires	62.3% (767/1,231)	Acne, itching, greasy skin, erythematous rash, pain on mask border, dry skin, worsening of pre-existing dermatoses, abrasion.	Surgical mask, female sex, age < 40 years, having oily skin, having acne before starting to wear masks, longer periods of mask wearing (> 4 hours). #
Alsaidan MS et al. 2020. Saudi Arabia	Cross-sectional study	2,356 participants. HCWs (6.91%, n=163) and non-HCWs (93.1%, n=2,193)	21 (IQR 18–26)	0.78:1	- 1,779 surgical/face masks (75.5%) - 430 others (18.3%)	Online self-administer questionnaire	15.3% (360/2,356)	Dryness, scaling, itchiness, redness, change in texture, change in color, pain/burning, ulcer	Wearing a surgical mask compared to other types of mask¥

Itching									
Szepietowski et al. Poland	Cross-sectional study	2,315 Polish students	20.2 ± 1.7	4.07:1	- 755 three layers surgical mask (54.2%), - 891 cloth mask (64%) - 257 respirators (N95 + FFP) (18.4%) - 16 half-face elastomeric respirator (1.1%) - 8 full-face respirator: (0.4%)	Online questionnaire	19.6% (273/1,393)	The WI-NRS was assessed as 4.07 ± 2.06 points (range 0–10 points), indicating itch of moderate severity.	Sensitive skin, atopic predisposition, having atopic dermatitis, acne or seborrheic dermatitis and wearing face masks for longer periods (>5 hours). #
Krajewski PK et al. Poland	Cross-sectional study	2,329 participants (1156 HCW and 1173 students).	HCW: 40.5± 11.8 Students: 20.9± 2.9	HCW: 4.48:1 Students: 2.79:1	- 1,363 surgical mask (58.52%) - 591 cloth mask (25.37%) - 221 respirators (N95/FFP2) (9.49%) - 138 half-face mask: (5.93%)	Online questionnaire	All participants: 25.8% (602/2,329). HCWs: 31.6%, (365/1,156). Students 20.2%, (237/1,173).	The WI-NRS was 4.6±2.0 points for the whole population, 4.6±2.0 points for HCWs and 4.7±2.1 points for students, indicating a moderate itch severity.	Sensitive skin, atopic predispositions, facial dermatoses, wearing face masks for longer periods (>4 hours), wearing a N95/FFP2 mask compared to other types of masks. ¶

AD, atopic dermatitis; FFP2, filtering respirator mask coded filtering facepiece 2; HCW, healthcare workers; NRS, numeric rating scale, SCH, stratum corneum hidration, TEWL, transepidermal water loss; WI-NRS, worst intensity of itch

Continuous data is expressed as media ± SD or median (interquartile range) and categorical data are presented as n or n/N (%).

#Logistic regression analyses

¥Chi-square ($\chi 2$) test

¶Kruskal–Wallis one-way analysis of variance on ranks

Table 3. Studies regarding skin barrier dysfunction related to mask use.

Study and site	Design	Participants	Age (years)	Sex (female:male ratio)	Type of masks	Assesment tools	Outcomes after mask removal	Outcomes comparing types of masks
Scarano A et al. Italy	Prospective observational crossover study	20 non-HCWs	NS	NS	- Surgical mask - N95 mask Wearing it for one hour.	Skin temperature, humidity, heat, discomfort, mask touching	Temperature increased at the perioral region and superior lip immediately after removal of the mask compared tobaseline.	Higher increases in temperature were observed with N95 wearing (1.2±0.5) compared to surgical masks (0.7±0.5ºC). Humidity heat, breathing difficulty, discomfort and mask touching were also higher under the N95.
Park SR et al. Republic of Korea.	Prospective observational study	21 non-HCWs	From 20 to 49	NS	Korea Filter 94 mask for 6 hours	Temperature, redness, sebum secretion, SCH, TEWL, elasticity.	Temperature and redness increased while SCH decreased on the mask covered area compared to the non-covered area. Sebum secretion, TEWL and elasticity did not change.	NS
Montero-Vilchez et al. Spain	Cross-sectional study	34 HCWs	44.97±11.97	1.6:1	- Surgical masks (52,94%, n=18) - FFP2 masks (47.06%, n=16)	TEWL, SCH, temperature, erythema	TEWL, temperature and erythema were higher on the area covered by masks compared to the non-covered area while SCH was lower.	TEWL was significantly greater at the area covered by a surgical mask than at the FFP2 one (12.54 vs 5.28 $g \cdot h^{-1} \cdot m^{-2}$, p= 0.026).
Kim J et al. Korea	Prospective observational study	20 non-HCWs	28.10 ± 3.49	0.8:1	Korea Filter 94 mask for 6 hours daily for 2 weeks	Temperature, redness, pore volume, texture, elasticity,	Temperature and pore volume increased after mask use. Elasticity and pH decreased. No differences in redness, roughness, TEWL and sebum were observed.	NS

						TEWL, sebum content, pH.		
Hua W et al. China	A randomized crossover study with repeated measurements	20 non-HCWs	34.3±11.5	10:1	- N95 respirators - Surgical masks	TEWL, SCH, erythema, pH and sebum secretion.	SCH, TEWL, pH and erythema increased significantly after mask use and were higher at the area covered by the mask than at the non-covered area.	There was no significant difference between the physiological values between the two types of masks. More adverse reactions and a higher score of discomfort and incompliance were reported following N95 mask use that following use of medical mask.

AD, atopic dermatitis; FFP2, filtering respirator mask coded filtering facepiece 2; HCW, healthcare workers; NRS, numeric rating scale, SCH, stratum corneum hydration, TEWL, transepidermal water loss; WI-NRS, worst intensity of itch

Continuous data is expressed as media ± SD or median (interquartile range) and categorical data are presented as n or n/N (%).

Table 4. Skin adverse events related to gloves use and hand washing.

Study and site	Design	Participants	Age (years)	Sex (female:male ratio)	Assesment tools	Aim	Main outcome	Other outcomes	Risk factors
Overall prevalence of skin adverse events									
Dindarloo K et al. Iran	Cross-sectional study	1,090 non-HCWs	35.22 (range from 15 to 70)	1.12:1	Self-administered questionnaire	Overall prevalence of skin adverse events	41.4% (451/1,090).	Most common skin adverse events: dryness, itching, redness and injuries.	NS
Altuniski Toplu S et al. Turkey	Cross-sectional study	267 HCWs	35.0 ± 6.9	1.63:1	Self-administered questionnaire	Overall prevalence of skin adverse events	73.6% (203/267)	Most commons skin adverse events: dryness, erythema, hand fissure, itching, burning-pain, vesicle.	Female sex, working in units without COVID-19 patients. ¶
Alsaidan MS et al. 2020. Saudi Arabia	Cross-sectional study	2,356 participants. HCWs (6.91%, n=163) and non-HCWs (93.1%, n=2,193)	21.00 (IQR: 18–26)	0.78:1	Online self-administered questionnaire	Overall prevalence of skin adverse events	34.85% (821/2356)	Most commons skin adverse events: dryness, change in texture, scaling, itchiness, change in color, redness, pain/burning, ulcer	Hand washing > 10 times/day, alcohol concentration >60%, using hand gloves. ¥
Prevalence of a specific skin condition									
Simonsen AB et al. Denmark	Cross-sectional study	6,858 children using daycare	3.4±1.37	1:1	Parental self-administered questionnaire.	Prevalence of hand eczema	38.3% (2,627/6,858)	The prevalence of hand eczema increased by 26.2% after the pandemic	Atopic dermatitis, female gender, older age, high frequency of hand washing. #
Pourani MR et al. Iran	Cross-sectional study	390 HCWs	34.57 ± 9.41	2.9:1	Online self-administered questionnaire	Prevalence of hand contact urticaria	8.2% (32/390).	The rate of hypersensitivity to latex gloves was 32.6% (123/390) in all HCWs and 53.1% (17/32) in HCWs with contact urticaria.	Longer work hours per week, history of dermatological diseases, allergic conjunctivitis, asthma, hypersensitivity to latex gloves.*

Guertler A et al.	Cross-sectional study	114 HCWs: 35.9% (40/114) HCWs involved in intensive care and 64.91% (74/114) HCWs not involved.	35.23 ± 10.78	1.59:1	Self-administered questionnaire	Prevalence of hand eczema	14.9% (17/114)	No differences in hand eczema between HCWs involved in intensive care of COVID-19 patients and HCWs without direct contact with COVID-19 patients were found	NS
Erdem Y et al. Turkey	Cross-sectional study	107 HCWs	29.6±6.3	2.06:1	Clinical evaluation	Prevalence of hand eczema	50.5% (54/107)	The median HECSI score was 24 (range 3–84)	The use of moisturizing hand cream in daily life, a previous history of hand eczema, hand washing frequency (>20 times/day). #
Borch L. Denmark	Cross-sectional study	6,273 children	6.70±3.12	1:1	Self-administered questionnaire	Prevalence of irritant contact dermatitis	42.4% (4,496/6,273)	NS	Female gender, schoolchildren compared to preschool, hand washing > 7 times/day. ʔ
Assessment of skin barrier function parameters									
Montero-Vilchez T et al. Spain	Cross-sectional study	34 HCWs	44.97±11.97	1.62:1	Skin homeostasis parameters: TEWL, SCH, temperature, erythema.	To evaluate the effect of using nitrile gloves on epidermal barrier function.	TEWL (31.11 vs 14.24 $g/h^{-1}/m^{-2}$, $p < 0.001$), SCH (43.26 vs 58.28 AU, $p < 0.001$), temperature (33.29°C vs 32.57°C, $p < 0.001$) and erythema (243.97 vs 215.55 AU, $p<0.001$) were higher at the area covered by gloves compared to the non-covered area.	NS

HCWs, Healthcare workers; HECSI, Hand Eczema Severity Index; SCH, stratum corneum hydration, TEWL, transepidermal water loss.
Continuous data is expressed as media ± SD or median (interquartile range) and categorical data are presented as n or n/N (%).
*Analysis not specified.
#Logistic regression analyses
¥Chi-square ($\chi 2$) test
¶ McNemar test
ʔPoisson regression with robust error variance

Table 5. Prevention measures adopted to prevent skin adverse events related to personal protective equipment.

Study and site	Design	Participants	Age (years)	Sex (female:male ratio)	Aim	Comparison groups	Follow-up	Assesment tools	Main outcomes
Zhou N et al. China	Clinical trial	26 HCWs wearing N95 masks	NS	NS	To explore whether hydrogel patches protect the nasal bridge and cheeks from skin injury by an N95 mask use	-Control Group (n=10): operating without a Wshaped hydrogel patch - Experimental group (n=16): operating with a Wshaped hydrogel patch over their cheeks and nasal bridge.	2 weeks	Questionnaries NRS (from 0 to 5; 5 indicating most severe)	Hydrogel use decreased pain, itching and indentation both on cheeks and nasal bridge. Burning was only reduced on the nasal bridge.
Yildiz A et al. Turkey	Clinical trial	48 HCWs using goggle, face shield, surgical mask and FFP3 mask together as standard PPE	34.21 ± 6.02	8.6:1	To determinate the effect of prophylactic dressing on the prevention of skin injuries due to the use of PPE in HCWs	-Control group (n=10): non using prophylactic dressing - Experimental group 1 (n=20): Using prophylactic dressing - Experimental group 2 (n=8): Using prophylactic dressing and nasal strip.	From 24 hours to 5 days Mean duration: 3.79+-1.18 hours.	HCWs' satisfaction (VAS) Dermatological evaluation NPIAP PI staging system	Overall rate of skin injuries related to PPE was 47.9% (23/48). Skin injuries were 2.5 time higher in CG (100%) than in EG2 (12.5%) and in EG1 (10%). The mean number of skin injuries was higher in CG (2.45±0.24) than in EG1 (0.1±0.06) and EG2 (0.13±0.12). Percentage of participants suffering from itching was higher in CG (40%, 8/20), than in EG2 (12.5%, 1/8) and EG1 (0%).

Gasparino RC et al. Brazil.	Clinical trial	88 HCWs wearing N95 masks.	38.0±9.0	3.6:1	To compare foam and extra-thin hydrocolloid in preventing DRPI associated with PPE.	-Group 1 (n=44): foam -Group 2 (n=44): extra-thin hydrocolloid.	12 hours	Participants disconfort reported	No participant developed DRPI. Four areas with erythema were observed in both groups. No differences in hyperemia, itching, pain or discomfort were observed between groups.
Dong L et al. China.	Short-term, self-controlled study	19 HCWs	NS	NS	To assess whether hydrogel patch application relieve the skin damage caused by mask wearing	- Right side (n=19): N95 mask. - Left side (n=19): N95 mask with hydrogel patch	4 hours	Photographs Questionnaire	Skin reactions rate reported in the control side (13.32±2.06) was higher than in the intervention one (3.47± 1.39). Hydrogel application decreased indentation by 1.74, redness, and pain.

Data is expressed as media ± SD or median (interquartile range)

DRPI, device-related pressure injury CG, control group; EG, experimental group; HCWs, Health Care Workers; NPIAP, National Pressure Injury Advisory Panel; PI, Pressure injuries; PPE, personal protective equipment; NRS, numeric rating scale; Visual Analogue Scale (VAS)

Table S1. Studies exploring specific adverse cutaneous events related to personal protective equipment.

Study and site	Design	Participants	Age (years)	Female:male ratio	Assesment tools	Main outcome assessed	Other outcomes	Anatomical regions most damaged	Culprit agents	Risk factors
Prevalence of specific skin conditions										
O'Neill H et al. UK and Ireland.	Cross-sectional study	337 HCWs with dermatosis	NS	NS	NS	Prevalence of occupational dermatosis: 93.5% (315/337).	Most frequent occupational dermatosis: Irritant contact dermatitis, acne, atopic eczema, allergic contact dermatitis, facial pressure injuries, urticaria.	NS	Facial pressure injury was most frequent in participants wearing respirators (15%, 4/26) than when using a fluid-resistant surgical mask (0.5%, 1/208). Acne was not related with mask type	Longer PPE wearing periods was related to pressure injuries incidence. ¥
Kiely LF. Ireland	Cross-sectional study	270 HCWs	NS	3.5:1	Self-administer questionnaire	Prevalence of irritant contact dermatitis: 82.6% (223/270)	The most frequently reported symptom was dry skin, redness and itching.	Hands, nose and cheeks.	NS	A previous history of dermatitis.*
Jiang Q et al. China	Cross-sectional study	4,306 HCWs	32.5± 7.1	7.3:1	Online self-administer questionnaire	Prevalence of skin injuries: 42.8% (1,844/4,306).	The prevalence of DRPI was 30% (1,293/4,306): 81.1% in stage 1, 18.3% in stage 2, and 0.6%.	NS	NS	Sweating, daily wearing time, male sex, and grade 3 PPE. #
Alluhayyan OB et al. Saudi Arabia	Cross-sectional stud	408 HCWs	34 ±9	2:1	Nordic Occupational Skin Questionnaire	Prevalence of irritant contact dermatitis: 46.32% (189/408)	The most frequent symptom reported was dryness, redness and itchiness.	Hands, nasal bridge, wrist, forearms	Hand cleaners and soaps, antiseptics/desinfectants, gloves, face mask, goggles.	Female sex, being a pharmacist. #

Characterizing PPE-induced dermatosis										
Mushtaq S et al. 2020. Turkey	Cross-sectional study	101 participants with skin problems related to PPE: 46HCWs and 55 non-HCW.	36.71± 15.72	1.3:1	History and clinical examination	Type of PPE-induced dermatoses	Contact dermatitis, acne and related disorders, eczema, urticaria, pruritus, burning and stinging.	Hands, face and trunk.	Soap and water, gloves, sanitize, mask and full body suit.	Using PPE longer than 4 hours. ¥
Metin N. Turkey	Cross-sectional study	526 HCWs with skin problems	34 ± 7	2.2:1	Questionnaire	Type of PPE-induced dermatoses	Xerosis, eczema, acne, palmar hyperqueratosis, xeromycteria, urticaria, seborrheic dermatitis.	Nasal bridge, ear, periocular areas, foreheads.	NS	An age < 30 years, the female sex, HADS-A score <7, hand washing > 10 times /day, wearing gloves > 1 hour, diabetes and hypertension. #

DRPI, device-related pressure injury; HCWs, healthcare workers; NS, not specified; PPE, personal protective equipment.

Continuous data is expressed as media ± SD or median (interquartile range) and categorical data are presented as n or n/N (%).

#Logistic regression analyses

¥Chi-square ($\chi 2$) test

Figure S1. Flow chart of the studies included.

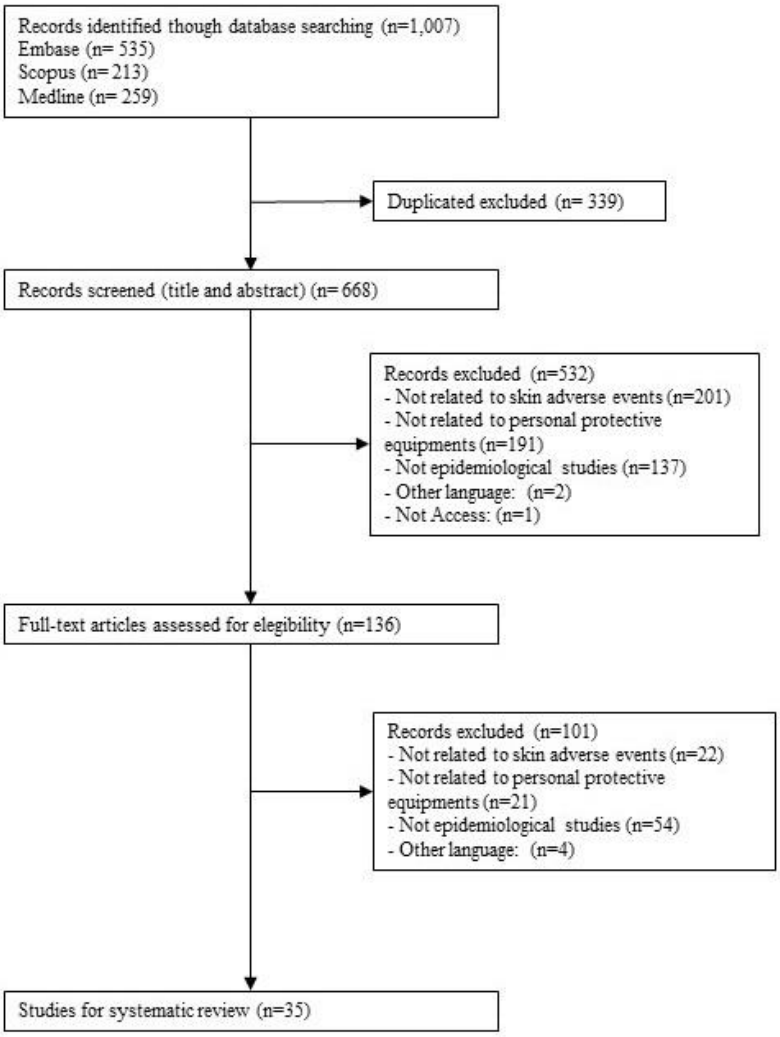


Figure S2. Metanalysis of the prevalence of skin side events related to PPE.

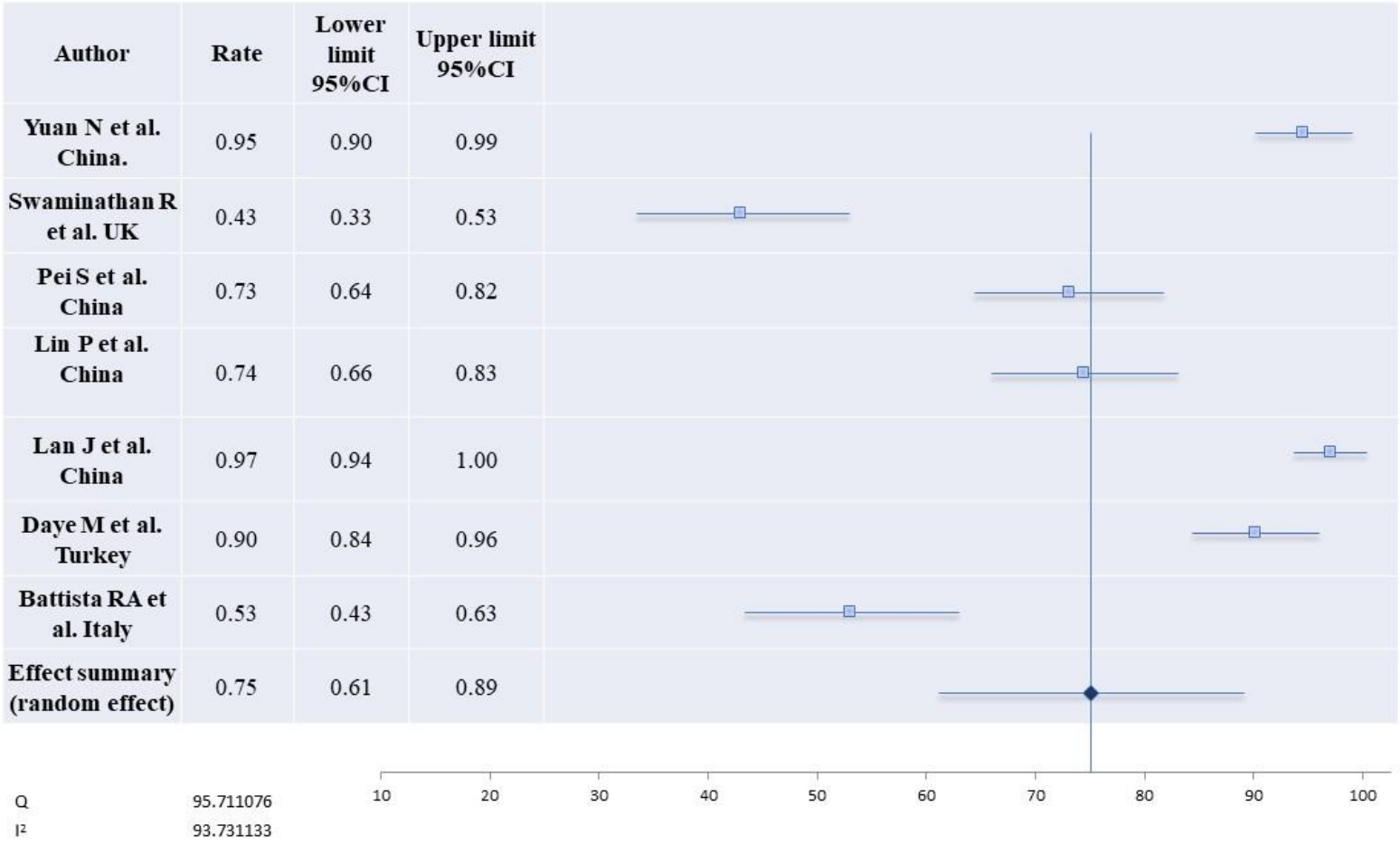
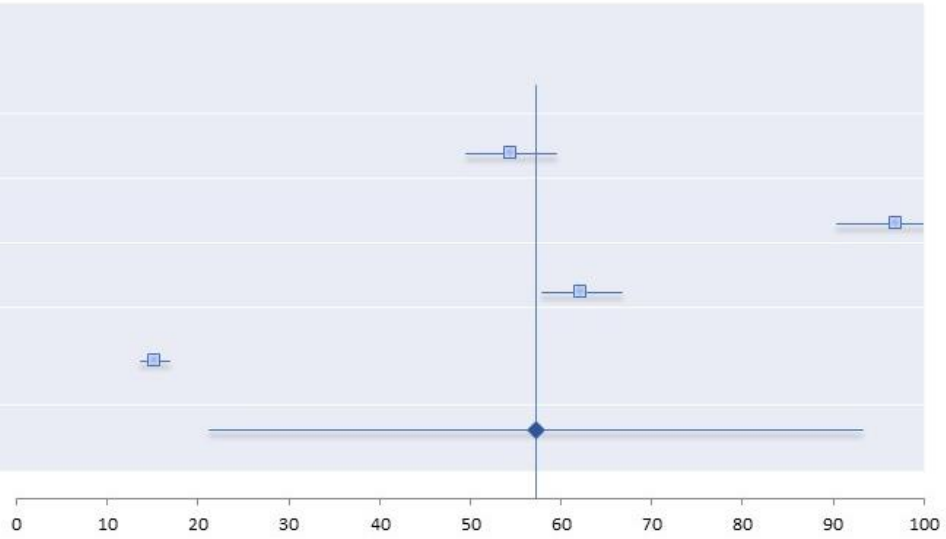


Figure S3. Metanalysis of the prevalence of skin side events related to mask use.

Author	Rate	Lower limit 95%CI	Upper limit 95%CI
Techasatian L et al. Thailand	0.55	0.49	0.60
Matusiak, Ł et al. Poland	0.97	0.90	1.00
Chaiyabutr C et al. Thailand	0.62	0.58	0.67
Alsaidan MS et al. 2020. Saudi Arabia	0.15	0.14	0.17
Effect summary (random effect)	0.57	0.21	0.93



Q	1015.3584
I^2	99.704538

Figure S4. Metanalysis of the prevalence of skin side events related to mask use between HCWs and non-HCWs.

	HCW			Non-HCWs		
Author	**Rate**	**Lower limit 95%CI**	**Upper limit 95%CI**	**Rate**	**Lower limit 95%CI**	**Upper limit 95%CI**
Techasatian L et al. Thailand	0.59	0.51	0.67	0.51	0.45	0.57
Matusiak, Ł et al. Poland	0.97	0.90	1.03	-	-	-
Chaiyabutr C et al. Thailand	-	-	-	0.62	0.58	0.67
Alsaidan MS et al. Saudi Arabia	0.33	0.24	0.42	0.14	0.12	0.16
Effect summary (random effect)	0.63	0.27	0.99	0.42	0.07	0.78

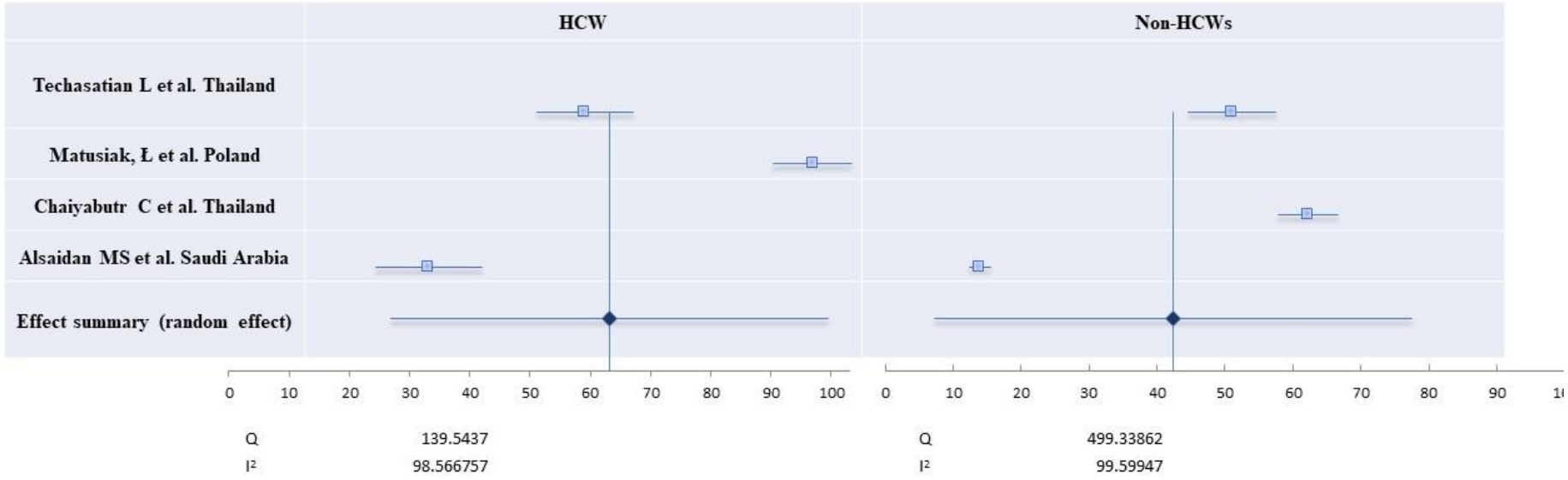
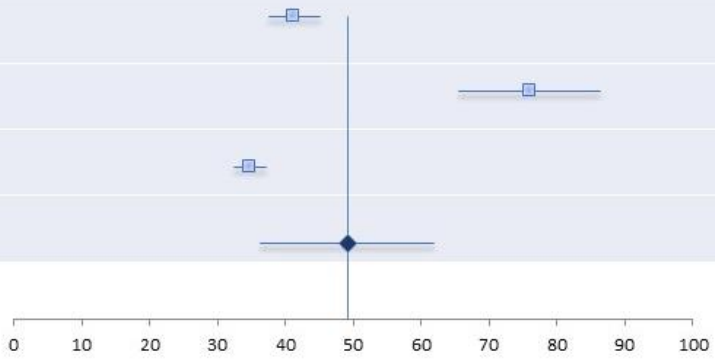


Figure S5. Metanalysis of the prevalence of skin side events related to gloves and hand-hygiene products.

Author	Rate	Lower limit 95%CI	Upper limit 95%CI
Dindarloo K et al. Iran	0.41	0.38	0.45
Altuniski Toplu S et al. Turkey	0.76	0.66	0.86
Alsaidan MS et al. Saudi Arabia	0.34	0.32	0.3
Effect summary (random effect)	0.49	0.36	0.62



Q	60.504304
I^2	96.69445

Figure S6. Metanalysis of the prevalence of skin side events related to gloves and hand-hygiene products between HCWs and non-HCWs.

	HCW			Non-HCWs		
Author	**Rate**	**Lower limit 95%CI**	**Upper limit 95%CI**	**Rate**	**Lower limit 95%CI**	**Upper limit 95%CI**
Dindarloo K et al. Iran	-	-	-	0.41	0.38	0.45
Altuniski Toplu S et al. Turkey	0.76	0.66	0.86	-	-	-
Alsaidan MS et al. Saudi Arabia	0.58	0.47	0.70	0.33	0.31	0.36
Effect summary (random effect)	0.68	0.61	0.76	0.37	0.32	0.42

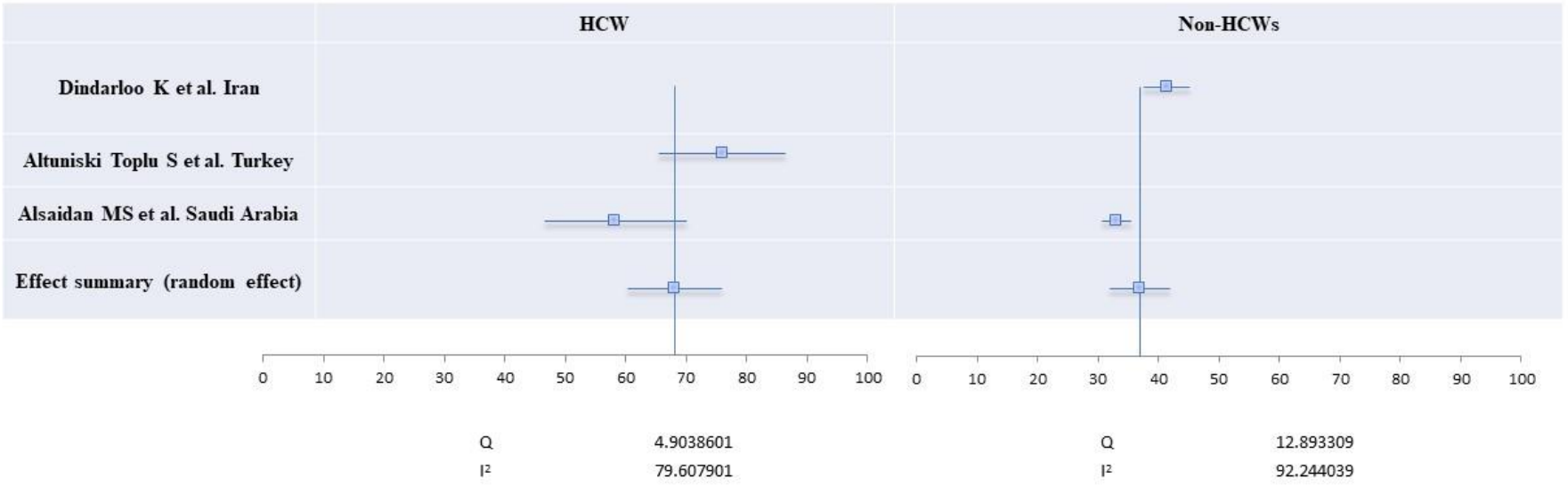


Figure S7. Type of masks.

N95 respirators

Surgical mask

Filtering facepiece type 2 or KN95 respirator

Cloth mask

PRISMA guidelines check list.

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	6
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	6
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6-7

Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	7

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	7
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	7
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	8
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	8
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	8-11
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	8-11,Figure

			S2-Figure S6
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	11
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	10-12
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	13
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	15
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	16
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	1

6.DISCUSSION

6. DISCUSSION

Epidermal barrier function (EBF) and cutaneous homeostasis (CH) differs between anatomical regions. Skin barrier function is disrupted in patients with psoriasis and atopic dermatitis (AD) and is related to disease severity. Phototherapy changes EBF and CH parameters, helping clinicians to select the most appropriate patient with psoriasis to be treated with this therapeutic option. Skin barrier is impaired by mask, gloves and hand hygiene procedures. The use of personal protective equipment (PPE) is related to skin adverse events.

6.1. Skin barrier in healthy individuals

The skin barrier plays a crucial protective role against water loss and penetration of pathogens from the external environment. This study revealed differences in TEWL, SCH, erythema, melanin and pH among three anatomic sites (cheek, volar forearm and palm) in healthy individuals. This fact might be explained by the variations in the amount of sebaceous glands, lipids and natural moisturizing factor, in the size of corneocytes, in exogenous compounds on skin surface and occlusion[113,114].

TEWL is a key characteristic of skin barrier but no consensus has been reached on the definition of "normal" TEWL[115]. According to this study, TEWL values in healthy individuals widely differ among anatomic locations, which has been attributed to differences in the number of corneocyte cell layers, and in the size and turnover rates of corneocytes[116]. TEWL values were higher on the cheek than on the volar forearm, consistent with previous reports[114,117]. This might be related to the smaller corneocytes, fewer cell layers, faster cell turnover, and greater vascularization in facial areas[113]. The quantity and composition of intercellular lipid bilayers might also affect inside-out water diffusion, and the greater density of sebaceous glands on the face than on the forearm

would also be related to the higher TEWL on facial areas[118]. The highest TEWL value was observed on the palms, attributable to its thicker stratum corneum, higher exposure to friction and damage, and greater density of eccrine sweat glands[119]. Our findings agree with the results of a recent systematic review, which found the highest TEWL values to be on the palm, followed by the face and forearm[115].

The highest SCH values were found on the palm, which may be explained by its higher density of eccrine sweat glands[119]. Higher SCH values on the cheek than on the forearm may be influenced by the greater ease of measuring water content in the thinner skin of the face, given that hydration gradually increases at deeper layers[114].

We found higher levels of erythema and melanin on the cheek than on the forearm and the palm, which may be due to the increased blood circulation in this sun-exposed area[119,120]. As expected, the lowest melanin value was on the palm of the hand, which contains low melanocytes or melanin[121]. Our finding of virtually no change in pH values among locations agrees with previous studies[119,122]. The negative correlation found between melanin and pH on the cheek may be due to the more acidic melanocytic dendrites on type IV–V *versus* type I-II skin. These transfer more melanosomes to the stratum corneum, and melanosome secretion contributes to the more acidic pH of type IV–V skin[123], providing darkly-pigmented skin with a superior permeability barrier function[124].

Adjusted linear regression analysis revealed that a one-year increase in age was associated with an increase in TEWL of 0.45 $g{\cdot}m^{-2}{\cdot}h^{-1}$ on the cheek and 0.32 $g{\cdot}m^{-2}{\cdot}h^{-1}$ on the volar forearm. The relationship between age and TEWL has been controversial[115,120,125,126]. Although the rate of intrinsic skin aging does not differ among body areas[120], some locations are more exposed to UV radiation, cold dry weather, and

pollution, among other extrinsic factors. Hence, the relationship between age and TEWL may vary among anatomic sites and different age ranges. We propose to our best knowledge for the first time, a model to predict TEWL on the volar forearm and on the cheek as a function of the SCH value and age within an age range of 20 to 40 years. This fact may help clinicians to make more emphasis on skin care recommendations for patients who are more likely to suffer epidermal damage with age.

In comparison to the females, the males had higher erythema values at all three locations and a higher melanin index on the cheek, similar to previously published findings and attributed to the greater exposure of males to outdoor activities[13,117]. Nevertheless, this difference might have been influenced by a volunteer bias, given that the majority of participants were female.

6.2. Skin barrier in patients with psoriasis and atopic dermatitis

We have observed differences in EBF and CH between healthy skin, psoriatic skin, and AD skin. In psoriatic patients, SCH was lower at psoriatic plaques than uninvolved psoriatic skin and healthy controls. Psoriatic plaques showed higher TEWL, temperature, and erythema values than uninvolved psoriatic skin. Temperature and TEWL at psoriatic plaques could help to identify moderate/severe psoriatic patients. In AD patients, TEWL was higher at eczematous lesions than at uninvolved AD skin and healthy controls, while SCH was lower. Eczematous lesions showed higher temperature than uninvolved AD skin. Moreover, AD patients with a more severe disease showed higher temperature, higher TEWL, and lower SCH at their eczematous lesions. Temperature and TEWL at eczematous lesions in AD patients could help to identify AD moderate/severe patients.

This report shows that the whole epidermal barrier is affected in psoriatic patients, not only at psoriatic plaques. Some homeostasis parameters have previously been evaluated in psoriatic patients. Other research showed higher TEWL at psoriatic plaques than at uninvolved psoriatic skin and healthy controls[39,40]. Nevertheless, differences in TEWL values between uninvolved psoriatic skin and healthy controls are controversial[39,40]. Lower SCH values have been found at psoriatic plaques than at uninvolved psoriatic skin and healthy controls, in agreement with our results[39,41]. The differences in TEWL and SCH between psoriatic plaques and uninvolved skin in the same patient could be explained by a decrease in AQP3 expression in plaques and perilesional skin[127]. Controversial results have been reported for pH values. Cannavo et al. found lower pH values for psoriatic skin[41], while Delfino et al. reported no change[128]. Temperature and erythema were also higher at psoriatic skin, explained by its inflammatory pathogenesis[129]. Changes in elasticity have been only evaluated by Choi et al. who found lower values for psoriatic patients assessed by R7[130], the ratio of elastic recovery to total deformation, a less reliable parameter for measuring elasticity than the one we used (R2, overall elasticity)[131]. There is a need for reliable assessment of psoriasis severity[132] and, to our knowledge, there is no information regarding a cutaneous homeostasis parameter to assess psoriasis severity. We observed that a value for temperature on psoriatic plaques higher than 30.85 °C indicates, with a sensitivity of 72.7%, that psoriasis is moderate/severe, and that a value for TEWL higher than 13.85 $g \cdot m^{-2} \cdot h^{-1}$ indicates, with a sensitivity of 81.8%, that psoriasis is moderate/severe. This may help clinicians to objectively measure psoriasis severity.

Furthermore, this study shows that the whole epidermal barrier is affected in patients with AD. TEWL is the most studied parameter in them. Like previous reports, this study shows that TEWL is higher at eczematous AD lesions than at uninvolved AD

lesions and healthy skin[133-135]. Jungersted et al. also showed that erythema was increases at AD lesions compared to healthy control skin, while SCH was lower and pH was similar at both locations in 49 participants[136]. Moreover, other previous reports, evaluating a smaller number of participants, showed that SCH was higher in healthy controls than at uninvolved AD skin and at eczematous lesions[137]. In agreement with our results, this report shows that the skin barrier function is degraded in AD patients, which is specifically expressed in lesioned skin[137]. This could be explained by a filaggrin deficiency, as this protein is a major constituent of the stratum corneum and contributes to keratin filament aggregation[136,138]. Temperature and erythema were also higher at eczematous lesions than at uninvolved AD skin and healthy skin, showing inflammatory changes in this disease[139]. To our knowledge, only one previous report has evaluated elasticity parameters in AD patients[140]. Like our results, they observed a more decreased elasticity at AD eczematous lesions than at uninvolved AD skin in 22 patients, without including a healthy control group. Differences in elasticity may reveal that collagen or elastin, the main proteins responsible for skin elasticity[141], are other proteins altered in AD patients.

There is scarce information regarding EBF and CH parameters and AD severity. Correlations between skin hydration and SCORAD[142,143], and between TEWL and SCORAD[144], have been previously observed. Moreover, it has been shown that TEWL values at non-involved AD skin predicts the development of AD[145,146]. Nevertheless, cut-off points have not been established to assess disease severity. We observed that a value for temperature on the eczematous lesion higher than 31.75 °C indicates, with a sensitivity of 81.8%, that AD is moderate/severe, and that a value for TEWL higher than 23.19 $g \cdot m^{-2} \cdot h^{-1}$ indicates, with a sensitivity of 73.5%, that AD is moderate/severe. This research could help clinicians to select AD patients that need to be treated intensively.

Moreover, the skin barrier function measurement could also help to resolve the current need for accurate and reproducible scoring systems for the grading of AD[57].

6.3. The effect of phototherapy on skin barrier

We have observed that phototherapy may improve EBF and CH in patients with psoriasis. SCH, temperature and erythema increased at psoriatic plaques after one and fifteen phototherapy sessions. Moreover, TEWL at psoriatic plaques decreased after fifteen phototherapy sessions. Erythema increases after one phototherapy session could help clinicians to select psoriasis patients with more probability of responding to phototherapy.

There is scarce research on the role of phototherapy in EBF. It has previously been reported that phototherapy decreases TEWL and increases SCH[66,74]. Brazzelli et al. have already examined changes in SCH and TEWL levels between pre- and post-treatment with eight sessions of phototherapy and active topical vitamin D3 ointment in psoriasis showing the recovery of epidermal hydration and TEWL level before the clinical improvement of the lesion[74]. Darlenski et al. have reported clinical improvement in psoriatic plaques with fourteen sessions of NB-UVB therapy, shown by a decreased PASI and reflected by an increase in SCH and a decrease in TEWL[66]. Our study also showed an increased SCH at the psoriatic plaque after one and fifteen phototherapy sessions. SCH and TEWL changes were greater at psoriatic plaques than in uninvolved psoriatic skin, which might underline a local effect on psoriasis plaques[72,147].

Temperature, erythema and melanin index increased after the phototherapy session, in accordance with previous reports[148-151]. Assessment of temperature and erythema increase may help clinicians optimize phototherapy to treat patients with an

effective dosage without adverse events. The pH increased in healthy skin, uninvolved psoriatic skin, and psoriatic plaques, suggesting that time may influence pH changes. Antioxidant capacity also decreased in healthy skin, uninvolved psoriatic skin, and psoriatic plaque. This fact might mean that the time have also an impact in antioxidant capacity or that the sticks used might lose their capacity to measure the antioxidant capacity along the time. There is little in-formation regarding the effect of phototherapy on antioxidant capacity. Oxidative stress has been evaluated by measuring different parameters of a blood sample, with controversial results. Darlenski et al. found a slight decrease in the detoxifying activity of catalase without significant differences after phototherapy[66]. On the other hand, Pektas et al. observed total oxidant status and oxidative stress index increased after phototherapy[152]. Our results showed total antioxidant capacity decreases after phototherapy, in agreement with this research by Pektas. Elasticity did not change after phototherapy, with no previous information found to contrast these results.

Brazzelli et al. suggested that SCH improvement at psoriatic plaques might pre-cede clinical improvement[74]. As far as we know, it is not known any parameter that might predict clinical improvement in psoriatic patients treated with phototherapy. We observed that SCH changes after one phototherapy session might predict PASI improvement after fifteen phototherapy sessions. Moreover, a value for erythema increases exceeding 53.23 AU after the first phototherapy session, with a sensitivity of 71.4% and specificity of 84.2%, indicates that a patient may improve PASI by ≥3 points after fifteen phototherapy sessions. This research could help clinicians select psoriatic patients for phototherapy treatment. Therefore, patients who do not reach this value of erythema after the first session can be treated with another therapeutic alternative. Moreover, this research would also be interesting for selecting candidates for home phototherapy, as patients who have

an erythema increase exceeding 53.23 AU after the first phototherapy session may improve during treatment.

6.4. Impact of gloves and mask on skin barrier

We have observed that EBF and CH may be impaired by gloves and mask. An increased TEWL, temperature and erythema in the area covered by gloves and an increased TEWL, temperature and erythema and a decreased SCH in the area covered by masks was observed. Moreover, surgical masks are more harmful for skin than FFP2 mask, showing higher TEWL in areas covered by surgical masks.

Hands are the most common site affected by PPE-related adverse skin reactions during COVID-19 outbreak[83]. This is due to excessive hand washing and gloves use[153]. Medical gloves are mostly made of different polymers such as latex and nitrile[93], being the nitrile one the preferred during the COVID-19 pandemic because of its high protection and durability[154]. Many adverse skin reactions has been described associated to its use, such as irritant contact dermatitis, allergic contact dermatitis, and contact urticaria[93]. Gloves use often causes skin maceration presenting as softening, whitening, wrinkling of the skin, and sometimes, skin peeling[155]. This study showed higher SCH values at the gloves covered area which may be explained in part by the increases sweat production in the covered area[6]. Nevertheless, the difference in TEWL between two near areas, gloves covered and non-covered, reflect a skin barrier damage related to gloves use. This may explain the increased cases of hand eczema, allergic contact dermatitis, secondary superficial fungal infection and pompholyx between HCW gloves users[155,156]. Previously, it has also been described higher TEWL values during 30 minutes of gloves use[95]. Nevertheless, the effects of glove occlusion is controversial in the literature[94]. This study also shows high erythema and temperature at the area covered by gloves, in agreement

with previous reports as erythema is the second most reported skin adverse sign between HCWs[157].

Moreover, the high erythema and temperature are markers of inflammation and increased skin permeability[15]. Although, SARS-CoV spreads mainly via the respiratory route, other possible pathways of infection have been proposed, including skin surface[158,159]. So the permeability increased by gloves, added to the abundantly presentation of angiotensin-converting enzyme 2, the cell receptor for SARS-CoV-2, in the basal layer of the epidermis and the blood vessels of the skin may increase the risk for being infected with SARS-CoV-2[158,159], while transepidermal transmission of this virus is still theoretical. Possible solutions to prevent PPE and hand hygiene-related injuries have been described such as increase protective skincare measures after washing hands[160] or use ABHS containing glycerin as moisturizer[153].

Cheeks are the second area most affected by PPE-related adverse skin reactions during COVID-19 outbreak[83]. In fact, masks are the most common culprit agent among all PPE causing skin damage[157], leading to indentations, ecchymosis, maceration, abrasion and erosion[90]. This study observed higher TEWL values at the mask covered area compared to the non-covered, revealing a skin impairment associated to mask use. This may explain some skin reactions associated with mask such as allergic contact dermatitis or urticarial facial eruption[161]. In contrast to gloves, mask covered areas showed lower SCH values than non-covered. This may be explained because the lower density of eccrine sweat glands at the cheek[119]. Moreover, this study shows that mask covered area have high temperature and erythema than near non-covered areas, relating to increased permeability[15], explaining the mask-induced itch[162]. The increased temperature is also a contributor for developing acne and seborrheic dermatitis[161,163].

This report also shows high TEWL increased at areas covered by surgical mask than at FFP-2 mask covered areas, likely due to the different material they are made from[164]. This may mean that surgical masks are more harmful for skin barrier. This is the first research that report differences between different types of masks. As FFP-2 masks also have more filter efficiency[165], meaning they are more protective to avoid COVID-19 transmission[166], it would be recommended wear this type of masks.

6.5. Impact of hand hygiene procedures on skin barrier

We have evaluated the impact of different hand hygiene procedures on the skin of the hands after a work-shift of 8 hours in HCWs, which is difficult to compare with other studies which usually have this evaluation after longer periods and mostly in experimental settings, outside the regular work setting[167,168]. In our study, we noticed that already after a single working day there were important differences between the three procedures of hand sanitation in TEWL, bacteria and fungi colony-forming unit (CFU) and tolerability rates.

Disinfectant wipes showed the highest TEWL increase. Water and soap also led to increase of TEWL values, similarly to disinfectant wipes. ABHS showed the best results, as it was the only hand hygiene procedure that did not increase TEWL values, likely in relation to lower skin barrier impairment. Previous studies showed that TEWL is increased by soaps[14] and is decreased by ABHS[106] but it has been also stated that the skin barrier function is impaired by ABHS when applied on skin areas previously exposed to water immersion[169]. To our knowledge, the single previous study that assessed the impact of different hand hygiene procedures on skin barrier function in the clinical practice, evaluated the effects of soap and water vs. ABHS and showed no significant differences in TEWL changes[167]. Moreover, in experimental settings, with a lower

participants number, ABHS caused less skin irritation and less skin barrier disruption than detergents[168,170,171]. ABHS and disinfectant wipes contain additional skin care substances, such as glycerin, a moisturizing agent which may replenish lipids and trap water, improving epidermal barrier[172]. Moreover, cleaning hands with soap and water removes skin lipids as they are rinsed off, whereas they remain on the skin when using ABHS[171]. Lipids may be also potentially wiped off when using disinfectant wipes[173] explaining their higher epidermal disruption compared to ABHS. Furthermore, the type of hand hygiene product was found to be an independent predictor for change in TEWL after adjusting for other variables namely gender and age, whose influence on TEWL is controversial[173]. Other factors, including the number of hand hygiene procedures and skin temperatures, which may have an impact on TEWL[8], were similar in the three groups.

pH increase observed in the water and soap group may be explained by the alkaline pH of soap, or related to stratum corneum swelling, lipid rigidity and skin irritation[11]. TAC decreased in all groups, both fast antioxidants and slow antioxidants. TAC decreases when using all hand hygiene products may be due to the reduction in biological and chemical antioxidant substances, such as gallic acid equivalents or vitamin C equivalents[174], while the lack of differences between procedures could be explained because the increases oxidative damage to lipids and proteins is not being considered in this measure[175]. It would be interesting to use different measurements of individual antioxidants and markers of oxidative damage to accurately assess differences in antioxidant capacity between hand hygiene procedures[175,176].

Regarding the antimicrobial power, water and soap showed the lowest reduction in bacterial and fungi CFU count. ABHS and disinfect wipes had similar CFU reduction rates and both higher than water and soap. ABHS kills microorganism by penetrating though their membrane and inducing cellular lysis while soaps only remove debris from

the skin[172]. Therefore, ABHS and disinfectant wipes may be more effective in reducing live bacteria and fungi that are able to form colonies in culture (reduced CFU) than water and soap, as shown in our study. Most studies observed higher rates of microorganism decontamination with ABHS[177] compared to soaps, including in the everyday use[101,172], which is also in agreement with *in vitro* studies[178]. In agreement, WHO guidelines on hand hygiene in health care recommends using ABHS instead of water and soap if hands are not visibly dirty[105]. Viruses are more difficult to study *in vivo* and there are scarce studies that compare the viral load reduction with different types of hand hygiene products. *In vitro*, both soaps and ABHS are effective in inactivating enveloped virus[179]. ABHS has also a high activity against non-enveloped viruses[10]. Regarding disinfectant wipes, previously it has been observed that they are non-inferior compared to water and soap[180] and less effective than ABHS[181] in reducing bacteria from the hands. These studies evaluated the antimicrobial power of the product after artificial contamination of the hands with Escherichia coli[180,181] while our study evaluated the effectiveness in removing usual microorganisms on the hand without any bacteria addition. The differences observed in the antimicrobial power between studies may depend on the predominant type of bacteria on the hand.

Hand hygiene products also have to be tolerable and acceptable to the user[182]. The lowest rating of tolerability and acceptability in the present study was for disinfectant wipes, as they were considered as having the highest drying effect and being the least easy to use. Tolerability rates did not differ between ABHS and water and soap. Previous studies showed that ABHS are well accepted and tolerated among HCWs[182], and during working hours they could be even more time-saving than water and soap[183]. There are no studies evaluating the tolerability of disinfectant wipes. In our study, the lowest rating of acceptability for disinfectant wipes might be explained by the fact that people are less

used to employ them, and their application is more difficult and time-consuming than using a solution. Regarding tolerability objective evaluation, disinfectant wipes showed the highest rates for erythema increase, which might be explained by skin irritation.

6.6. Systematic review and metanalysis regarding adverse events related to personal protective equipment.

In this systematic review we observed that the prevalence of skin adverse events related to PPE is high. Contact dermatitis, acne, eczema and itching are the most common skin adverse events. Masks and gloves are the agent most frequently related to cutaneous side events. Longer duration of wearing PPE is the most frequent risk factor for developing cutaneous reactions. Prevention measures are focused on skin injuries related to mask use.

Three out four individuals could develop skin adverse events related to PPE. Nevertheless, this rate showed high variation between studies[84,85,184-188]. Differences in participants (non-HCWs, HCWs in frequently contact with COVID-19 patients or HCWs not working in COVID-19 units) and the evaluation by self-administered questionnaires could explain these disparity[85]. High variability rate was also observed in skin side events associated with masks[189-192], gloves and hand washing[192-194]. It was observed that the rate of skin side events related to both mask or gloves was almost double in HCWs and non-HCWs, what may be explained because HCWs needs to wear mask or gloves for longer periods. This fact makes it necessary to establish preventive measures in HCWs to avoid adverse events.

Most common adverse events were contact dermatitis, dryness, acne and eczema pressure related symptoms and itching[187,190,193]. Contac dermatitis, dryness and itching were related to masks, gloves and hand-washing[192,193]. Pressure related symptoms was

mainly associated with mask wearing[85,195]. Other conditions were also reported, such as acne and related disorders, urticaria[196], palmar hyperqueratosis[197] or pigmentation[189].

The face and the hands were the most frequently damaged regions[185,186]. Hand eczema was a frequent condition on the hands[198]. Face was a common location for developing skin injuries related to mask wearing, mainly on the nasal bridge and the cheeks[85,195,199]. Acne was also frequent on mask-covered areas[189,200].

Studies agreed that longer PPE use and frequent hand washing were the main risk factor to develop skin adverse events[85,185,186,189,196,198,201]. Having a previous history of atopy or hand eczema were also risk factors for developing hand problems[196,198,201]. A previous history of acne or seborrheic dermatitis and having an oily skin were risk for developing acne aggravated by masks[190]. Nevertheless, there is controversial information regarding other kind of risk factors, such as sex or the mask type. Researches showed that female sex was a risk factor for the overall rate of skin adverse events associated with PPE[186], skin adverse events related to mask use[190], irritant contact dermatitis[202,203] and hand eczema[201]. The prevalence of contact dermatitis and occupational dermatosis was also higher in female sex[204,205]. However, female sex was considered a protective factor for skin injuries related to PPE in another research[195]. Differences between sexes could be due to a greater rate of nurse, mainly women, that could use PPE longer than doctors, where the female:male ratio would be more homogeneous.

There are also controversial results concerning the type of mask. N95 respirators were a risk factor for the overall rate of skin adverse events related to PPE[187]. Warming and sweating were less frequent with surgical masks than with other types[206], while acne rate did not differ between different kind of masks[207]. It could be concluded that mask type that most damaged the skin, in descending order, are: N95 respirators, surgical mask, FFP2 and cloth masks. These differences could be due to the type of material they are

made of. When deciding to wear a kind of mask, it should also be kept in mind that they might provide different protection for COVID-19 transmission. Similar rates of virus infection have been reported between N95, surgical mask and FFP2 one, while cloth masks are not recommended as PPE[208].

Regarding prevention measures, only studies using hydrocolloid to prevent skin injuries have been reported[86,209-211]. Moisturizers use also reduced skin adverse events related to PPE and frequent hand washing[101]. As longer PPE wearing is a common risk factor to develop skin side events[85,185,186,196,201], permitting several daily rest periods could reduce skin damage. It would be also important to wash the face with noncomedogenic cleanser to avoid acne development[212]. The frequent use of emollient creams and the use of alcohol-based hand sanitizers (ABHS), instead of washing hand with soap and water, would be also advisable to decrease side events on the hand[99.] . Furthermore, developing educational programs to teach people how to use PPE could be a recommendable measure to reduce the rate of skin side events.

6.7. Limitations

We could have introduced a selection bias as all participants were volunteers and individuals more worried about their health may be more likely to participate. This would be a non-differential bias as the real differences would be even higher that the observed in these studies.

We used objective and validated tools to measure EBF and CH parameters[8,13]. Nevertheless, antioxidant capacity measurement was a problematic issue as the proper way to measure oxidative stress and antioxidants in biological samples is still a topic of debate in the literature. We assessed total antioxidant capacity (TAC) using an electromechanical method, that carries out a complete oxidation of the sample,

considering individual peaks as the response of a specific antioxidant and obtaining the TAC measure through a mathematic algorithm. TAC has been used as an inverse biomarker of oxidative stress, as it is an indicator of the sample ability to scavenge free radicals[109]. TAC predominantly measures chain breaking antioxidants, including uric acid and ascorbic acid, and exclude contribution of metal binding proteins while damage to lipids and proteins is not being considered in this measure[175].

Regarding the studies designs, we conducted cross-sectional studies to resolve objectives 1,2 and 5 but it is difficult to evaluate the direction of the observation detected using this type of design.

The most important bias of our study evaluating EBF and CH after phototherapy was the losses after the follow-up, due in part to COVID-19 outbreak that made participants did not go to the hospital to receive their phototherapy session. Moreover, to avoid that other factors, and not only the phototherapy, could be the responsible for the changes observed in EBF an CH parameters after the follow-up, we included a non-exposed group. The non-exposed group were healthy individuals that did not received phototherapy and were follow the same time that patients exposed. We can't not guarantee that these two groups (psoriasis patients and healthy individuals) are comparable. Ideally, the non-exposed group should be patients with psoriasis that had not received any treatment but ethically we can't leave them with any treatment.

To measure the impact of masks and gloves on skin barrier, measurements were evaluated on a cheek region covered by a mask and on a non-covered area 2 cm away from it, and on the distal right volar forearm covered by the glove and on a non-covered area 2 cm away from it. The distal volar forearm may not be the area primarily affected by glove use, meaning that the glove impact may have been underestimated. This location

was selected instead of the palm to increases similarities between skin properties in covered and non-covered areas.

We designed a clinical trial to compare the impact of different hand hygiene products on EPB and CH. This type of study is ideal for finding causal inferences[213]. The limitation of this study was its short follow-up, as the effect of the hand hygiene product was evaluated after one work-shift, but it was also an advantage as the assessment of EBF and CH parameters after only one day allowed to evaluate the overall impact of the hand hygiene products avoiding that other factors could bias this effect. Only one type of hand hygiene product was tested and bacterial and fungal colony forming units (CFU) were not differentiated, meaning an inability to determine what type of product was most effective in eliminating the different types of micro-organisms. Moreover, there was a risk that evaporation of wash water was measured when assessing the TEWL, but the 30-minute adaptation period before TEWL measurements reduced this possible bias. Regarding the measurements' location, the palms and not the dorsum of the hands were selected for measuring the skin bioengineering parameters, in contrast to other studies. Despite the thicker stratum corneum of the palms may induce a distinct response to the hygiene procedures, we selected this area because the dorsum of the hands might be more influenced by external factors[6,8].

In the systematic review, we chose broad terms for the search algorithm to include all relevant research. However, as there are different types of personal protective equipment (PPE) and there are multiples skin adverse manifestations, we can't guarantee that we have not missed any research in the databases analysed. Our systematic review is also limited by the lack of contact to the authors of the articles and the quality of the studies included as most researches were cross-sectional and the absence of dermatological assessment makes it difficult to know the real influence of previous

history of acne, atopy or other dermatoses on the development of these adverse events. The population included vary between studies (HCWs, non-HCWs, students, children) and many selection biases may have affected these reports, as the samples came from hospital settings, schools or daycare. Moreover, the absence of patch testing during COVID-19 pandemic, did not allow to really distinguish irritative hand eczema from allergic hand eczema related to glove chemicals, disinfectants, preservatives or fragrances from hand washing soaps.

7. FUTURE PERSPECTIVES

7. FUTURE PERSPECTIVES

This doctoral thesis is the starting point to develop further research to evaluate epidermal barrier function (EBF) and cutaneous homeostasis (CH) parameters as markers of clinical response to different treatments in patients with psoriasis and atopic dermatitis (AD). The increasing number of drugs for these diseases and the lack of objective variables to evaluate clinical outcomes, make necessary to develop easy and non-invasive tools to assess disease severity and treatment effectiveness. Assessment of EBF and CH could help clinicians to perform a personalized medicine, selecting the most appropriate treatment for each patient. Furthermore, using an effective treatment as the first therapeutic choice would help to reduce healthcare costs, an important fact for a public healthcare system with limited resources. Applying early and effective treatments would also improve patients cares and quality of life, avoiding patients' psychological stress associated to treatment failure and preventing comorbidities related to disease progression.

The new drugs approved and commercialized for AD treatment, including dupilumab, tralokinumab and JAK-inhibitors, have changed the paradigm of AD therapeutic. Our nearest future work will focus on how EBF and CH change after all these treatments looking for early modifications that could predict treatments response. We will also explore the correlation between skin barrier dysfunction and cytokines production in patients with AD. Moreover, we will work on how is skin impaired in other skin diseases such as alopecia areata.

To commercialize any type of personal protective equipment (PPE) and hand hygiene product, it would be important to assess their impact on the skin objectively. This doctoral thesis is the starting point to develop further clinical trials for evaluating objectively the impact of all types of PPE, including masks, gloves and googles, on EBF

and CH. Regarding hand hygiene strategies, we have compared only one type of soap, one type of alcohol-based hand sanitizers (ABHS), and one type of disinfectant wipes. It would be recommended develop further clinicals trial with different types of these products to evaluate the most harmful components and excipients of them.

There are also other external factors that could modify skin barrier function, including sun exposure, air pollution, tobacco smoke, hormones, diet and sleep disturbances. We will study the impact of these factors both in vitro, using human tissue engineering skin substitute, and in healthy volunteers.

8.CONCLUSION

8. CONCLUSION

1) Normative data for epidermal barrier function (EBF) and cutaneous homeostasis (CH) in healthy individuals are different in the volar forearm, the cheek and the palm.
2) EBF and CH differs between healthy individuals, patients with psoriasis and patients with AD. Temperature and TEWL values may help clinicians to determinate objectively disease severity.
3) Stratum corneum hydration (SCH), temperature and erythema increase at psoriatic plaques after one and fifteen phototherapy sessions. TEWL at psoriatic plaques decreases after fifteen phototherapy sessions.
4) A cut-off point in erythema increases after the first phototherapy session could help clinicians to select psoriasis patients with more likelihood of responding to fifteen phototherapy sessions.
5) Gloves and mask wearing impair EBF and CH. Surgical masks use is associated with higher TEWL values than wearing FFP2 masks.
6) Daily hand hygiene with alcohol-based hand sanitizers (ABHS) is the hand hygiene strategy with the lowest rates of skin barrier impairment, the most effective method to reduce bacterial and fungi colony-forming unit and is considered the most convenient and easy method to use.
7) The rate of cutaneous adverse events related to personal protective equipment (PPE) is high. Most skin adverse events are mild, being dryness, pressure related symptoms and itching the most frequent.

8)

9.REFERENCES

9. REFERENCES

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