Psoriasis y factores de riesgo cardiovascular: Estudio poblacional, ateromatosis subclínica y vasa vasorum adventiciales

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Psoriasis y factores de riesgo cardiovascular: Estudio poblacional, ateromatosis subclínica y vasa vasorum adventiciales

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Resum

Antecedents y objectius: La psoriasi és una malaltia inmunoinflamatòria de la pell molt prevalent (afectació del 1-3% de la població mundial) de la que existeixen pocs estudis de prevalença realitzats a Espanya. També hi ha escassetat d'estudis de gravetat, la majoria dels quals s'han fet per dermatòlegs de països del nord d'Europa i els Estats Units, basant-se en el PASI o el BSA. S'associa a múltiples comorbiditats (artritis, fetge greixós, síndrome metabòlica i factors de risc cardiovascular clàssics), essent els events cardiovasculars majors la principal causa de mort en aquests pacients i la seva freqüència és més gran que en la població general. Així mateix sembla que hi ha una major prevalença d'ateromatosi en aquests pacients, el que es correlaciona amb un major risc de malaltia cardiovascular. Per tant, un diagnòstic precoç de malaltia arterial subclínica és important en aquests pacients, i cada vegada s'està investigant més la manera de detectar l'ateromatosi en les seves formes més inicials com són el dany endotelial i l'augment de la densitat de *vasa vasorum* adventicials. **Objectius**: 1) Analitzar mitjançant un estudi epidemiològic la prevalença de psoriasi en el nostre entorn, la seva distribució segons edat i sexe, i la seva severitat; 2) Determinar la associació amb els factors de risc cardiovascular i els esdeveniments cardiovasculars majors en un àrea on la dieta i la cultura tenen característiques diferents; 3) Valorar la presència de malaltia ateromatosa en un grup de pacients amb psoriasi i una població control, comparar-lo amb les escales de risc predictiu cardiovascular SCORE i REGICOR i obtenir els valors de densitat de vasa vasorum adventicials carotidis en ambdós grups. **Resultats**: Sobre una base de dades poblacional amb 398.701 individus, la prevalença de psoriasi va ser del 1.72%, essent major en homes (1.88% vs 1.56%). Un 7.27% del grup amb psoriasi va presentar una intensitat moderada-severa. Els pacients amb psoriasi van presentar major freqüència de síndrome metabòlica i de la resta de factors de risc cardiovascular clàssics, així com d'events cardiovasculars majors. L'ateromatosi subclínica va tendir a ser més prevalent en el grup amb psoriasi (46% vs 36%, p = 0.309). La presència d'ateromatosi carotídia va ser més prevalent en el grup de psoriasi moderada-severa que en el grup control (44.4% vs 18.0%; p = 0,026%) i, en el grup amb psoriasi, el 35.0% dels individus classificats com de risc baix segons SCORE i el 40.9% segons REGICOR van presentar una placa d'ateroma en algun dels territoris explorats. També es va evidenciar un augment en la densitat dels *vasa vasorum* adventicials carotidis en el grup de pacients amb psoriasi, així com també una associació amb l'obesitat i el perímetre alterat de cintura. **Conclusions**: En el nostre entorn, el 1.72% dels individus pateixen psoriasi, i el 7.27% d'aquests han estat classificats dins el grup de psoriasi moderada-greu. Aquesta xifra es molt diferent a la trobada en altres series del nord de Europa i els EE.UU on troben que els casos de psoriasi moderada-greu son del voltant del 25%. En part podria ser degut a que hem utilitzat com sistema de classificació la terapèutica emprada però també podria tenir relació amb l'estil de vida al aire lliure del nostre país, la diferent dieta i la menor utilització dels immunomoduladors. Hem corroborat la important associació entre psoriasi i factors de risc cardiovascular clàssics ja

detectats en estudis d'altres entorns, malgrat les diferencies culturals. Això reforçaria que l'abordatge de la psoriasi hauria de ser multidisciplinar i que s'hauria de descartar en l'estudi inicial patologies com la dislipèmia, la hipertensió i la diabetis, reduir factors de risc cardiovascular com el tabaquisme i l'alcoholisme i intervenir amb modificacions de la dieta i l'activitat per reduir pes. Igualment hem evidenciat la presencia d'ateromatosi subclínica malgrat un SCORE i REGICOR baixos (determinats en molts pocs estudis) el que indicaria que en aquests estudis inicials i de seguiment s'hauria d'incloure una ecografia femoral i carotídia. Finalment hem evidenciat també per primer cop en aquesta malaltia que es pot detectar d'una forma precoç la presència d'ateromatosi subclínica mitjançant la detecció de *vasa vasorum* adventicials per ecografia de microbombolles.

Resumen:

Antecedentes y objetivos: La psoriasis es una enfermedad inmunoinflamatoria de la piel muy prevalente (afectación del 1-3% de la población mundial) de la que existen pocos estudios de prevalencia realizados en España. También hay escasos estudios de gravedad, en su mayoría hechos por dermatólogos del norte de Europa y Estados Unidos, basándose en el PASI o el BSA. Se asocia a múltiples comorbilidades (artritis, hígado graso, síndrome metabólico y factores de riesgo cardiovascular clásicos) siendo los eventos cardiovasculares mayores la principal causa de muerte en estos pacientes y su frecuencia es mayor que en la población general. Así mismo parece que hay una mayor prevalencia de ateromatosis en estos pacientes, tanto a nivel carotídeo como femoral, lo que se correlaciona con un mayor riesgo de enfermedad cardiovascular. Por lo tanto, un diagnóstico precoz de enfermedad arterial subclínica es importante en estos pacientes, y cada vez se está investigando más la forma de detectar la ateromatosis en sus formas más iniciales como son el daño endotelial y el aumento de la densidad de vasa vasorum adventiciales. **Objetivos:** 1) Analizar mediante un estudio epidemiológico la prevalencia de psoriasis en la provincia de Lleida, su distribución según edad y sexo y su severidad; 2) Determinar la asociación con los factores de riesgo cardiovascular y los eventos cardiovasculares mayores en un área donde la dieta y la cultura tienen características diferentes a otras regiones; 3) Valorar la presencia de enfermedad ateromatosa carotídea y femoral en un grupo de pacientes con psoriasis y una población control, compararlo con las escalas de riesgo predictivo cardiovascular SCORE y REGICOR y obtener los valores de densidad de vasa vasorum adventiciales carotídeos en ambos grupos. **Resultados:** Sobre una base de datos poblacional con 398.701 individuos, la prevalencia de psoriasis fue del 1.72% y mayor en hombres (1.88% vs 1.56%). Un 7.27% de los pacientes con psoriasis presentaron una intensidad moderada-severa de la enfermedad. El grupo de pacientes con psoriasis presentaron mayor frecuencia de síndrome metabólico y del resto de factores de riesgo cardiovascular clásicos, así como de eventos cardiovasculares mayores. La ateromatosis subclínica tendió a ser más prevalente en el grupo con psoriasis (46% vs 36%,

p=0.309). La presencia de ateromatosis carotídea fue más prevalente en el grupo de psoriasis moderada-severa que en el grupo control (44.4% vs 18.0%; p=0.026%) y en el grupo con psoriasis, el 35.0% de los individuos clasificados como de riesgo bajo según SCORE y el 40.9% según REGICOR presentaron una placa de ateroma en alguno de los territorios explorados. También se evidenció un aumento en la densidad de los vasa vasorum adventiciales carotídeos en el grupo de pacientes con psoriasis, así como también una asociación con la obesidad y el perímetro alterado de cintura. **Conclusiones:** En nuestro entorno, el 1.72% de los individuos padecen psoriasis, y el 7.27% de estos han sido clasificados dentro del grupo de psoriasis moderada-grave. Esta cifra es muy diferente a la encontrada en otras series del norte de Europa y los EE.UU donde encuentran que los casos de psoriasis moderada-grave son de alrededor del 25%. En parte podría deberse a que hemos utilizado como sistema de clasificación la terapéutica empleada pero también podría tener relación con el estilo de vida al aire libre de nuestro país, la diferente dieta y la menor utilización de los inmunomoduladores. Hemos corroborado la importante asociación entre psoriasis y factores de riesgo cardiovascular clásicos ya detectados en estudios de otros entornos, a pesar de las diferencias culturales. Esto reforzaría que el abordaje de la psoriasis debería ser multidisciplinar y que se debería descartar en el estudio inicial patologías como la dislipemia, la hipertensión y la diabetes, reducir factores de riesgo cardiovascular como el tabaquismo y el alcoholismo e intervenir con modificaciones de la dieta y la actividad para reducir peso. Igualmente hemos evidenciado la presencia de ateromatosis subclínica a pesar de un SCORE y REGICOR bajos (determinados en muy pocos estudios) lo que indicaría que en estos estudios iniciales y de seguimiento se debería incluir una ecografía femoral y carotídea. Finalmente hemos evidenciado también por primera vez en esta enfermedad que se puede detectar de una forma precoz la presencia de ateromatosis subclínica mediante la detección de vasa vasorum adventiciales por ecografía de microburbujas.

Summary:

Background and objectives: Psoriasis is a very prevalent inflammatory skin disease (between 1-3% of the population). There are few prevalence and severity studies performed in Spain. Most of them involve northern Europe and United States and BSA and PASI were used to evaluate psoriasis severity. This disease has been associated to multiple comorbidities (arthritis, fatty liver, metabolic syndrome and classic cardiovascular risk factors). Major cardiovascular events are the main cause of death in these patients and their frequency is higher than in the general population. Likewise, it seems that there is a higher prevalence of atheromatosis in these patients, both at the carotid and femoral levels, which correlates with an increased risk of cardiovascular disease. Therefore, an early diagnosis of subclinical arterial disease is important in these patients, and plenty of research has been done to detect atheromatosis in its most initial forms such as endothelial damage and increased density of adventitial vasa vasorum. **Objectives:** 1) To analyze

through an epidemiological study the prevalence of psoriasis in the province of Lleida, its distribution according to age, sex and severity; 2) Avaluate its possible association with cardiovascular risk factors and major cardiovascular events; 3) In addition, to assess the presence of carotid and femoral atheromatous disease in a group of patients with psoriasis and a control population, compare it with the SCORE and REGICOR cardiovascular predictive risk scales and obtain the carotid adventitial vasa vasorum density in both groups. **Results:** Our database contained 398,701 individuals. The prevalence of psoriasis was 1.72% and higher in men (1.88% vs 1.56%). The prevalence of moderate-severe psoriasis was 7.27%. The group of patients with psoriasis had higher frequency of metabolic syndrome and the rest of classic cardiovascular risk factors, as well as a higher prevalence of major cardiovascular events. Subclinical atheromatosis tended to be more prevalent in the group with psoriasis (46% vs 36%, p = 0.309). The presence of carotid atheromatosis was more prevalent in the group of moderate-severe psoriasis than in the control group (44.4% vs. 18.0%, p = 0.026%). From the psoriasis cohort, 35.0% of the individuals which were classified in the low risk group according to SCORE and 40.9% according to REGICOR presented an atheromatous plaque in some of the explored territories. There was also a higher density of the carotid adventitial vasa vasorum in the group of patients with psoriasis, as well as an association between higher density vasa vasorum and obesity and altered waist circumference. **Conclusions:** In our environment, 1.72% of individuals suffer from psoriasis, and 7.27% of these have been classified within the group of moderate-severe psoriasis. These data are very different from other northern Europe and USA series where they find that cases of moderate to severe psoriasis are around 25% of the total psoriasis group. In part, it could be due to the fact that we have used the therapy used as a classification system but it could also be related to the outdoor lifestyle of our country, the different diet and the lesser use of immunomodulators. We have corroborated the important association between psoriasis and classic cardiovascular risk factors already published in other studies, despite cultural differences. This would reinforce that the approach to psoriasis should be multidisciplinary and pathologies such as dyslipidemia, hypertension and diabetes should be ruled out in the initial study, reducing cardiovascular risk factors such as smoking and alcoholism and intervening with changes in diet and activity to reduce weight. We have also demonstrated the presence of subclinical atheromatosis despite a low SCORE and REGICOR (determined in very few studies) which would indicate that a femoral and carotid ultrasound should be included in these initial and follow-up studies. Finally, we have also shown for the first time in this disease that the presence of subclinical atheromatosis can be detected early studying adventitial vasa vasorum by contrast-enhanced ultrasound.

2. Introducción y objetivos

La psoriasis es una enfermedad inmunoinflamatoria multisistémica que afecta preferentemente la piel, donde se manifiesta frecuentemente por placas eritematodescamativas[1]. Su prevalencia

mundial oscila entre el 1 y el 3%[2] de la población y series españolas sitúan la prevalencia nacional entre el 1.4[3] y 2.7%[4] mediante encuestas telefónicas. Aunque tanto la inmunidad innata como adaptativa juegan un papel importante en la patogénesis de la psoriasis, las células protagonistas en esta enfermedad son principalmente linfocitos T (sobre todo Th1 y Th17) así como citoquinas derivadas de éstos como el factor de necrosis tumoral α e interleucinas (IL-17 e IL-23)[5].

La psoriasis afecta de forma significativa la calidad de vida y la autoestima de las personas afectas. Tanto es así que se ha reportado una alteración de la calidad de vida en los pacientes con psoriasis moderada-severa parecida a la de pacientes con insuficiencia cardíaca o cáncer de mama[6]. Hasta hace unos años solamente se conocía la artritis psoriásica como comorbilidad asociada a esta enfermedad, con una prevalencia aproximada del 15-30% de los casos diagnosticados de psoriasis[7]. Por otro lado, debido a las muchas comorbilidades que se han ido publicando por diferentes autores, actualmente se considera la psoriasis una enfermedad inflamatoria sistémica.

Los eventos cardiovasculares mayores (como el infarto de miocardio y los ictus) son la principal causa de mortalidad de los pacientes con psoriasis[2], y de igual forma los factores de riesgo cardiovascular clásicos también son más prevalentes en esta población. Así pues se ha descrito asociación entre la psoriasis y la obesidad[8], dislipemia[9], diabetes mellitus 2[10] y la hipertensión[11]. También se ha confirmado mediante metaanálisis la asociación entre la psoriasis y el síndrome metabólico (una enfermedad sistémica inflamatoria y protrombótica que consiste en la conjunción de hiperglicemia, obesidad central, hipertensión y dislipemia)[12]. Igualmente la mayor parte de los estudios sobre riesgo cardiovascular y psoriasis provienen de Estados Unidos y el norte de Europa, regiones donde la cultura, la dieta y la irradiación solar son diferentes de la región mediterránea.

La asociación entre psoriasis y factores de riesgo cardiovascular es probablemente debida a factores genéticos, ambientales (conductas poco saludables como tabaquismo, obesidad, alcoholismo y sedentarismo) e inmunológicos comunes como la activación de las vías inflamatorias mediadas por Th1 y Th17, citoquinas proinflamatorias y aumento del estrés oxidativo, un fenómeno implicado en la patogénesis de la disfunción endotelial y la ateromatosis vascular[13,14]. Todo esto conlleva un aumento en la incidencia de eventos cardiovasculares mayores como infarto de miocardio (OR 3.04, 95% CI, 0.65-14.35) e ictus (OR 1.59, 95% CI, 1.34-1.89), así como un aumento en la mortalidad (OR 1.37: 95% CI 1.17-1.60)[15] que parece mayor en las psoriasis más severas[16].

En España, SCORE y REGICOR son dos escalas usadas para valorar el riesgo cardiovascular de un paciente. Estas escalas incluyen la edad, sexo, tabaquismo, diabetes mellitus, hipercolesterolemia y presión arterial[17]. Debido a que los pacientes con psoriasis podrían presentar un riesgo cardiovascular aumentado, el cálculo de la probabilidad de un evento cardiovascular mayor futuro usando estas escalas podría infraestimar el riesgo en los pacientes con psoriasis.

Actualmente el estudio de ateromatosis carotídea y femoral es otro de los indicadores de enfermedad vascular subclínica y predictor de enfermedad coronaria y eventos cardiovasculares mayores futuros[18]. En fases iniciales de la ateromatosis, los fenómenos inflamatorios mediados por linfocitos Th1 y Th17, monocitos y macrófagos tienen un papel relevante en la disfunción endotelial, mecanismos que son comunes a la patogénesis de la psoriasis[19-21]. Así mismo ciertos autores han publicado datos donde se observa un aumento del riesgo cardiovascular en otras patologías sistémicas inflamatorias como la artritis reumatoide, el lupus sistémico y la enfermedad inflamatoria intestinal[22].

Estudios recientes identifican un aumento significativo del grosor de la íntima-media carotídea y femoral en los pacientes con psoriasis, y algunos de estos autores concluyen que la psoriasis actúa como un factor de riesgo independiente de ateromatosis subclínica[23-25]. Así mismo, los pacientes con una severidad mayor de psoriasis también tendrían un mayor riesgo de ateromatosis[26]. La ecografía carotídea es una prueba fácil, no invasiva, repetible y barata para detectar ateromatosis a nivel carotídeo y femoral. Igualmente estudios recientes también concluyen que un manejo adecuado de la psoriasis podría favorecer un mejor control de los factores de riesgo cardiovascular presentes en estos pacientes, así como de la ateromatosis subclínica carotídea[27] y coronaria[28].

Actualmente existe mucha bibliografía respecto a los fenómenos iniciales de la ateromatosis para así poder describir marcadores precoces de riesgo cardiovascular previos a la formación de las placas de ateroma. Uno de los mecanismos implicados ha sido el aumento de la densidad de vasa vasorum adventiciales.

En condiciones normales existe una red vascular accesoria en vasos sanguíneos mayores de 0.5mm con el objetivo de nutrir las paredes de estos vasos[29]. Aquí, condiciones de hipoxia e isquemia promueven en la capa adventicial procesos inflamatorios mediados por neutrófilos, macrófagos y linfocitos así como mediadores proangiogénicos como el factor de crecimiento vascular endotelial. Todo esto contribuye a la formación de una nueva red de vasa vasorum adventiciales, llamados también de segundo orden o patológicos que se encuentran orientados de forma transversal a la luz vascular para así poder asegurar una correcta oxigenación de estos vasos[21,30].

Existen diversas causas ya establecidas de aumento de la densidad de vasa vasorum adventiciales como son la edad[31], la hipercolesterolemia[32], la hipertensión arterial[33], la diabetes mellitus tipo 1[34] y 2[35,36], la obesidad[37], la enfermedad renal crónica[38], el hiperparatidoidismo[39], el déficit de vitamina D[40], la anemia[41] y el síndrome de apnea-hipopnea del sueño[36]. Como se ha descrito previamente, la inflamación tiene un papel relevante en el proceso de neoangiogénesis. Así mismo, los pacientes con psoriasis presentan un aumento en la prevalencia de ateromatosis, lo que haría pensar que presentan a su vez un aumento en la densidad de los vasa vasorum adventiciales a nivel carotídeo.

Teniendo en cuenta la información comentada previamente, los objetivos de nuestro estudio fueron los siguientes:

A) En el estudio epidemiológico

1. Mediante un estudio poblacional de la región sanitaria de Lleida, determinar el número de casos registrados con el diagnóstico de psoriasis, y determinar los casos de psoriasis moderada-severa en esta población, dado que los estudios epidemiológicos hechos en España se hicieron mediante entrevistas telefónicas y a un grupo de población no muy numeroso
2. Valorar la prevalencia de factores de riesgo cardiovascular y síndrome metabólico en la población anterior y compararla con la población sin esta enfermedad.
3. Analizar la probabilidad de síndrome metabólico dependiendo del sexo, edad, diagnóstico de psoriasis y severidad.
4. Valorar la prevalencia de antecedentes de eventos cardiovasculares mayores (infarto de miocardio e ictus) en el grupo con psoriasis y compararlo con el resto de la población.

Estudio de ateromatosis carotídea y femoral:

1. Analizar la prevalencia de factores de riesgo cardiovascular clásicos en un grupo de pacientes con psoriasis y compararlo con una población control.
2. Estudiar la prevalencia de ateromatosis subclínica (carotídea y femoral) en estos dos grupos.
3. Evaluar mediante SCORE y REGICOR el riesgo cardiovascular estimado en estas dos poblaciones y compararlo con los datos de ateromatosis.

Estudio de neovascularización carotídea:

1. Medir la densidad de vasa vasorum adventiciales carotídeos en un grupo de pacientes con psoriasis y uno control para valorar diferencias.

2. Evaluar la posible asociación entre el aumento de densidad de vasa vasorum adventiciales con otros factores de riesgo cardiovascular clásicos.

3. Metodología utilizada

En relación al estudio poblacional realizado en la provincia de Lleida sobre epidemiología de la psoriasis y factores de riesgo cardiovascular, se obtuvieron los resultados de dos bases de datos electrónicas: los registros del ECAP y del SAP. El ECAP es un registro realizado por médicos de atención primaria de todos los centros de la región sanitaria de la provincia de Lleida, en la que estaban censados en 2016 411.189 habitantes, excepto el Solsonès y Vall d'Aran. Esta base de datos está activa desde 2003. El SAP es el registro del Hospital Arnau de Vilanova de Lleida, el

único hospital en la provincia con servicio de Dermatología. Se encuentra activo desde 2010. Posteriormente la información de estas dos bases de datos hasta junio de 2016 se unificó en una, se eliminaron los registros duplicados y los que contenían datos inconsistentes (edad > 120 años, peso > 250 kg, altura > 2,20 m, etc) y se anonimizó para realizar el análisis de los resultados obtenidos.

Se escogieron solamente datos relevantes para el estudio: edad, sexo, medidas antropométricas, diagnóstico de psoriasis, diagnóstico de factores de riesgo cardiovascular clásicos (diabetes mellitus 2, hipertensión, hipercolesterolemia, disminución de HDL, hipertrigliceridemia), el historial de medicación prescrita y la presencia de un evento cardiovascular mayor (ictus cerebral e infarto agudo de miocardio). Con estos datos además estudiamos la presencia de síndrome metabólico según los criterios de la American Heart Association y el National Heart, Lung and Blood Institute[42]. El diagnóstico de psoriasis se realizó en aquellos individuos a los que se les había codificado este diagnóstico (DL20, 696.1) según la clasificación internacional ICD.10 a los que se añadieron pacientes que habían recibido tratamiento con análogos tópicos de la vitamina D (solos o combinados con betametasona tópica) y aquellos que hubiesen recibido acitretina oral. Debido a que actualmente no se incluye en los sistemas informáticos ECAP ni SAP un campo en el que se registre la severidad de la psoriasis mediante BSA o PASI, se definió la psoriasis moderada-severa como aquella en que hubiese un registro histórico o actual de tratamiento con fototerapia UVB o PUVA (psoraleno y ultravioleta A), fármacos tradicionales sistémicos (acitretina, metotrexato o ciclosporina) o terapia biológica (infliximab, etanercept, adalimumab, ustekinumab, secukinumab), considerando el resto de pacientes de psoriasis como de severidad leve. Este método ya había sido previamente usado por otros autores[43]. Esta base de datos anonimizada fue posteriormente analizada mediante el software SPSS v24.0 (IBM Corporation, Armonk, NY, USA).

En relación al estudio de ateromatosis carotídea y femoral en los pacientes con psoriasis y el posterior estudio de vasa vasorum adventicial se reclutaron 50 pacientes con psoriasis provenientes de las consultas de dermatología (tanto genéricas como la consulta de psoriasis moderada-severa) del Hospital Arnau de Vilanova de Lleida y 50 individuos control que provenían de las consultas de dermatología y que no habían sido diagnosticados de esta enfermedad. Estos dos grupos fueron apareados por edad y sexo. Ambos grupos solamente contenían individuos mayores de 18 años. Se consideró un criterio de inclusión en el grupo con psoriasis el diagnóstico de una psoriasis en placas y otras formas fueron excluidas, así como no haber recibido terapia sistémica o biológica en el último mes (3 meses en el caso de ustekinumab). En el grupo control también se excluyeron individuos tratados con inmunosupresores sistémicos por otro motivo en el último mes. En ambos grupos se excluyeron pacientes con enfermedad cardíaca, respiratoria, renal o diabetes, así como embarazo, lactancia y contraindicaciones para la administración de hexafluoruro de azufre para el estudio de vasa vasorum.

Los datos que se recogieron en ambos grupos fueron: edad, sexo, diagnóstico de diabetes mellitus, hipercolesterolemia, hipertrigliceridemia, hipertensión arterial, síndrome metabólico, tabaquismo y tratamiento actual para la hipertensión, dislipemia o diabetes mellitus. Los pacientes fumadores y exfumadores fueron agrupados juntos. Datos de la exploración física relevantes fueron la cifras tensionales, índice de masa corporal y perímetro abdominal. En el análisis de sangre se valoraron las cifras glicémicas y lipídicas y parámetros inflamatorios (PCR y VSG). La escala PASI (Psoriasis Area Severity Index) fue la utilizada para medir la severidad de la psoriasis, considerando una psoriasis moderada-severa con valores superiores a 10.

La ecografía vascular y el estudio de vasa vasorum fue realizada en la UDETMA (Unidad de detección precoz de enfermedad ateromatosa) del Hospital Arnau de Vilanova. Aquí se valoró la presencia de placas de ateroma en territorios carotídeo y femoral bilateral y se consideró como placa ateromatosa aquella con un grosor íntima-media superior a 1.5 mm según el consenso de Mannheim[44]. El estudio de vasa vasorum adventicial se realizó mediante la administración de un contraste de hexafluoruro de azufre por vía periférica y la posterior visualización y cuantificación de la densidad de vasa vasorum adventiciales en ambas carótidas comunes. Se realizó un estudio mediante las escalas SCORE y REGICOR en todos los individuos que posteriormente se comparó con los datos de ateromatosis femoral y carotídea. Igualmente, este estudio fue aprobado por el comité ético del Hospital Arnau de Vilanova de Lleida (CEIC-1655).

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ORIGINAL

Características epidemiológicas de la psoriasis. Un estudio poblacional

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PALABRAS CLAVE
Psoriasis;
Epidemiología;
Poblacional;
Prevalencia

Resumen

Antecedentes y objetivo: La psoriasis es una enfermedad inmunoinflamatoria crónica de la piel muy frecuente en el mundo occidental. Muchos autores han intentado calcular su prevalencia en diversas regiones, aunque en la mayoría de los casos esta se ha obtenido mediante encuestas y existen escasas publicaciones procedentes del área mediterránea.

El objetivo de nuestro estudio era analizar la prevalencia y severidad de la psoriasis en Lleida (región del noreste de España), identificar diferencias en edad y sexo, y comparar nuestros resultados con otras series europeas.

Materiales y métodos: Se obtuvo una base de datos conjunta entre medicina primaria y el departamento de dermatología de toda la provincia de Lleida con datos epidemiológicos, diagnóstico de psoriasis y codificación de tratamiento.

Resultados: La base de datos final comprendía a 398.701 individuos y 6.868 de ellos (1,72%) fueron codificados con el diagnóstico de psoriasis. La prevalencia de psoriasis fue significativamente mayor en hombres que en mujeres (1,88 vs. 1,56%; OR = 1,21; IC 95%: 1,15-1,27). La prevalencia más alta de psoriasis se encontró en el grupo de edad de los 61-70 años (2,90%) y la prevalencia de psoriasis en menores de 18 años fue del 0,30%. En nuestra población, el 7,27% de los pacientes fueron clasificados como psoriasis moderada-severa (499/6.868).

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Conclusiones: Este estudio reporta la prevalencia y severidad de la psoriasis en una muestra amplia de una región mediterránea, obteniendo la información mediante una base de datos electrónica. Además, se evidencia una prevalencia menor de psoriasis comparada con otros países europeos y una proporción de psoriasis severa (basado en criterios de tratamiento) menor que en otros estudios. Estas diferencias podrían deberse a factores genéticos, estilo de vida y dieta.

KEYWORDS
Psoriasis;
Epidemiology;
Population;
Prevalence

Epidemiology of Psoriasis. A Population-Based Study

Abstract
Background and objectives: Psoriasis is a chronic immunoinflammatory skin disease very frequent in the western world. Several authors have tried to calculate its prevalence in different regions, although most of them obtained the data from surveys and there are few publications from Mediterranean areas.

The objective of our study was to analyze the prevalence and severity of psoriasis in Lleida (a northeastern region in Spain), identify age and sex specific differences and compare our results with other European series.

Materials and methods: A joint database of primary care medicine and the dermatology department was obtained from the entire province of Lleida with epidemiological data and psoriasis diagnosis and treatment codification.

Results: A corrected database was obtained with 398,701 individuals and 6,868 of them (1.72%) were coded with the diagnosis of psoriasis. The prevalence was significantly higher in men than in women (1.88% *vs* 1.56%, OR = 1.21, 95% CI: 1.15-1.27). The highest prevalence of psoriasis was found in the 61-70 years group (2.90%) and psoriasis in population under 18 years of age was 0.30%. In our sample, 7.27% of the patients were classified as moderate-severe psoriasis (499/6,868).

Conclusion: This study reports the prevalence and severity of psoriasis in a large Mediterranean region sample, obtaining the information through a electronic database. This study reveals a lower prevalence of psoriasis compared to other European countries, and the proportion of severe psoriasis (based on treatment criteria) is lower than in other studies. We emphasize that these differences could probably due to genetic background, life style and diet.

Introducción

La psoriasis es una enfermedad cutánea, crónica e inmunoinflamatoria que afecta al 1-3% de la población mundial[1,2]; esto corresponde aproximadamente a 125 millones de individuos[3]. En España, la prevalencia de psoriasis se estimó a través de 2 encuestas telefónicas, obteniendo un 1,4-2,7%[4,5]. Por otro lado, la psoriasis tiene un impacto importante en la autoestima y en la calidad de vida de los pacientes; se ha observado que los pacientes con psoriasis moderada-severa presentarán una calidad de vida similar a la de los pacientes con insuficiencia cardiaca o cáncer de mama[6].

La mayor parte de los estudios realizados para determinar la prevalencia de enfermedades crónicas como es el caso de la psoriasis se han llevado a cabo a través de encuestas, estudiando únicamente una parte representativa de la población. Si bien la prevalencia de la psoriasis se verá modificada por el área geográfica[7], existen escasos estudios epidemiológicos en el área mediterránea, área donde la dieta así como los hábitos de esta población pueden desempeñar un papel importante[8]. El objetivo de este estudio fue conocer la prevalencia, así como la severidad de la psoriasis (tanto global, como por subgrupos) a través del análisis de la historia clínica computarizada (eCAP), en la cual se encuentran incluidos todos los habitantes de Lleida, una provincia al noreste de España, Cataluña.

Materiales y métodos

Este es un estudio observacional y de corte transversal basado en los datos médicos recogidos en la historia clínica electrónica (eCAP y SAP) de los habitantes que residen en la provincia de Lleida.

El registro computarizado del área de Atención Primaria se obtuvo a partir de la estación clínica del ECAP, la que abarca la provincia de Lleida, con excepción del área de Solsonès. Esta base de datos está activa desde el año 2003 e incluye aproximadamente 1.000.000 de habitantes que hayan estado por algún motivo en contacto con los servicios de atención primaria. Los datos del servicio de dermatología fueron obtenidos del SAP, un registro médico electrónico utilizado en el Hospital Arnau de Vilanova, el único hospital de la provincia de Lleida que cuenta con servicio de

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dermatología. Este registro está activo desde el año 2010. Nuestra base de datos no incluyó a los pacientes que no fueron vistos en el sistema público de salud.

La información de ambas bases de datos fue recogida (desde su inicio hasta junio del 2016) y posteriormente fusionada. Para realizar este estudio solo los datos más relevantes fueron extraídos (sexo, edad, altura, peso, diagnóstico de psoriasis y tratamientos utilizados para la psoriasis). Una vez completada la base de datos, los individuos que no pertenecían a esta área fueron excluidos de la misma. De la base de datos resultante, aquellos duplicados fueron eliminados y finalmente los registros relacionados con el diagnóstico de psoriasis cutánea fueron los seleccionados (DL20, 696,1), para lo que se utilizó la clasificación internacional ICD-10. La información de los tratamientos prescritos se obtuvo desde el año 2005 (para el programa ECAP) y desde el año 2010 (para el programa SAP). Posteriormente dicha información fue fusionada y finalmente comparada con el registro nacional catalán de prescripciones.

En la base de datos resultante, cada individuo contaba con: una identificación anonimizada (una vez que se había correlacionado con la base de datos del hospital), edad al momento del estudio, si se tenía la información disponible del hospital o no (con sus respectivos valores), género y el resto de las variables antes mencionadas. Todos los datos fueron guardados de manera segura y el anonimizar la identificación de cada individuo hizo posible revisar y verificar la información de cada registro cuando fuese necesario.

Debido a la posibilidad de que algunos pacientes no estuvieran registrados en el Sistema de salud público, se decidió agregar además a los pacientes que recibieron algún tratamiento con análogos de la vitamina D tópicos (ya sea solos o en combinación con betametasona tópica), así como aquellos tratados con acitretino oral.

La base de datos anonimizada se analizó con el programa SPSS v24.0 (IBM Corporation, Armonk, NY, EE. UU.). La comparación de las proporciones, así como los rangos de las variables entre los diversos grupos, se determinaron mediante la prueba de chi-cuadrado, la prueba de «Student» o ANOVA unidireccional, según fuera lo más apropiado. Las diferencias se consideraron como estadísticamente significativas cuando tenían un valor de $p < 0,05$.

La psoriasis se clasificó como moderada-severa si en la historia clínica se encontraba el antecedente de haber utilizado UVB de banda estrecha (UVBbe), UVA con psoraleno (PUVA), tratamiento sistémico tradicional (acitretino, metotrexate o ciclosporina) o terapia biológica (infliximab, etanercept, adalimumab, ustekinumab, secukinumab o ixekizumab); los casos restantes se consideraron dentro del grupo de psoriasis leve. Esta clasificación ya había sido utilizada anteriormente en otros estudios[9]. Este estudio contó con la aprobación del «Comité de Ética del Hospital Arnau de Vilanova de Lleida».

Resultados

La suma de ambas bases de datos, tanto la hospitalaria como la de atención primaria, recogió un total de 398.860 registros. Después de excluir inconsistencias, así como aquellos casos con algún dato perdido, la base de datos incluyó un total de 398.701 pacientes. La edad media fue de 42,34 (la mediana 42 y el rango intercuartílico de 25-59 años); el porcentaje de pacientes del sexo masculino fue del 50,66% (201.977 varones). De estos pacientes, 72.230 tenían menos de 18 años (18,12% de la muestra total) (tabla 1).

En la base de datos inicial se contaba con 6.,556 registros de pacientes diagnosticados de psoriasis. A este grupo se agregaron además 298 pacientes, que eran los que, a pesar de no contar con ningún registro previo referente al diagnóstico de psoriasis, habían sido tratados con algún análogo de la vitamina D tópico (solo o en combinación con betametasona tópica) y otros 14 que habían recibido acitretino oral. La muestra final fue de 6.868 sujetos (1,72% de la población). Los pacientes de sexo masculino (3.799/6.868 sujetos) representaron el 55,31% del total, con una prevalencia del 1,88% en este subgrupo (3.799/201,97). La prevalencia de psoriasis en mujeres fue del 1,56% (3.069/196.724); por lo tanto, el ser del sexo masculino fue un factor asociado a un mayor riesgo de presentar psoriasis (OR = 1,21; IC 95%: 1,15-1,27).

La edad media del grupo de pacientes con psoriasis fue mayor que la de la población general (52,08 vs. 42,34 años, $p < 0,001$). Doscientos diecisiete individuos tenían menos de 18 años (217/6.867), lo que representó un 3,16% de todos los pacientes con psoriasis y un 0,29% de aquellos menores de 18 años) (tabla 1). La prevalencia de psoriasis en mujeres menores de 18 años fue mayor que la de los varones, pero sin que esta diferencia fuese estadísticamente significativa (0,33 vs. 0,27%; OR = 1,210; IC 95%: 0,926-1,581). El grupo de pacientes que tenían entre 51 y 60 años fue el que tuvo un mayor número absoluto de pacientes con psoriasis (1.350/6.868 individuos y un 19,66% del grupo con psoriasis). Sin embargo, la mayor prevalencia de psoriasis se encontró en el grupo de pacientes entre los 61-70 años (1.122/38.740

Tabla 1 Características poblacionales

	Población general	Grupo sin psoriasis	Grupo con psoriasis
Tamaño de la muestra	398.701	391.833	6.868 (1,72%)
Edad media (Q1-Q3), años	42,34 (25-59)	42,17 (24-59)	52,08 (39-66)
Varones[a]/mujeres[b]	201.977/196.724	198.178/193.655	3.799/3.069
%Varones	50,66%	50,58%	55,31%
%Edad < 18 años[c]	18,40%	18,42%	3,16%

[a] Prevalencia de psoriasis en varones: 1,88% (OR: 1,21; IC 95%: 1,15-1,27).
[b] Prevalencia de psoriasis en mujeres: 1,56%.
[c] Prevalencia de psoriasis en población < 18 años: 0,30%.

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Tabla 2 Distribución de la población en relación con la edad y sexo

Grupo por edad	Población general		Grupo sin psoriasis		Grupo con psoriasis	
	Varones, n (%)	Mujeres, n (%)	Varones, n (%)	Mujeres, n (%)	Varones, n (%)	Mujeres, n (%)
0-10	23.327 (11,55)	22.276 (11,33)	23.293 (11,75)	22.245 (11,49)	34 (0,89)	31 (1,01)
11-20	19.442 (9,63)	18.158 (9,23)	19.335 (9,76)	18.012 (9,30)	107 (2,82)	146 (4,76)
21-30	21.246 (10,52)	20.620 (10,48)	20.976 (10,58)	20.347 (10,51)	270 (7,11)	273 (8,90)
31-40	33.797 (16,73)	29.475 (14,99)	33.200 (16,75)	28.994 (14,97)	597 (15,71)	481 (15,68)
41-50	34.940 (17,30)	29.941 (15,22)	34.208 (17,26)	29.405 (15,19)	732 (19,27)	536 (17,47)
51-60	27.911 (13,82)	25.467 (12,95)	27.156 (13,70)	24.872 (12,85)	755 (19,87)	595 (19,39)
61-70	19.051 (9,43)	19.689 (10,01)	18.392 (9,28)	19.226 (9,93)	659 (17,35)	463 (15,09)
71-80	12.481 (6,18)	15.226 (7,74)	12.070 (6,09)	14.923 (7,71)	411 (10,82)	303 (9,88)
81-90	8.489 (4,20)	12.957 (6,59)	8.267 (4,17)	12.747 (6,58)	222 (5,84)	210 (6,84)
91 o más	1.293 (0,64)	2.878 (1,46)	1.281 (0,65)	2.848 (1,47)	12 (0,32)	30 (0,98)

individuos), representando un 2,90% de este grupo (tabla 2, fig. 1). La psoriasis se etiquetó como moderada-severa en 499 pacientes (7,27% de los pacientes con psoriasis).

Discusión

La prevalencia de psoriasis (1,72%) en la provincia de Lleida, España, fue similar a los valores vistos en estudios realizados previamente en España (1,43% en 2001[4] y 2,31% en 2013[5]), con poblaciones de 12.938 y 12.711 individuos respectivamente. Se debería resaltar que el método de registro usado anteriormente fue mediante una encuesta telefónica y no una base de datos médica. Como nuestro estudio existen otros estudios en Europa que han utilizado bases de datos para determinar la prevalencia de la psoriasis (tabla 3); por ejemplo, en el estudio de Springate et al.[10] en el Reino Unido y Radtke et al.[11] en Alemania, con una prevalencia del 2,8% y del 2,78% respectivamente. Estos estudios se han realizado con metodologías similares, por lo que las diferencias en la prevalencia en comparación con nuestro estudio podrían atribuirse a las variaciones poblacionales, medioambientales y de la dieta[8]. Los resultados obtenidos en otros estudios europeos demuestran igualmente que existe una gran variabilidad respecto a la prevalencia de la psoriasis. La prevalencia más baja se registró en Escocia (0,73%)[12] y la más alta en Noruega (11,43%)[13], siendo esta última

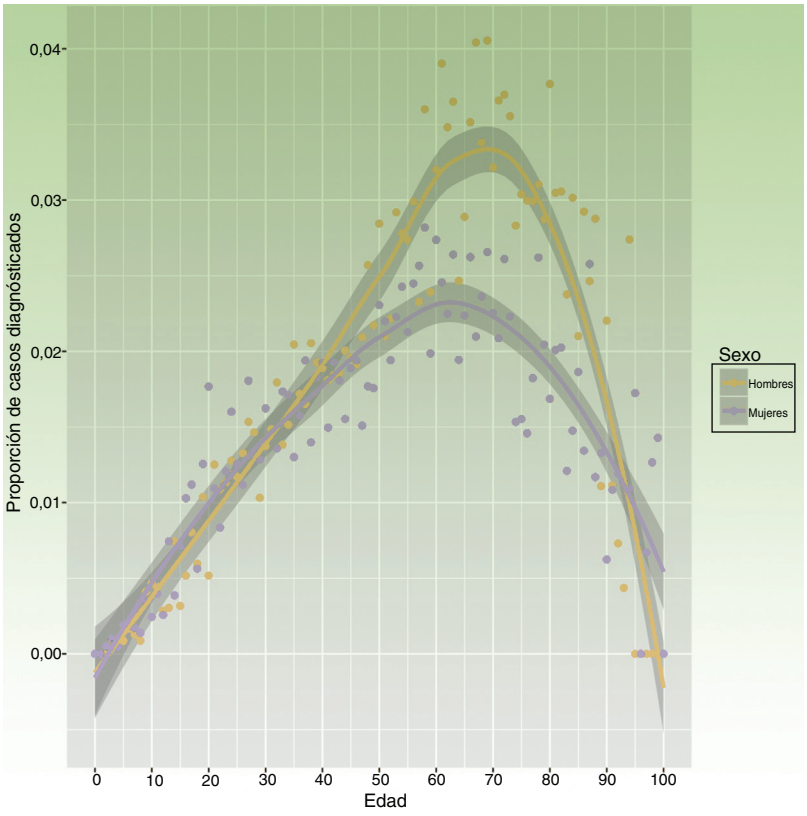

Figura 1 Proporción de casos diagnosticados según edad y sexo.

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Tabla 3 Prevalencia global y en varios grupos de psoriasis en estudios relevantes previos europeos

Estudio	País	Año	Método diagnóstico	Población (n)	Edad	Prevalencia global de psoriasis (%)	Prevalencia varones (%)	Prevalencia mujeres (%)	Prevalencia en menores de 18 años (%)
Saraceno et al. (2008)[14]	Italia	2006	Encuesta	4.109	Todas	2,9	-	-	-
Wolkenstein et al. (2009)[15]	Francia	2005	Encuesta	6.887	15+	5,2	-	-	-
Seminara et al. (2011)[22]	Reino Unido	2009	Base de datos + encuesta	7.520.293	Todas	1,9	1,8	1.9	0,40
Ferrándiz et al. (2014)[5]		2013	Encuesta telefónica	12.711	Todas	2,3	2,7	1,9	0,5 (< 16 años)
Cantarutti et al. (2015)[16]	Italia	2006-2012	Encuesta	145.233	0-14	-	-	-	0,22 (2012)
Radtke et al. (2017)[11]	Alemania	2009	Base de datos	1.349.671	18+	2,78	2,94	2,59	-
Springate et al. (2017)[10]	Reino Unido	1999-2013	Base de datos	15.436.637 (2013)	Todas	2,8	2,81	2,83	-

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marcadamente elevada en comparación con el resto de estudios poblacionales (1-3%). Esto se deberá probablemente a que el estudio noruego se realizó en una comunidad cerrada utilizando una encuesta, lo que implicaba que la información del diagnóstico de psoriasis se obtenía preguntando al propio paciente sin tener en cuenta una opinión médica. Si nos centramos en los países del área mediterránea, los datos más recientes y fiables son los de los estudios italiano (2,9%)[14] y francés (5,2%)[15] (tabla 3). La prevalencia estimada en nuestro estudio fue similar a la observada en la población italiana, lo que indicaría que tanto los factores culturales como medioambientales tendrán una influencia en la prevalencia de la psoriasis. Por otro lado, algunas diferencias observadas entre los países del área mediterránea podrían deberse a variaciones metodológicas (el uso de encuestas en lugar de una base de datos).

La edad media de la población general en nuestro estudio fue de 42,34 años (rango intercuartílico 25-59 años); es interesante que en el grupo de pacientes con psoriasis la edad media estaba incrementada (52,08 años), lo que refleja que esta enfermedad se presentará generalmente después de la adolescencia. En cuanto a la distribución de los pacientes con psoriasis por subgrupos etarios, el porcentaje más alto de pacientes con psoriasis tenían entre 51-60 años (19,66% de la población con psoriasis) (tabla 2), sin embargo, la prevalencia máxima se observó en el grupo entre 61-70 años (2,90%). Estos datos son similares a los vistos en la mayoría de los estudios, donde existe un incremento en la prevalencia de psoriasis directamente proporcional a la edad hasta los 60-70 años, momento en el cual la frecuencia de esta enfermedad disminuye[5,13] (tabla 3). Estos resultados demuestran que esta es una enfermedad crónica, donde los pacientes diagnosticados a edades tempranas se acumularán a lo largo de los años. Por otro lado, en algunos estudios se ha evidenciado un pico de prevalencia en el subgrupo de pacientes entre los 20 y los 30 años[4,10], hecho que no fue observado en nuestro estudio.

El porcentaje de diagnóstico de psoriasis en pacientes menores de 18 años fue del 0,30%, lo que corresponde a un 3,16% de la población general con psoriasis (tabla 1). Estos resultados son similares a los publicados por Cantarutti et al. en Italia (0,22%)[16] (tabla 3) y Augustin et al. en Alemania (0,45%)[17]. En un estudio sobre la psoriasis infantil en Italia se estimó una prevalencia del 2,1% en pacientes entre los 12 y 17 años de edad, observando además una correlación entre el diagnóstico de dermatitis atópica y psoriasis[18]. En este estudio los autores sugirieron que esta mayor prevalencia en los niños italianos podría deberse a un error en el diagnóstico diferencial entre eccemas y lesiones psoriasiformes. De forma similar, la prevalencia de psoriasis infantil en países europeos será mayor que en otros estudios publicados en poblaciones africanas o asiáticas[19,20], lo que es similar a lo que ocurre generalmente en la población adulta. Pese a que los autores de este estudio no han sugerido ninguna hipótesis que explique estos resultados, las diferencias medioambientales, como por ejemplo la dieta, podrían estar relacionadas.

El sexo masculino fue una variable que se asoció con un mayor riesgo de desarrollar psoriasis (1,88 vs. 1,56%; OR: 1,21; IC 95%: 1,15-1,27) (tabla 1). Esto también se vio en el estudio de Ferrándiz et al. en España[5] (tabla 3) (2,4 vs. 1,9%) y Radtke et al. en Alemania[11] (tabla 3) (2,90 vs. 2,59%). Por el contrario, otros estudios han mostrado una mayor prevalencia de psoriasis en mujeres, como el de Stern et al. en EE. UU. (2,5% en mujeres vs. 1,9 en varones)[21]; sin embargo, en 2 estudios del Reino Unido no se encontraron diferencias significativas entre ambos sexos[22,23] (tabla 3). En el estudio de Augustin et al., que incluía niños alemanes, el diagnóstico de psoriasis fue más frecuente en pacientes del sexo femenino (0,76 vs. 0,66)[24]. En nuestro estudio la prevalencia de psoriasis en la población infantil fue menor, mostrando una mayor proporción de psoriasis en niñas (0,33 vs. 0,27%; OR = 1,210; IC 95%: 0,926-1,581) aunque sin una significación estadística. Debido a que no existe consenso en cuanto a la asociación entre género y psoriasis en los estudios publicados, sería de gran interés el determinar qué factores podrían interferir en las diferencias encontradas.

En la actualidad existen escasos estudios publicados que diferencien la prevalencia de psoriasis leve y psoriasis moderada-severa. En nuestra población, 499 pacientes (7,27% de todos los pacientes con psoriasis) fueron clasificados dentro del grupo de psoriasis moderada-severa, una prevalencia menor que la de otras series, como en la de Takeshita et al. en EE. UU. (27,3%)[9] y Yeung et al. en el Reino Unido (38,2%)[25]. Una probable hipótesis es que el utilizar como criterio de severidad el haber recibido tratamiento sistémico podría conllevar a una infraestimación del porcentaje de pacientes con psoriasis moderada-severa. Sin embargo, consideramos que obtener estos datos utilizando las escalas de severidad de psoriasis (BSA o PASI) no hubiera sido factible, debido a que estas no son usadas normalmente en los servicios de atención primaria y no estaban disponibles en todos los pacientes. Otro factor a considerar son las psoriasis moderadas-severas infratratadas con medicación tópica, sobre todo en un país de clima soleado[26]. Asimismo, la dieta[8] podría tener un efecto protector y prevenir el empeoramiento de estos pacientes.

Limitaciones del estudio

Debido a que se trata de un estudio poblacional transversal, algunos datos no se pudieron recuperar ya que no habían sido registrados en la base de datos. Por otro lado, nuestra base de datos se realizó a partir de registros tanto de atención primaria como del servicio de dermatología, por lo que los pacientes que nunca habían sido vistos en el sistema público de salud no fueron incluidos.

Asimismo, algunos de los pacientes fueron evaluados únicamente por médicos generales, por lo que en un escaso porcentaje de casos el diagnóstico podría estar equivocado. El haber recibido tratamiento sistémico no es la forma más adecuada de clasificar la severidad de la psoriasis, mientras que el uso de escalas como el BSA o PASI hubiera sido lo más idóneo. Sin embargo, la mayoría de los pacientes en nuestro estudio no contaban con BSA o PASI (escalas que no son utilizadas normalmente por médicos de atención primaria).

Los pacientes que recibieron acitretino y análogos tópicos de la vitamina D también fueron incluidos en el grupo de pacientes con psoriasis ya que estos tratamientos normalmente se indicarán en esta enfermedad. Esto se hizo con la finalidad de agregar pacientes al estudio que por algún

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motivo no estaban codificados para el diagnóstico de psoriasis; sin embargo, habría que resaltar que esto podría implicar un cierto sesgo en los resultados.

Debido a que en esta población solo un centro es el responsable de la prescripción de tratamientos sistémicos y biológicos, el criterio de inicio de estos tratamientos podría diferir al de otros centros.

Conclusión

Nuestro estudio refleja una menor prevalencia y severidad de psoriasis en la población general, si se compara con la mayor parte de estudios realizados en países occidentales; asimismo nuestro estudio demostró una mayor asociación con el sexo masculino. La variabilidad entre las diferentes poblaciones demuestra la importancia de reproducir en regiones distintas del mundo los mismos estudios. De esta forma se logrará una mejor comprensión de esta enfermedad, así como de las variables externas que podrían estar relacionadas con ella. Factores de tipo metodológico podrían explicar algunas de las diferencias observadas en nuestro estudio; estudios subsecuentes serán necesarios para comparar las diferencias encontradas en una misma región y al mismo tiempo corroborar o cuestionar otros factores genéticos o epidemiológicos relacionados.

Conflicto de intereses

Los autores declaran no tener ningún conflicto de intereses.

Bibliografía

1. Parisi R, Symmons DPM, Griffiths CEM, Ashcroft DM. Global epidemiology of psoriasis: A systematic review of incidence and prevalence. J Invest Dermatol. 2013, http://dx.doi.org/10.1038/jid.2012.339.
2. Michalek IM, Loring B, John SM. A systematic review of worldwide epidemiology of psoriasis. J Eur Acad Dermatology Venereol. 2017, http://dx.doi.org/10.1111/jdv.13854.
3. Takeshita J, Grewal S, Langan SM, Mehta NN, Ogdie A, Van Voorhees AS, et al. Psoriasis and comorbid diseases: Epidemiology. J Am Acad Dermatol. 2017, http://dx.doi.org/10.1016/j.jaad.2016.07.064.
4. Ferrándiz C, Bordas X, García-Patos V, Puig S, Pujol R, Smandía A. Prevalence of psoriasis in Spain (epiderma project: Phase I). J Eur Acad Dermatology Venereol. 2001, http://dx.doi.org/10.1046/j.1468-3083.2001.00191.x.
5. Ferrándiz C, Carrascosa JM, Toro M. Prevalence of psoriasis in Spain in the age of biologics. Actas Dermo-Sifiliográficas (English Ed. 2014, http://dx.doi.org/10.1016/j.adengl.2014.04.016.
6. Zachariae R, Zachariae C, Ibsen HHW, Mortensen JT, Wulf HC. Psychological symptoms and quality of life of dermatology outpatients and hospitalized dermatology patients. Acta Derm Venereol. 2004, http://dx.doi.org/10.1080/00015550410023284.
7. Greb JE, Goldminz AM, Elder JT, Lebwohl MG, Gladman DD, Wu JJ, et al. Psoriasis. Nat Rev Dis Prim. 2016, http://dx.doi.org/10.1038/nrdp.2016.82.
8. Barrea L, Balato N, Di Somma C, Macchia PE, Napolitano M, Savanelli MC, et al. Nutrition and psoriasis: Is there any association between the severity of the disease and adherence to the Mediterranean diet? J Transl Med. 2015, http://dx.doi.org/10.1186/s12967-014-0372-1.
9. Takeshita J, Gelfand JM, Li P, Pinto L, Yu X, Rao P, et al. Psoriasis in the US medicare population: Prevalence, treatment, and factors associated with biologic use. J Invest Dermatol. 2015, http://dx.doi.org/10.1038/jid.2015.296.
10. Springate DA, Parisi R, Kontopantelis E, Reeves D, Griffiths CEM, Ashcroft DM. Incidence, prevalence and mortality of patients with psoriasis: A U.K. population-based cohort study. Br J Dermatol. 2017, http://dx.doi.org/10.1111/bjd.15021.
11. Radtke MA, Schäfer I, Glaeske G, Jacobi A, Augustin M. Prevalence and comorbidities in adults with psoriasis compared to atopic eczema. J Eur Acad Dermatology Venereol. 2017, http://dx.doi.org/10.1111/jdv.13813.
12. Simpson CR, Anderson WJA, Helms PJ, Taylor MW, Watson L, Prescott GJ, et al. Coincidence of immune-mediated diseases driven by TH1 and TH2 subsets suggests a common aetiology. A population-based study using computerized General Practice data. Clin Exp Allergy. 2002, http://dx.doi.org/10.1046/j.0022-0477.2001.01250.x.
13. Danielsen K, Olsen AO, Wilsgaard T, Furberg AS. Is the prevalence of psoriasis increasing? A 30-year follow-up of a population-based cohort. Br J Dermatol. 2013, http://dx.doi.org/10.1111/bjd.12230.
14. Saraceno R, Mannheimer R, Chimenti S. Regional distribution of psoriasis in Italy. J Eur Acad Dermatology Venereol. 2008, http://dx.doi.org/10.1111/j.1468-3083.2007.02423.x.
15. Wolkenstein P, Revuz J, Roujeau JC, Bonnelye G, Grob JJ, Bastuji-Garin S. Psoriasis in France and associated risk factors: Results of a case-control study based on a large community survey. Dermatology. 2009, http://dx.doi.org/10.1159/000182258.
16. Cantarutti A, Donà D, Visentin F, Borgia E, Scamarcia A, Cantarutti L, et al. Epidemiology of frequently occurring skin diseases in Italian children from 2006 to 2012: A retrospective, population-based study. Pediatr Dermatol. 2015, http://dx.doi.org/10.1111/pde.12568.
17. Augustin M, Radtke MA, Glaeske G, Reich K, Christophers E, Schaefer I, et al. Epidemiology and comorbidity in children with psoriasis and atopic eczema. Dermatology. 2015, http://dx.doi.org/10.1159/000381913.
18. Naldi L, Parazzini F, Gallus S, GISED Study Centres. Prevalence of atopic dermatitis in Italian schoolchildren: Factors affecting its variation. Acta Derm Venereol. 2009, http://dx.doi.org/10.2340/00015555-0591.
19. Yang YC, Cheng YW, Lai CS, Chen W. Prevalence of childhood acne, ephelides, warts, atopic dermatitis, psoriasis, alopecia areata and keloid in Kaohsiung County, Taiwan: A community-based clinical survey. J Eur Acad Dermatology Venereol. 2007, http://dx.doi.org/10.1111/j.1468-3083.2006.02036.x.
20. Yamamah GA, Emam HM, Abdelhamid MF, Elsaie ML, Shehata H, Farid T, et al. Epidemiologic study of dermatologic disorders among children in South Sinai, Egypt. Int J Dermatol. 2012, http://dx.doi.org/10.1111/j.1365-4632.2012.05475.x.
21. Stern RS, Nijsten T, Feldman SR, Margolis DJ, Rolstad T. Psoriasis is common, carries a substantial burden even when not extensive, and is associated with widespread treatment dissatisfaction. J Investig Dermatology Symp Proc. 2004, http://dx.doi.org/10.1046/j.1087-0024.2003.09102.x.
22. Seminara NM, Abuabara K, Shin DB, Langan SM, Kimmel SE, Margolis D, et al. Validity of The Health Improvement Network (THIN) for the study of psoriasis. Br J Dermatol. 2011, http://dx.doi.org/10.1111/j.1365-2133.2010.10134.x.
23. Gelfand JM, Weinstein R, Porter SB, Neimann AL, Berlin JA, Margolis DJ. Prevalence and treatment of psoriasis in the United Kingdom: A population-based study. Arch Dermatol. 2005, http://dx.doi.org/10.1001/archderm.141.12.1537.
24. Augustin M, Glaeske G, Radtke MA, Christophers E, Reich K, Schäfer I. Epidemiology and comorbidity of psoriasis in

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children. Br J Dermatol. 2010, http://dx.doi.org/10.1111/j.1365-2133.2009.09593.x.

25. Yeung H, Takeshita J, Mehta NN, Kimmel SE, Ogdie A, Margolis DJ, et al. Psoriasis severity and the prevalence of major medical comorbidity: A population-based study. JAMA Dermatol. 2013, http://dx.doi.org/10.1001/jamadermatol.2013.5015.

26. Karppinen TT, Ylianttila L, Kautiainen H, Reunala T, Snellman E. Empowering heliotherapy improves clinical outcome and quality of life of psoriasis and atopic dermatitis patients. Acta Derm Venereol. 2015, http://dx.doi.org/10.2340/00015555-2028.

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ORIGINAL ARTICLE

Psoriasis, metabolic syndrome and cardiovascular risk factors. A population-based study

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Abstract

Background Psoriasis is a very prevalent systemic chronic inflammatory disease. Major cardiovascular events are the main cause of mortality in these patients which suggests an association between psoriasis and traditional cardiovascular risk factors.

Objective To identify classic cardiovascular risk factors and metabolic syndrome (MS) in patients with psoriasis, their possible association with its severity and compare it with the non-psoriatic population.

Methods This is an observational and cross-sectional population study in Lleida (Spain) from a joint hospital/primary care database.

Results The database comprised 398 701 individuals. There were 6868 cases registered as psoriasis (1.7%), and 499 of them (7.3%) were classified as moderate–severe psoriasis. Patients with psoriasis had a higher prevalence of traditional cardiovascular risk factors than non-psoriatic population: diabetes mellitus 2 (13.9% vs 7.4%, OR 2.01), dyslipidaemia (28.8% vs 17.4%, OR 1.92), arterial hypertension (31.2% vs 19.0%, OR 1.93), obesity (33.7% vs 28.1%, OR 1.30), altered fasting basal glycaemia (21.4% vs 15.1%, OR 1.54), low cholesterol HDL (38.1% vs 32.3%, OR 1.29), hypertriglyceridaemia (45.7% vs 35.2%, OR 1.55) and high waist circumference (75.7% vs 72.3%, OR 1.19). MS was more prevalent in psoriatic patients (28.3% vs 15.1%, OR 2.21), and cardiovascular risk factors were similar between psoriasis severity groups. Psoriatic patients had a higher prevalence of ischaemic heart disease (3.3% vs 1.8%, OR 1.87) and vascular cerebral accidents (1.8% vs 1.2%, OR 1.55). A model for MS showed a significant nonlinear relationship with age and sex and significant differences between patients with and without psoriasis.

Conclusion We found statistically significant differences in relation to the prevalence of cardiovascular risk factors, MS and major cardiovascular events in psoriatic patients. However, differences were not seen between psoriasis severity groups. Our work reinforces the need for a multidisciplinary approach and close monitoring of cardiovascular risk factors in these patients to prevent a cardiovascular event.

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Conflict of interests

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Introduction

Psoriasis is a very prevalent chronic inflammatory disease.[1] In recent years, this disease has been associated with several comorbidities, and nowadays, it is considered a systemic inflammatory disease. Major cardiovascular events are the main cause of mortality in patients with psoriasis,[2] which suggests that there are associations between psoriasis and traditional cardiovascular risk factors. It has been described a link between psoriasis and obesity,[3] dyslipidaemia,[4] diabetes mellitus 2 (DM2)[5] and hypertension.[6] This association is probably due to genetic, environmental and immunological factors, such as Th1 and Th17 pathway activation, proinflammatory cytokines and increased oxidative stress. All these factors induce endothelial dysfunction,[7,8] which promotes leucocyte adhesion and favours a prothrombotic state.[9] Regarding the metabolic syndrome (MS), a systemic inflammatory and prothrombotic disease, a recent meta-analysis confirmed a strong association between this syndrome and psoriasis (OR 2.14; 95% CI 1.84–2.48).[10] All this would lead to a higher cardiovascular disease mortality in psoriasis (OR 1.37: 95% CI 1.17–1.60), myocardial infarction (OR 3.04, 95% CI, 0.65–14.35) and stroke (OR 1.59, 95% CI, 1.34–1.89).[11] This risk seems to be higher in patients with severe psoriasis.[12]

As not all studies confirm a link between psoriasis and cardiovascular risk factors, this topic is still controversial. Furthermore, most studies were conducted in the United States, northern Europe and Asia,[10] regions where culture, diet and other risk factors for metabolic and cardiovascular disease are different from the Mediterranean region. We decided to conduct a population study in Lleida, Catalonia, in the north-east of Spain. Conclusive results of an association between cardiovascular risk factors and psoriasis would reinforce the need for a multidisciplinary assessment of these patients, not only by the dermatologist, as well as a modification of their lifestyle and a strict cardiovascular risk management.

Objectives

(1) To obtain the prevalence of MS and classical risk factors: hyperglycaemia and DM2, hypercholesterolaemia, decreased cholesterol-HDL, hypertriglyceridaemia, increased abdominal perimeter and arterial hypertension in patients with psoriasis (subdivided into severity groups) and control population.
(2) To calculate the percentage of major cardiovascular events (acute myocardial infarction and stroke) in the psoriasis group and compare it to the non-psoriatic group.
(3) To analyse the probability of MS depending on sex, age, psoriasis diagnosis and severity.

Materials and methods

This is an observational and cross-sectional population study on electronic records of residents in the province of Lleida, Catalonia, Spain. Databases from Primary Care and the Dermatology Department of the Hospital Universitario Arnau de Vilanova de Lleida (the only Dermatology Department in the province) were collected in June 2016, provided by the 'Unitat de Recerca de l'Institut Català de Salut' of Lleida (UR-ICS-Lleida). From the resulting database, duplications were eliminated and the records with the diagnosis of cutaneous psoriasis (L40) were selected. The UR-ICS-Lleida built the final database, erasing identifiers. The cases were assigned an internal code the UR-ICS-Lleida knows and that allowed to review or to verify the information of each register if it were necessary. This dissociated database (anonymous for researchers) only contained variables relevant to the study. These variables included sex, age, height, weight (to obtain the body mass index), diagnosis of psoriasis, drugs used for the treatment of psoriasis, cardiovascular risk factors such as DM2 (E11), hypertension (I10), hypercholesterolaemia (E78.0), decreased HDL (E78.6), hypertriglyceridaemia (E78.1), major cardiovascular disease: acute myocardial infarct (I21, I22) and stroke (I63).

Table 1 Diagnostic criteria of some classic cardiovascular risk factors

Diabetes mellitus* **(any of the following)**	• Fasting plasma glucose ≥126 mg/dL • Random plasma glucose ≥200 mg/dL in a patient with classical symptoms of hyperglycaemia (polyuria, polydipsia, polyphagia and weight loss) • 2-h plasma glucose level ≥200 mg/dL during a 75-g oral glucose tolerance test • HbA1c level of 6.5% or higher • Registered diagnosis of diabetes mellitus
Arterial hypertension† **(any of the following)**	• Elevated blood pressure (>140/90 mmHg) on at least 3 separate occasions • Registered diagnosis of hypertension
Dyslipidaemia‡	• Hypercholesterolaemia (total cholesterol ≥250 mg/dL or registered diagnosis of hypercholesterolaemia) ± hypertriglyceridaemia (plasma triglycerides ≥150 mg/dL or registered diagnosis of hypertriglyceridaemia)
Elevated Body Mass Index§	• 25–29.9 kg/m^2: overweight • ≥30/m^2: obesity

Extracted from: *Chamberlain JJ, 2016; †Chobanian AV, 2003; ‡Diaz A, 2014; §National Institutes of Health (NIH), National Heart, Lung, and Blood Institute (NHLBI), 2000.

Table 2 Diagnostic criteria of metabolic syndrome

Metabolic syndrome* (at least 3 criteria†):	• Fasting glucose ≥100 mg/dL (or receiving drug therapy for hyperglycaemia) • Blood pressure ≥130/85 mmHg (or receiving drug therapy for hypertension) • Triglycerides ≥150 mg/dL (or receiving drug therapy for hypertriglyceridaemia) • HDL <40 mg/dL in men or <50 mg/dL in women (or receiving drug therapy for reduced HDL) • Waist circumference ≥102 cm in men or ≥88 cm in women

*National Heart, Lung and Blood Institute (NHLKI) and American Heart Association (AHA), 2005.
†The lack of data in a criterion was considered a non-pathological value.

Diagnostic criteria of classical cardiovascular risk factors and MS are summarized in Tables 1 and 2, and the lack of data in a MS criterion was considered a non-pathological value.

As BSA and PASI are not usually registered in Primary Care, we defined moderate–severe psoriasis according to the treatment prescribed. This method has been used previously by some authors.[13] Each subject was registered as a moderate–severe psoriatic patient when he or she had been treated with narrowband UVB (NB-UVB), psoralen and ultraviolet A (PUVA), traditional systemic drugs (acitretin, methotrexate or cyclosporine) or biological therapy (infliximab, etanercept, adalimumab, ustekinumab, secukinumab or ixekizumab), defining the rest as mild psoriasis. The study was approved by the 'Hospital Arnau de Vilanova de Lleida ethics committee' (CEIC-1655).

The anonymized database was captured and analysed with SPSS v24.0 software (IBM Corporation, Armonk, NY, USA). Comparisons of proportions and ranges of variables between different groups were performed by chi-square, Student's *t*-test or one-way ANOVA as appropriate. The calculated odds ratios compared the occurrence of each cardiovascular risk factor or major cardiovascular event in the presence or absence of psoriasis. The selected *P* value for considering differences as statistically significant in all analyses was $P < 0.05$.

A model to assess the association between metabolic syndrome and having a psoriasis diagnosis once adjusted by the relationship with age and sex was modelled by multivariable logistic regression model. Nonlinear association with age was allowed using natural cubic splines. The existence of first- and second-order interactions was also assessed. Statistical contribution of variables or interaction terms was assessed by likelihood ratio test. Model calibration and discrimination were assessed by Hosmer–Lemeshow test and AUC estimation. A graphic was drawn to facilitate the interpretation of the resulting model (Fig. 1). A second model was fitted with the psoriasis diagnosis graded in three levels: none, mild or moderate/severe (Fig. 2). A significance level of 0.05 and the software R14 were used.[14]

Results

The joint hospital/primary care database collected a total of 398,701 individuals. The mean age was 42.34 years, and the percentage of males was 50.7%. We obtained 6868 patients (1.7% of the population) catalogued as psoriatic (55.3% were males). Male prevalence of psoriasis was 1.9% and in women was 1.6%. There were 499 patients whose psoriasis was classified as moderate–severe (7.27% of patients with psoriasis).

Firstly, prevalence and odds ratio of classical cardiovascular factors were calculated comparing psoriatic and non-psoriatic population (Table 3a). The psoriasis group had a higher prevalence of DM2 (13.9%; OR 2.01, 95% CI: 1.87–2.15, $P < 0.001$); dyslipidaemia (28.8%; OR 1.92, 95% CI: 1.82–2.03, $P < 0.001$); arterial hypertension (31.2%; OR 1.93, 95% CI: 1.83–2.03, $P < 0.001$); and obesity (33.7%; OR 1.30, 95% CI: 1.22–1.39, $P < 0.001$). In this first statistical evaluation, the lack of any pathological data was considered as a non-pathological individual according to each criterion.

The occurrence of major cardiovascular events was studied in patients with psoriasis and non-psoriatic population (Table 3b). The history of ischaemic heart disease was evidenced in 229 patients with psoriasis (3.3%) (OR 1.87, 95% CI: 1.63–2.13, $P < 0.001$). In relation to vascular-cerebral disease, the proportion was higher in patients with psoriasis (1.8%) than in the non-psoriatic population (OR 1.55, 95% CI: 1.29–1.86, $P < 0.001$).

To demonstrate the accuracy of these data, a further analysis focusing on MS was performed. This evaluation only included individuals who had at least one recorded data (whether pathological or not), and not all the individuals from the psoriasis and non-psoriasis groups. MS was more prevalent in the psoriasis group (28.3% vs 15.1%), with an OR of 2.21 (95% CI: 2.10–2.33, $P < 0.001$). All of the MS criteria were analysed individually (Table 3c) and were also more prevalent in the psoriasis group. Focusing on major cardiovascular events in patients with MS, a 7.4% of these patients presented an acute coronary event and 4.3% had suffered a vascular-cerebral disease.

Moreover, the prevalence of MS, other classic cardiovascular risk factors and cardiovascular major events was studied depending on psoriasis severity. In this case, the proportion of these diagnoses was not higher in the moderate–severe psoriasis group, and only a tendency was seen between a more severe disease and prevalence of metabolic syndrome (Table 4).

The model for metabolic syndrome included the variables sex, age and psoriasis diagnosis. The resulting model showed a significant nonlinear relationship with age and only one significant interaction, the one between sex and the nonlinear effect of age, modelled by natural cubic splines of 3 degrees of freedom. No

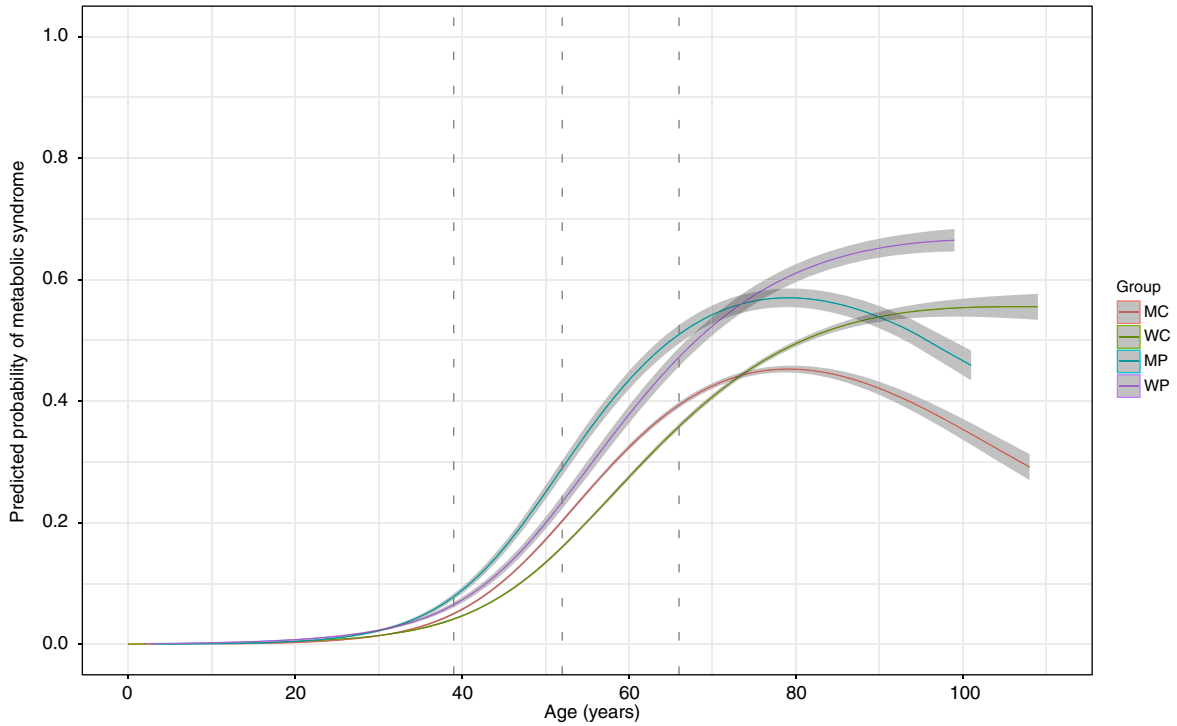

Figure 1 Predicted probability of metabolic syndrome depending on age, sex and psoriasis. M and W stand for men and women, while P and C stand for patients with and without a diagnosis of psoriasis, respectively. Dotted vertical grey lines show the three quartiles of age for the psoriasis group.

significant interaction was obtained with psoriasis diagnosis. Thus, the nonlinear association between age and the metabolic syndrome was significantly different for men and women, as shown in Fig. 1. This figure shows the estimated probability of metabolic syndrome in association with age for the groups defined by the combinations of sex and psoriasis diagnosis. Both models, the one for psoriasis diagnosis and the other one for psoriasis grade, showed good calibration (predicted and observed probabilities were very close to each other) and good discrimination, both with a 0.855 area under the curve.

Figure 1 shows the predicted probability of metabolic syndrome depending on age, sex and psoriasis diagnosis. A nonlinear association with age that is dependent on sex was identified. Significant differences in the estimated probability of metabolic syndrome between patients with and without psoriasis already appear around the age of 30 years, showing higher probabilities in patients with psoriasis, men or women. Besides, men with psoriasis diagnosis showed a significantly higher probability of metabolic syndrome than women with psoriasis till the age of almost 70 years, where estimated probabilities became very similar. Women older than around 75 years old showed increasing estimated probabilities of metabolic syndrome, in contrast with men, who showed an inflexion point around that age and a decreasing estimated trend from that age. This inflexion point is common to non-psoriasis patients. The OR of metabolic syndrome for psoriasis vs. non-psoriasis patients (the only variable in the model showing an additive effect) was 1.60, with 95% CI = [1.51, 1.70]. Thus, for example, if we try to estimate the probability of metabolic syndrome for a 52-year-old patient (the median age of patients with psoriasis), the expected probability of metabolic syndrome is 0.16 if a woman without psoriasis, 0.20 if it a man without psoriasis, 0.23 if a women with psoriasis and 0.29 if a man with psoriasis. These differences are increased for older ages, and for a 66-year-old patient, these estimates are 0.36, 0.39, 0.47 and 0.51, respectively.

Figure 2 shows the predicted probability of metabolic syndrome depending on age, sex and psoriasis grade of severity. The psoriasis group was divided into mild or moderate/severe disease. Although estimated probabilities are higher for the moderate/severe psoriasis group in both, men and women, their confidence intervals are overlapped. This overlap is consequence of the wide confidence interval obtained from the small number of patients with moderate–severe psoriasis. The OR of metabolic syndrome of mild psoriasis vs. non-psoriasis patients and for moderate/severe psoriasis vs. non-psoriasis (the only variable in the model showing an additive effect)

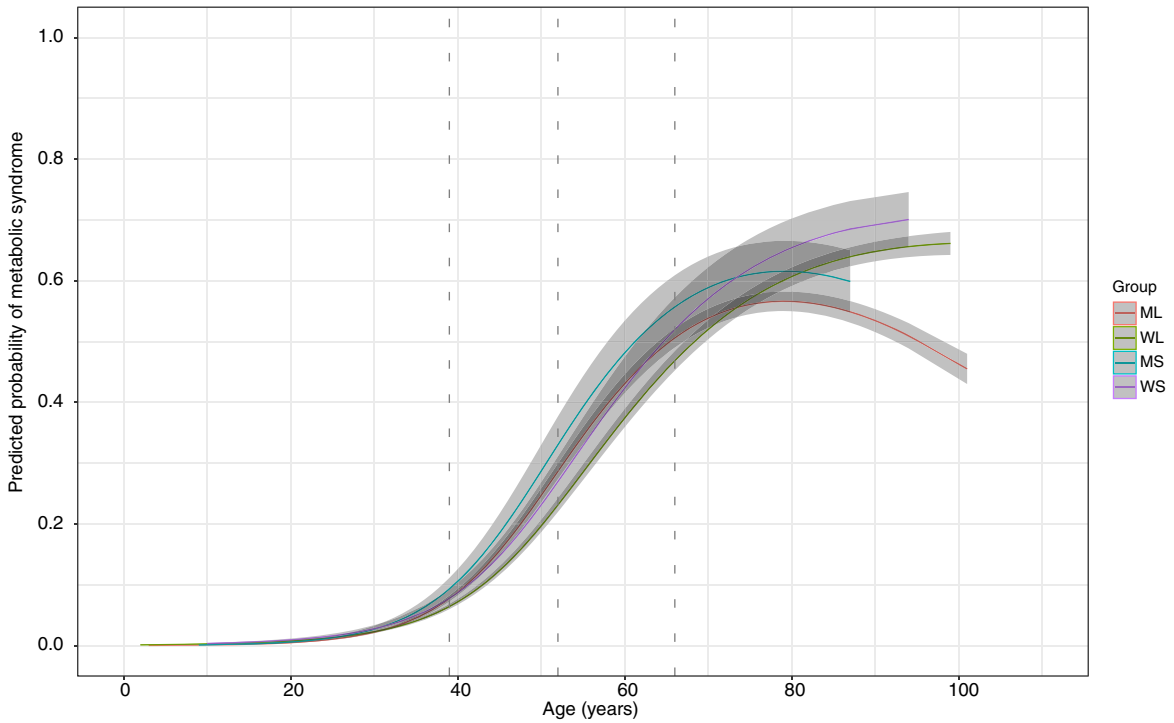

Figure 2 Predicted probability of metabolic syndrome depending on age, sex and psoriasis grade. M and W stand for men and women, while S and L stand for patients with moderate/severe or mild grade of psoriasis, respectively. The estimated probabilities for the control group C are not shown as they are the same already in Figure 1. Dotted vertical grey lines show the three quartiles of age for the psoriasis group.

was 1.58, with 95% CI = [1.48, 1.68] and 1.94 with 95% CI = [1.56, 2.39], respectively. No significant differences were observed, independently of patient age, between the probabilities of metabolic syndrome for mild versus moderate/severe psoriasis patients.

Discussion

In our study, statistically significant differences were found in relation to the prevalence of cardiovascular risk factors in patients with psoriasis, presenting a higher frequency of DM2, dyslipidaemia, hypertension and obesity. In this first statistical evaluation, the lack of any pathological data was considered as a non-pathological individual according to each criterion. We know individuals with these factors have a higher rate of cardiovascular events such as a heart attack or stroke, which are the main cause of death in patients with psoriasis, and this association has already been objectified in multiple studies (Table 5). As it seems to be an association between DM2, dyslipidaemia, hypertension, obesity and psoriasis, some authors suggest that there is an early common pathogenesis (involving several adipokines and inflammatory cytokines) both in the cutaneous disease and in the other risk factors.[15]

In addition, the proportion of MS in the population with psoriasis was also higher than in the general population and we designed a model which predicted the probability of MS that showed a significant nonlinear relationship with age, sex and psoriasis.

Our results were slightly smaller than other similar published studies (Table 6), although some other authors did not find this association (25.81% vs 21.02%, $P > 0.05$).[16] Our data were obtained from a joint database between hospital and primary care and include one of the largest series ever published related to psoriasis and cardiovascular risk factors in Mediterranean regions, a factor that is increasingly involved in cardiovascular morbidity and mortality. We believe this makes the sample of individuals more representative of the population, and the fact that this evaluation only included individuals who had at least one recorded data, whether pathological or not, may be more reliable. It should be considered that carrying out prevalence studies in different populations with a similar methodology would help us to assess which factors influence in the variability of the results obtained.

Analogously, we obtained a higher prevalence of each MS diagnostic criteria (altered fasting glycaemia, altered blood

Table 3 (a) Prevalence of cardiovascular risk factors, metabolic syndrome and its criteria in psoriasis and general population. (b) Prevalence of major cardiovascular events in psoriasis and general population. (c) Prevalence of metabolic syndrome and its criteria in psoriasis and general population

(a)	Psoriasis	Non-psoriasis	OR (CI 95%)
Diabetes mellitus 2	952 (13.9%)	29 171 (7.4%)	2.01 (1.87–2.15, $P < 0.001$)
Dyslipidaemia	1979 (28.8%)	68 201 (17.4%)	1.92 (1.82–2.03, $P < 0.001$)
Arterial hypertension	2140 (31.2%)	74 489 (19.0%)	1.93 (1.83–2.03, $P < 0.001$)
Obesity	1497 (33.7%)	47 184 (28.1%)	1.30 (1.22–1.39, $P < 0.001$)
(b)	**Psoriasis**	**Non-psoriasis**	**OR (CI 95%)**
Ischaemic cardiomyopathy	229 (3.3%)	7116 (1.8%)	1.87 (1.63–2.13, $P < 0.001$)
Cerebrovascular disease	122 (1.8%)	4520 (1.2%)	1.55 (1.29–1.86, $P < 0.001$)
Total	6868	391 833	
(c)	**Psoriasis**	**Non-psoriasis**	**OR (CI 95%)**
Fasting glucose ≥100 mg/dL	1333/6222 (21.4%)	42 417/281 436 (15.1%)	1.54 (1.45–1.63, $P < 0.001$)
HDL <40 mg/dL in men or <50 mg/dL in women	2067/5429 (38.1%)	71 574/221 678 (32.3%)	1.29 (1.22–1.36, $P < 0.001$)
Triglycerides ≥150 mg/dL	2754/6021 (45.7%)	92 140/261 647 (35.2%)	1.55 (1.47–1.63, $P < 0.001$)
Blood pressure ≥130/85 mmHg	3174/6356 (49.9%)	111 860/315 177 (35.5%)	1.81 (1.73–1.91, $P < 0.001$)
Waist circumference ≥102 cm in men or ≥88 cm in women	1787/2362 (75.7%)	58 311/80 613 (72.3%)	1.19 (1.08–1.31, $P < 0.001$)
Metabolic syndrome	1941/6868 (28.3%)	59 280/391 833 (15.1%)	2.21 (2.10–2.33, $P < 0.001$)

The calculated odds ratios compare the occurrence of each cardiovascular risk factor in the presence or absence of psoriasis.
*Based on National Heart, Lung and Blood Institute (NHLKI) and American Heart Association (AHA), 2005.

Table 4 Prevalence of cardiovascular risk factors, metabolic syndrome and major cardiovascular events according to severity of psoriasis

	Mild psoriasis	Moderate–severe psoriasis	OR (CI 95%)
Diabetes mellitus	885 (13.9%)	67 (13.4%)	0.96 (0.74–1.26, $P = 0.771$)
Dyslipidaemia	1845 (29%)	134 (26.9%)	0.90 (0.73–1.11, $P = 0.315$)
Arterial hypertension	2008 (31.5%)	132 (26.5%)	0.78 (0.64–0.96, $P = 0.018$)
Metabolic syndrome	1784 (28%)	157 (31.5%)	1.18 (0.97–1.44, $P = 0.099$)
Ischaemic cardiomyopathy	207 (3.3%)	22 (4.4%)	1.37 (0.88–2.15, $P = 0.165$)
Cerebrovascular accident	116 (1.8%)	6 (1.2%)	0.66 (0.29–1.50, $P = 0.314$)
Total	6369	499	

pressure, low HDL, hypertriglyceridaemia and altered waist circumference) in patients with psoriasis, which reinforces the close association and burden of cardiovascular morbidity in this cutaneous disease.

It would be interesting to investigate in future studies whether there is also a correlation between these parameters and other comorbidities associated with psoriasis such as non-alcoholic fatty liver disease (NAFLD). This entity, which according to some authors is closely linked to obesity and metabolic syndrome, is the most prevalent liver disease,[17] and its incidence is increased in patients with psoriasis.[18] Due to the risk of hepatocarcinoma from NAFLD, it would be appropriate to assess whether there is a carcinogenic risk from psoriasis itself or a negative influence of skin lesions on lifestyle.

Moreover and surprisingly, no statistically significant differences were found between a higher severity of psoriasis and a greater association with cardiovascular risk factors, and there was only a tendency between psoriasis severity and MS prevalence (1.18, 95% CI: 0.97–1.44, $P = 0.099$). Some authors obtained a greater risk of MS in patients with psoriasis than general population (OR 1.91; 95% CI 1.47–2.49).[19] These authors also classified psoriasis severity depending on their treatment and moderate–severe psoriasis prevalence calculated is similar, so we think that geographical or cultural factors could explain these differences. Curcó *et al.*[20] could neither find an association, even though a link between psoriasis severity and diabetes mellitus was described.

Focusing on the risk of major cardiovascular risk events in psoriasis, Parisi *et al.*[21] did not find this link in a Manchester cohort study (2.59% vs 2.30%), as well as in a recent meta-analysis which neither found an association with cerebrovascular disease (OR 1.1; CI 0.9–1.3). On the contrary, an increased risk of ischaemic heart disease in patients with psoriasis (OR 1.5; 95% CI 1.2–1.9) was obtained.[22] Our data corroborate the increased risk of

Table 5 Prevalence of cardiovascular risk factors and major cardiovascular events in psoriasis and general population

Risk factor/cardiovascular event	Prevalence in psoriasis	Prevalence in non-psoriasis group	OR (IC 95%)	Author
Diabetes mellitus	952 (13.9%)	29 171 (7.4%)	2.01 (1.87–2.15, $P < 0.001$)	Our results (2018)
	15 (11.3%)			Jacobi *et al.* (2013)[26]
			1.59 (1.38–1.83)	Armstrong et. al. (2013)[5]
			1.9 (1.5–2.5)	Miller *et al.* (2013)[22]
			1.76 (1.59–1.96)	Coto-Segura *et al.* (2013)[27]
Dyslipidaemia	1979 (28.8%)	68 201 (17.4%)	1.92 (1.82–2.03, $P < 0.001$)	Our results (2018)
			1.04–5.55	Ma *et al.* (2013)[4]
			1.5 (1.4–1.7)	Miller et. al. (2013)[22]
Decreased HDL	2067 (38.1%)	71 574 (32.3%)	1.29 (1.22–1.36, $P < 0.001$)	Our results (2018)
	29.8%			Belinchón *et al.* (2015)[25]
	26 (27.37%)	4 (4.21%)	8.57 ($P < 0.001$)	Salunke *et al.* (2017)[28]
Hypertriglyceridaemia	2754 (45.7%)	92 140 (35.2%)	1.55 (1.47–1.63, $P < 0.001$)	Our results (2018)
	34.7%			Belinchón *et al.* (2015)[25]
	43 (45.26%)	11 (11.58%)	6.31 (<0.001)	Salunke *et al.* (2017)[28]
Arterial hypertension	2140 (31.2%)	74 489 (19.0%)	1.93 (1.83–2.03, $P < 0.001$)	Our results (2018)
	52 (39.1%)			Jacobi *et al.* (2013)[26]
			1.8 (1.6–2.0)	Miller *et al.* (2013)[22]
			1.58 (1.42–1.76)	Armstrong *et al.* (2013)[6]
Obesity	1497 (33.7%)	47 184 (28.1%)	1.30 (1.22–1.39, $P < 0.001$)	Our results (2018)
			1.8 (1.4–2.2)	Miller *et al.* (2013)[22]
High waist circumference	1787 (75.7%)	58 311 (72.3%)	1.19 (1.08–1.31, $P < 0.001$)	Our results (2018)
	58.8%			Belinchón et. al. (2015)[25]
	31 (32.63%)	15 (15.79%)	2.58 ($P = 0.007$)	Salunke *et al.* (2017)[28]
			1.6 (1.2–2.3)	Miller *et al.* (2013)[22]
Ischaemic cardiomyopathy	229 (3.3%)	7116 (1.8%)	1.87 (1.63–2.13, $P < 0.001$)	Our results (2018)
			1.5 (1.2–1.9)	Miller *et al.* (2013)[22]
Cerebrovascular accident	122 (1.8%)	4520 (1.2%)	1.55 (1.29–1.86, $P < 0.001$)	Our results (2018)
			1.1 (0.9–1.3)	Miller *et al.* (2013)[22]

Table 6 Prevalence and association between psoriasis and metabolic syndrome according to some recent studies

Author	Country	Patients with psoriasis	Patients with metabolic syndrome in psoriasis group	Patients with metabolic syndrome in control group	Association between metabolic syndrome in patients with psoriasis
Langan *et al.* (2012)[29]	United Kingdom	4065	1389 (34.2%)	10 515 (25.9%)	OR = 1.50 (1.40–1.61)
Owczarczyk-Saczonek (2015)[16]	Poland	62	16 (25.8%)	181 (21.02%)	$P > 0.05$
Albareda *et al.* (2014)[24]	Spain	102	53 (52.9%)	35 (34.31%)	$P < 0.016$
Parodi *et al.* (2014)[30]	Italy	380	102 (26.84%)	52 (15.16%)	OR = 1.96 ($P < 0.0001$)
Belinchón *et al.* (2015)[25]	Spain	352	132 (37.5%)	No control group	No control group
Danielsen *et al.* (2015)[31]	Norway	1137	33%	25%	OR = 1.43
Curcó *et al.* (2017)[20]	Spain	178	30%	No control group	No control group
Milčić *et al.* (2017)[32]	Serbia	244	110 (45.1%)	32 (19.6)	OR = 2.66 ($P < 0.001$)
Our results (2018)	Spain	6868	1941 (28.3%)	59 280 (15.1%)	OR = 2.21 (2.10–2.33, $P < 0.001$)

suffering a major cardiovascular event in patients with psoriasis, both ischaemic heart disease (OR 1.87, 95% CI: 1.63–2.13, $P < 0.001$) and cerebrovascular disease (OR 1.55, 95% CI: 1.29–1.86, $P < 0.001$). The hypothesis that a chronic inflammatory disease such as psoriasis may have an independent role in the pathogenesis of a cardiovascular event is not unreasonable, and many authors have linked systemic inflammatory diseases such as rheumatoid arthritis, systemic lupus erythematosus or

inflammatory bowel disease with an increased cardiovascular risk.[20,23–25] More publications should be performed to elucidate this topic.

Limitations

The main limitations of this study are those inherent in a cross-sectional population study, such as the lack of data from some patients. In addition, as it is a study focused on the MS, smoking was not included. Similarly, medications for cardiovascular risk factors such as antidiabetic or lipid-lowering drugs were not considered, so there could be patients without a coded diagnosis which would be excluded.

Conclusion

Taking into account the data presented above and the review of previous publications regarding the relation between psoriasis, MS and cardiovascular risk factors, we suggest that our work reinforces the need for close monitoring of cardiovascular risk factors in patients with psoriasis which are often only visited by the dermatologist[2] to prevent a major cardiovascular event. Further studies would help us to discern whether psoriasis really acts as an independent factor, and it would also be interesting to assess whether an adequate management of the cutaneous disease would help to control other risk factors or reduce its cardiovascular risk in the long term.

References

1 Michalek IM, Loring B, John SM. A systematic review of worldwide epidemiology of psoriasis. *J Eur Acad Dermatol Venereol* 2017; **31**: 205–212.
2 Takeshita J, Grewal S, Langan SM *et al.* Psoriasis and comorbid diseases: Epidemiology. *J Am Acad Dermatol* 2017; **76**: 377–390.
3 Kumar S, Han J, Li T *et al.* Obesity, waist circumference, weight change and the risk of psoriasis in US women. *J Eur Acad Dermatol Venereol* 2013; **27**: 1293–1298.
4 Ma C, Harskamp CT, Armstrong EJ *et al.* The association between psoriasis and dyslipidaemia: a systematic review. *Br J Dermatol* 2013; **168**: 486–495.
5 Armstrong AW, Harskamp CT, Armstrong EJ. Psoriasis and the risk of diabetes mellitus: a systematic review and meta-analysis. *JAMA Dermatol* 2013; **149**: 84–91.
6 Armstrong AW, Harskamp CT, Armstrong EJ. The association between psoriasis and hypertension: a systematic review and meta-analysis of observational studies. *J Hypertens* 2013; **31**: 433–442.
7 Correia B, Torres T. Obesity: a key component of psoriasis. *Acta Biomed* 2015; **86**: 121–129.
8 Gelfand JM, Neimann AL, Shin DB *et al.* Risk of myocardial infarction in patients with psoriasis. *JAMA* 2006; **296**: 1735–1741.
9 Steyers CM 3rd, Miller FJ Jr. Endothelial dysfunction in chronic inflammatory diseases. *Int J Mol Sci* 2014; **15**: 11324–11349.
10 Singh S, Young P, Armstrong AW. An update on psoriasis and metabolic syndrome: A meta-analysis of observational studies. *PLoS ONE* 2017; **12**: e0181039.
11 Samarasekera EJ, Neilson JM, Warren RB, Parnham J, Smith CH. Incidence of cardiovascular disease in individuals with psoriasis: a systematic review and meta-analysis. *J Invest Dermatol* 2013; **133**: 2340–2346.
12 Ogdie A, Troxel AB, Mehta NN, Gelfand JM. Psoriasis and cardiovascular risk: strength in numbers part 3. *J Invest Dermatol* 2015; **135**: 2148–2150.
13 Takeshita J, Gelfand JM, Li P *et al.* Psoriasis in the US Medicare population: prevalence, treatment, and factors associated with biologic use. *J Invest Dermatol* 2015; **135**: 2955–2963.
14 R Core Team (2018). R: A Language and Environment for Statistical Computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/.
15 Katsiki N, Anagnostis P, Athyros VG, Karagiannis A, Mikhailidis DP. Psoriasis and vascular risk: an update. *Curr Pharm Des* 2014; **20**: 6114–6125.
16 Owczarczyk-Saczonek AB, Nowicki RJ. Prevalence of cardiovascular disease risk factors, and metabolic syndrome and its components in patients with psoriasis aged 30 to 49 years. *Postepy Dermatol Alergol* 2015; **32**: 290–295.
17 Scalera A, Tarantino G. Could metabolic syndrome lead to hepatocarcinoma via non-alcoholic fatty liver disease? *World J Gastroenterol* 2014; **20**: 9217–9228.
18 Pietrzak D, Pietrzak A, Krasowska D *et al.* Digestive system in psoriasis: an update. *Arch Dermatol Res* 2017; **309**: 679–693.
19 Snekvik I, Nilsen TIL, Romundstad PR, Saunes M. Psoriasis and cardiovascular disease risk factors. The HUNT Study, Norway. *J Eur Acad Dermatol Venereol* 2018; **32**: 776–782.
20 Curcó N, Barriendos N, Barahona MJ *et al.* Factors influencing cardiometabolic risk profile in patients with psoriasis. *Australas J Dermatol* 2018; **59**: e93–e98.
21 Parisi R, Rutter MK, Lunt M *et al.* Psoriasis and the risk of major cardiovascular events: cohort study using the clinical practice research datalink. *J Invest Dermatol* 2015; **135**: 2189–2197.
22 Miller IM, Ellervik C, Yazdanyar S, Jemec GB. Meta-analysis of psoriasis, cardiovascular disease, and associated risk factors. *J Am Acad Dermatol* 2013; **69**: 1014–1024.
23 Sherer Y, Shoenfeld Y. Mechanisms of disease: atherosclerosis in autoimmune diseases. *Nat Clin Pract Rheumatol* 2006; **2**: 99–106.
24 Albareda M, Ravella A, Castelló M, Saborit S, Peramiquel L, Vila L. Metabolic syndrome and its components in patients with psoriasis. *Springerplus* 2014; **3**: 612.
25 Belinchón I, Vanaclocha F, De la cueva-dobao P *et al.* Metabolic syndrome in Spanish patients with psoriasis needing systemic therapy: Prevalence and association with cardiovascular disease in PSO-RISK, a cross-sectional study. *J Dermatolog Treat* 2015; **26**: 318–325.
26 Jacobi A, Kupke C, Behzad M, Hertl M. Comorbidities, metabolic risk profile and health-related quality of life in German patients with plaque-type psoriasis: a cross-sectional prospective study. *Int J Dermatol* 2013; **52**: 1081–1087.
27 Coto-segura P, Eiris-salvado N, González-lara L *et al.* Psoriasis, psoriatic arthritis and type 2 diabetes mellitus: a systematic review and meta-analysis. *Br J Dermatol* 2013; **169**: 783–793.
28 Salunke AS, Nagargoje MV, Belgaumkar VA, Tolat SN, Chavan RB. Association of metabolic syndrome in chronic plaque psoriasis patients and their correlation with disease severity, duration and age: a case control study from Western Maharashtra. *J Clin Diagn Res* 2017; **11**: WC06–WC10.
29 Langan SM, Seminara NM, Shin DB *et al.* Prevalence of metabolic syndrome in patients with psoriasis: a population-based study in the United Kingdom. *J Invest Dermatol* 2012; **132**: 556–562.
30 Parodi A, Aste N, Calvieri C *et al.* Metabolic syndrome prevalence in psoriasis: a cross-sectional study in the Italian population. *Am J Clin Dermatol* 2014; **15**: 371–377.
31 Danielsen K, Wilsgaard T, Olsen AO *et al.* Elevated odds of metabolic syndrome in psoriasis: a population-based study of age and sex differences. *Br J Dermatol* 2015; **172**: 419–427.
32 Milčić D, Janković S, Vesić S *et al.* Prevalence of metabolic syndrome in patients with psoriasis: a hospital-based cross-sectional study. *An Bras Dermatol* 2017; **92**: 46–51.

TITLE PAGE

Title of the paper: SCORE underestimates cardiovascular risk in patients with psoriasis

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Key words
Psoriasis, cardiovascular risk factors, atheromatosis, plaque, atheroma.

Highlights

1. Psoriasis is associated with classical cardiovascular risk factors.
2. Carotid and femoral atheromatosis is more prevalent in patients with psoriasis than in general population, especially in severe forms.
3. SCORE and REGICOR underestimate cardiovascular risk in patients with psoriasis.
4. Arterial ultrasonography in psoriatic patients improves cardiovascular risk classification.

Abstract

Introduction: Psoriasis is a multisystem immunoinflammatory disease which is usually associated with classic cardiovascular risk factors. Recent studies identify an increased carotid and femoral intima-media thickness in psoriatic patients. The aim of this study is to analyze the prevalence of cardiovascular risk factors and subclinical atheromatosis (carotid or/and femoral plaques) in patients with psoriasis, compare them to a control group without this dermatological disease and correlate them to predictive cardiovascular risk tests. **Methods:** Data from 50 patients with psoriasis and 50 controls were obtained (age, sex, classic cardiovascular risk factors, analytical parameters and psoriasis severity). Carotid and femoral plaques were diagnosed by ultrasonography. Predictive tests of cardiovascular risk (SCORE and REGICOR) were performed in all individuals. **Results:** In the psoriasis group there was a greater proportion of smoking habit (70% vs 46%, p=0.015), pathological waist circumference (61.22% vs 34%, p=0.008), low cholesterol HDL (42% vs 14%, p=0.002), metabolic syndrome (32% vs 8%, p=0.003) and hypertriglyceridemia (28% vs 8%, p=0.009). The prevalence of moderate-severe psoriasis in our population was 36%. This group had a higher prevalence of metabolic syndrome (50.0% vs 21.9%, p=0.041) and arterial hypertension (33.3% vs 6.3%, p=0.012), as well as higher glycated hemoglobin (HbA1c) (5.62% vs 5.19%, p <0.001) and body mass index (BMI) (30.69 vs 27.11, p = 0.044) compared to mild psoriasis group. Subclinical atheromatosis tends to be more prevalent in the psoriatic group (46% vs 36%, p = 0.309). Carotid plaques were more prevalent in moderate-severe psoriasis group than in the control group (44.4% vs 18% (p=0.026, OR=3.65, CI 1.12-11.76). In the psoriasis group, 35.0% of the low risk individuals by SCORE and 40.9% by REGICOR had at least one atheromatous plaque. **Conclusions:** Prevalence of subclinical atheromatosis in patients with psoriasis is very high. Since

REGICOR and SCORE underestimate the actual cardiovascular risk, routine ultrasound examination can improve cardiovascular risk classification.

Introduction

Psoriasis is an multisystem immunoinflammatory disease that is characterized by erythematous-desquamative plaques on the skin. It has an approximate prevalence of 1 to 3%[1] and in Spain it is between 1.4 and 2.7% according to different series[2-4]. Although both the innate and adaptive immune systems play a relevant role in its pathogenesis, the predominant cells involved are T lymphocytes (mainly Th1 and Th17) and cytokines derived from them, such as tumor necrosis factor α (TNF α) and interleukins (IL-17 and IL-23)[5]. The main and best known comorbidity is joint disease in 15-30% of cases[6]. The usual association between psoriasis, classic cardiovascular (CV) risk factors and the increase in CV morbidity and mortality has raised the interest of dermatologists and scientific community[7].

The classic CV risk factors are: gender, age, diabetes, obesity, hypercholesterolemia, hypertriglyceridemia, arterial hypertension and smoking[8]. The conjunction of hyperglycemia, central obesity, hypertension and dyslipidemia has been called metabolic syndrome (MS). This entity has a prominent role as a promoter of cardiovascular events[5,9] and it has been associated with psoriasis[4,10]. Major cardiovascular events are the leading cause of mortality in patients with psoriasis and are more frequent in psoriatic patients than in general population (hazard ratio 1.21, 95% CI 1.13-1.3)[11,12]. In addition, patients with greater severity of their skin disease have a higher associated mortality.

The pathophysiological mechanism by which these pathologies predispose to the formation of atheromatous plaques is not well known, although there are arguments to

think that in the initial phase of atheromatosis, inflammatory processes have a relevant role[14] at the expense of Th1, Th17 lymphocytes, monocytes and macrophages[10]. Recent studies identify a significant increase in the mean carotid and femoral intima-media thickness in patients with psoriasis, and some of them conclude that psoriasis acts as an independent risk factor for subclinical atherosclerosis[15-17]. In addition, those patients with a greater severity of the skin disease would produce an increased risk of atherosclerosis[18].

We currently know that atheromatosis precedes major cardiovascular events such as stroke and myocardial infarction and that the presence of atheromatous plaques at the carotid level has a good correlation with coronary arterial disease[19]. Arterial ultrasound imaging is tolerable, easy, repeatable and inexpensive, and some recent data suggest that a good management of psoriasis would favor an improvement in the control of classic cardiovascular risk factors as well as carotid[20] and coronary[21] subclinical atherosclerosis.

In Spain, SCORE and REGICOR scales are used to assess the individual cardiovascular risk. These tables include the CV risk sex, age, smoking, diabetes mellitus, hypercholesterolemia and blood pressure. Since there is a possible association between psoriasis and an increased cardiovascular risk, patients with this dermatosis could have an underestimated cardiovascular risk according to the risk scales that are normally used.

Objectives

Due to the before mentioned association between psoriasis and cardiovascular disease and the possible underestimation of cardiovascular risk in patients with psoriasis, we aimed:

1. Analyze the prevalence of classical CV risk factors (glycemia, cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides, hypertension, obesity, smoking, abdominal perimeter and MS) in a group of patients with psoriasis and compare them with a control group without psoriasis.

2. Study the prevalence of subclinical atheromatosis (carotid and femoral atheroma plaques) in these two groups.

3. Assess the burden of atheromatous disease according to predictive cardiovascular risk tests (SCORE and REGICORE).

Materials and methods

We included 50 consecutive patients with psoriasis from the general and moderate-severe psoriasis outpatient department of dermatology of the Hospital Universitario Arnau de Vilanova, Lleida (Spain) and 50 patients without psoriasis who came for any other dermatologic pathology (control group). These two groups were age and sex-matched.

The inclusion criteria in the psoriasis group were: over 18 years of age, having been diagnosed with plaque psoriasis (other forms of psoriasis were excluded) and not having received systemic or biological therapy for psoriasis in the last 4 weeks (3 months in the case of ustekinumab); no history of coronary disease, heart failure class III or IV, severe heart rhythm disorders, respiratory failure, pregnancy or lactation, renal failure or diabetes mellitus. We applied the same criteria for the control group.

Anamnesis, anthropometric measures and a fasting blood analysis were performed in all individuals. Anamnesis data contained: sex, age, diagnosis of diabetes mellitus, hypercholesterolemia, hypertriglyceridemia, hypertension, MS and smoking habit, as well as treatment for hypertension, dyslipidemia and diabetes mellitus. Current and

former smokers were grouped together. Relevant data from physical examination included systolic blood pressure (SBP), diastolic blood pressure (DBP), body mass index (BMI) and abdominal perimeter. Blood test parameters studied were glycemia, HbA1c, total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides, apolipoprotein A1 and B, erythrocyte sedimentation rate (ESR) and high sensitivity-CRP (hs-CRP). Diagnostic criteria for cardiovascular risk factors and metabolic syndrome are summarized in Supplementary table 1.

Severity of psoriasis:

PASI (Psoriasis Area and Severity) was used as a measure of severity. This scale evaluates the area, erythema, scaliness and thickness of the plaques. According to PASI, a score greater than 10 was considered a moderate-severe disease.

Vascular ultrasonography:

Vascular ultrasonography was performed following a method which was already described by Betriu et. al.[22] B-mode ultrasound of the carotid and femoral arteries was performed using the Vivid BT09 apparatus (GE Healthcare, Waukesha, WI) equipped with a 6- to 13-MHz broadband linear array probe. An atheromatous plaque presence analysis was performed in 10 territories (internal, bulb, and common carotids and both common and superficial femoral arteries) by a single reader in blinded fashion using semiautomatic software (EchoPAC Dimension; GE Healthcare). To assess intraobserver reliability, a sample of 20 individuals was measured three to five times on different days. A κ-coefficient of one was obtained for plaque assessment, indicating excellent intraobserver reliability. The reader was unaware of patients' clinical histories.

Carotid intima-media thickness (cIMT) was only measured in common carotid regions without plaque and calculated as the average between left and right sides. The presence of atheromatous plaques was defined as a cIMT>1.5 mm protruding into the lumen according to the American Society of Echocardiography Consensus Statement[23] and the Mannheim cIMT Consensus[24].

Cardiovascular risk scores

SCORE and REGICOR were performed in all individuals. In the Spanish population, high CV risk has been defined by a SCORE ≥5% or REGICOR ≥10 %[25]. Prevalence of carotid and femoral plaques was studied in each cardiovascular risk group.

The study was approved by the "Hospital Universitari Arnau de Vilanova de Lleida ethics committee" (CEIC-1655).

Statistical analysis

Data was analyzed with SPSS v24.0 software (IBM Corporation, Armonk, NY, USA). Data was summarized using standard descriptive statistics. Comparisons of proportions and ranges of variables between different groups were performed by Chi-square, Fisher's exact test, Student's t-test, or One-Way ANOVA as appropriate. Odds Ratios were calculated to evaluate the association of cardiovascular risk factors with the presence of psoriasis. The selected p value for considering differences as statistically significant in all analyses was $p < 0.05$.

Results

The mean age in the group with psoriasis was 47.10 years (SD 11.46) and 50% of these patients were men. In the control group, the mean age was 48.40 years (SD 11.58) and 52.0% were men. Using the PASI scale, 36% of this cohort was classified as moderate-severe psoriasis.

Classic CV risk factors in both groups are described in Table 1 and Supplementary table 2. It should be noted that in the psoriasis group there was a greater proportion of smokers (70 vs 46%, p=0.015), individuals with altered waist circumference (61.22% vs 34%, p=0.008), low levels of HDL-Cholesterol (42% vs 14%, p=0.002), diagnosis of MS (32% vs 8%, p=0.003) and hypertriglyceridemia (28% vs 8%, p=0.009). Furthermore, we found in the psoriasis group increased levels of hs-CRP levels (4.828mg/dL vs 1.779mg/dL, p=0.013).

The group of moderate-severe psoriasis had a higher frequency of MS (50.0% vs 21.9%, p=0.041) and arterial hypertension (33.3% vs 6.3%, p=0.012) compared to the mild severity group, as well as an increase in the average HbA1c levels (5.62% vs 5.19%, p<0.001) and BMI (30.69 vs 27.11, p=0.044) (Supplementary tables 3 and 4).

Regarding the carotid and femoral ultrasound study, we analyzed the presence of atheroma plaques in relation to age and sex. Prevalence of atheromatosis in individuals of both groups (psoriasis and controls) was 19.6% in individuals under 50 years of age and 68.2% in those over 50 years (p<0.001). Atheromatosis in men of both groups was 51.0% and in women 30.6% (p=0.029).

From the psoriasis group, 23 patients (46%) presented carotid or femoral plaques vs 18 individuals (36.0%) in the control group (p = 0.309). Based on psoriasis severity, atheroma plaques were identified by simple ultrasound in 12 patients with mild psoriasis (37.5%), and this figure increased in moderate-severe psoriasis to 11 patients (61.1%), without reaching to statistical significance (p = 0.108). When subdivided by

affected territories, the presence of carotid atheroma plaques was 44.4% in severe psoriasis and 18.0% in controls (p = 0.026, OR = 3.65, CI 1.12-11.76). At the femoral level, atheromatosis was 44.4% in severe psoriasis compared to 28.0% in the control population (p = 0.201, OR = 2.06). Carotid and femoral ultrasound study in the psoriasis and control groups depending on psoriasis severity is represented in figure 1. Differences in atheromatosis prevalence according to psoriasis severity in men and women are represented in figure 2.

SCORE and REGICOR results in both groups are summarized in table 2. In the psoriasis group, 40 (80.0%) presented a low risk SCORE, and 14 patients of this group (35.0%) had at least one atheromatous plaque in some territory. In relation to the REGICOR scale, 44 (88%) were classified as low risk individuals and 18 patients of this group (40.9%) had atheromatous plaques in some location. There were no statistical differences between controls and psoriatic patients according to SCORE results (p = 0.837) or REGICOR (p = 0.256).

Discussion

A higher proportion of smokers and former smokers, altered waist circumference, alteration of HDL in blood, MS and hypertriglyceridemia were found in the group with psoriasis despite the small sample size. When we compared our results from the ones from other Spanish and European series, we obtained a higher prevalence of altered HDL (42% vs 29.8%)[26], obesity (35.4% vs 33.7%)[27], waist perimeter (61.12% vs 58.8%)[26] and metabolic syndrome (32% vs 30%)[28]. However, hypertriglyceridemia and hypertension prevalence was lower in our study (28% vs 34.7%)[26] and (16% vs 39%)[29] respectively. There may be true differences in the prevalence of the different classic

cardiovascular risk factors between different populations, and successive studies could reveal which factors are involved in these variations.

When comparing the arithmetic means of the classic risk factors of the two groups, differences in HDL and abdominal perimeter levels were observed. Higher levels of hs-CRP in blood in patients with psoriasis could be argued both by the inflammation produced by psoriasis and also by the fact that these patients are more obese and have other cardiovascular risk factors such as MS, which are currently considered inflammatory processes per se[30,31].

We found a higher frequency of MS, hypertension, increased HbA1c and BMI in patients with severe psoriasis according to PASI. Snekvik et. al.[32] also obtained a higher odds ratio for being overweigth (1.94) and having MS (1.91) in people with moderate-severe psoriasis compared to mild psoriasis and Curcó et. at.[28] found psoriasis severity was associated with diabetes, insulin-resistance, smoking habit, higher homocysteine and lower HDL.

Carotid intima-media thickness has already been used to determine the cardiometabolic risk profile in patients with psoriasis[16,33], obtaining higher results in the psoriatic group. However, there are different carotid ultrasound phenotypes, and some authors have established that plaque area is a stronger predictor of risk than intima-media thickness[34,35]. According to this information, plaque area was employed in our study to determine subclinical atheromatosis. The prevalence of atheromatous plaques increased in the group over 50 years and was also higher in men, as previously described[36]. Focusing on the differences between the psoriasis and control groups, we found a high percentage of individuals in both groups with subclinical atheromatosis at the carotid and/or femoral level (46% in the psoriasis group and 36% in the control group) although these two groups had no statistical differences.

In relation to the distribution of the plaques, we found 12 patients with psoriasis with carotid plaques (24%) and 9 of the control group (18%). There are other studies similar to ours that did show a statistically significant increase in atheromatosis in people with psoriasis compared to the control population (Table 3). Prevalence of carotid atheromatosis in psoriatic patients in these studies is very similar to ours and we believe the higher prevalence of atheromatosis in our control population could explain why we did not find differences in our population.

It is also noteworthy the high prevalence of femoral plaques: 20 individuals with psoriasis (40%) and 14 controls (28%). Despite not finding statistically significant differences, there is a higher proportion of patients with psoriasis and atheromatosis, so we believe that increasing the sample in both groups would help confirm a higher prevalence of atherosclerotic femoral plaques in patients with psoriasis. Gonzalez et. al. found a greater prevalence of femoral atheromatosis in the psoriatic group (45.1%) vs controls (19.6%) $p<0.05$. More studies should be needed to confirm this association.

Finally, a comparison was made of the presence of atheromatosis in relation to the severity of psoriasis according to PASI. In relation to PASI, these values went from 37.5% of atheromatosis in mild psoriasis to 61.1% in moderate-severe psoriasis ($p = 0.108$). Even without finding statistically significant differences, an increase in the diagnosis of atheromatous plaques related to the severity of psoriasis is clearly observed, and increasing the sample would help to conclude this hypothesis.

Taking into account that atheromatosis prevalences in mild psoriasis (37.5%) and controls (36.0%) were similar, we decided to compare the group of moderate-severe psoriasis (61.1%) with the controls, obtaining an almost significant difference ($p=0.065$). Subsequently, when performing the analysis by subgroups according to the affected arterial territory, it is verified that there are differences at the carotid level

(p=0.026, OR=3.65). Thus, it seems that the severity of psoriasis increases the risk of atheromatosis and in our study the population with mild psoriasis behaves as the control population.

Within the group of psoriasis, 80% presented a low risk according to SCORE. It is interesting to note that 35% of these patients presented plaques at the carotid or femoral level at the time of the study. In the control group, 81.6% had a low risk and of these, 25% had atheromatous plaques. The assessment of the cardiovascular risk reclassification in subjects with low-intermediate risk according to SCORE was previously performed in a population without psoriasis[37], showing carotid plaques in 25.1% of the individuals, data similar to those obtained in our control population. In relation to REGICOR, 88% of the patients with psoriasis were classified as low risk and of these, 40.9% presented plaques in some location. In the control group, 79.6% had a low estimated risk and 23.1% of these had atheromatous plaques.

To present subclinical atheromatosis in individuals with an estimated low risk according to SCORE or REGICOR causes these patients to be reclassified as a greater risk of a major cardiovascular event. Therefore, these data are relevant because they show that there is a high percentage of patients who would have an underestimation of cardiovascular risk in both groups. Focusing on the group with psoriasis, the frequency of atheromatosis is higher, so it seems that psoriasis acts as a factor involved in the pathogenesis of atherosclerotic plaque formation. Since chronic inflammatory processes have a relevant role in the initial phase of atheromatosis, other diseases such as systemic lupus erythematosus[38] and rheumatoid arthritis[39] have also a higher prevalence of atheromatosis, and therefore, an increased risk of major cardiovascular events.

In addition, there were no significant differences in the cardiovascular risk evaluation from REGICOR and SCORE in the psoriasis and control groups. Since patients with

psoriasis had higher subclinical atheromatosis prevalence in our study, we can conclude that cardiovascular risk in psoriatic patients may have been underestimated using only the parameters included in these two cardiovascular risk tests. To date, few authors have used REGICOR and SCORE to evaluate cardiovascular risk in psoriatic patients[40]. However, since these publications had no control group, it may be difficult to obtain any conclusion and more studies should be needed.

Conclusions

Prevalence of traditional cardiovascular risk factors in patients with psoriasis is very high. Even though our study included a small proportion of the population, we obtained a higher prevalence of some cardiovascular risk factors. Therefore, we believe that a larger sample of patients would show greater disparity between the psoriasis groups and the controls, which would result in more statistically significant differences. Likewise, taking into account the low sensitivity of the predictive cardiovascular risk tests currently used and the high presence of subclinical atheromatosis at the carotid and femoral level in these patients, we believe that routine ultrasound examination in people with psoriasis can reclassify these patients for a more adequate management of comorbidities and to avoid major cardiovascular event in the future.

Conflict of interest

The authors have no conflicts of interest to disclose

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Author contributions

Dr. Fernandez, Dr. Betriu and Dr. Casanova conceptualized and designed the study, drafted the initial manuscript, and reviewed and revised the manuscript.

Dr. Fernandez and Dr. Gomez collected data, carried out the initial analyses, and reviewed and revised the manuscript.

Dr. Betriu, Dr. Garí, Dr. Portero and Dr. Casanova designed the data collection instruments, and coordinated and supervised data collection, and critically reviewed the manuscript.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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References

1. Michalek IM, Loring B, John. A systematic review of worldwide epidemiology of psoriasis. J Er Acad Dermatol Venereol. 2017;31(2):205-212.
2. Ferrándiz C, Bordas X, García-patos V, Puig S, Pujol R, Smandía A. Prevalence of psoriasis in Spain (Epiderma Project: phase I). J Eur Acad Dermatol Venereol. 2001;15(1):20-3.
3. Ferrándiz C, Carrascosa JM, Toro M. Prevalence of psoriasis in Spain in the age of biologics. Actas Dermosifiliogr. 2014;105(5):504-9.
4. Fernández-Armenteros JM, Gómez-Arbonés X, Buti-soler M, et al. Psoriasis, metabolic syndrome and cardiovascular risk factors. A population-based study. J Eur Acad Dermatol Venereol. 2018.
5. Sirje Kaur, Külli Kingo, Mihkel Zilmer. (Agosto 2017). Psoriasis and Cardiovascular Risk- Do promising new biomarkers have clinical impact?. 2018, de Hindawi.

Mediators of Inflamation Sitio web: https://www.hindawi.com/journals/mi/2017/7279818/.

6. Ibrahim G, Waxman R, Helliwell PS. The prevalence of psoriatic arthritis in people with psoriasis. Arthritis Rheum. 2009;61(10):1373-8.

7. Takeshita J, Grewal S, Langan SM, et al. Psoriasis and comorbid diseases: Epidemiology. J Am Acad Dermatol. 2017;76(3):377-390.

8. Eduardo Alegría Ezquerra, Ana Alegría Barrero, Eduardo Alegría Barrero. (Noviembre 2012). Estratificación del riesgo cardiovascular: importancia y aplicaciones. Revista Española de Cardiología, 12, 8-11.

9. Singh S, Young P, Armstrong AW. An update on psoriasis and metabolic syndrome: A meta-analysis of observational studies. PLoS ONE. 2017;12(7):e0181039.

10. Elgendy A, Alshawadfy E, Altaweel A, Elsaidi A (2016). Cardiovascular and metabolic comorbidities of psoriasis. Dermatol Case Rep 1:106.

11. Gelfand JM, Neimann AL, Shin DB, Wang X, Margolis DJ, Troxel AB. Risk of myocardial infarction in patients with psoriasis. JAMA. 2006;296(14):1735-41.

12. Springate DA, Parisi R, Kontopantelis E, Reeves D, Griffiths CE, Ashcroft DM. Incidence, prevalence and mortality of patients with psoriasis: a U.K. population-based cohort study. Br J Dermatol. 2017;176(3):650-658.

13. Gelfand J.M., Troxel A.B., Lewis J.D., Kurd S.K., Shin D.B., Wang X., Margolis D.J., Strom B.L. The risk of mortality in patients with psoriasis: Results from a population-based study. Arch. Dermatol.2007;143:1493–1499.

14. Castañeda S, Nurmohamed MT, González-gay MA. Cardiovascular disease in inflammatory rheumatic diseases. Best Pract Res Clin Rheumatol. 2016;30(5):851-869.

15. Shaharyar S, Warraich H, Mcevoy JW, et al. Subclinical cardiovascular disease in plaque psoriasis: association or causal link?. Atherosclerosis. 2014;232(1):72-8.

16. Dinić M, Zečević RD, Hajduković Z, et al. Psoriasis is the independent factor for early atherosclerosis: A prospective study of cardiometabolic risk profile. Vojnosanitetski pregled. 2016; 73(12):1094-1101.

17. Santilli S, Kast DR, Grozdev I, et al. Visualization of atherosclerosis as detected by coronary artery calcium and carotid intima-media thickness reveals significant atherosclerosis in a cross-sectional study of psoriasis patients in a tertiary care center. J Transl Med. 2016;14(1):217.

18. Bańska-kisiel K, Haberka M, Bergler-czop B, Brzezińska-wcisło L, Okopień B, Gąsior Z. Carotid intima-media thickness in patients with mild or moderate psoriasis. Postepy Dermatol Alergol. 2016;33(4):286-9.

19. Hu SC, Lan CE. Psoriasis and Cardiovascular Comorbidities: Focusing on Severe Vascular Events, Cardiovascular Risk Factors and Implications for Treatment. Int J Mol Sci. 2017;18(10).

20. Eder L, Joshi AA, Dey AK, et al. Association of Tumor Necrosis Factor Inhibitor Treatment With Reduced Indices of Subclinical Atherosclerosis in Patients With Psoriatic Disease. Arthritis Rheumatol. 2018;70(3):408-416.

21. Lerman JB, Joshi AA, Chaturvedi A, et al. Coronary Plaque Characterization in Psoriasis Reveals High-Risk Features That Improve After Treatment in a Prospective Observational Study. Circulation. 2017;136(3):263-276.

22. Betriu A, Martinez-alonso M, Arcidiacono MV, et al. Prevalence of subclinical atheromatosis and associated risk factors in chronic kidney disease: the NEFRONA study. Nephrol Dial Transplant. 2014;29(7):1415-22.

23. Stein JH, Korcarz CE, Hurst RT, et al. Use of carotid ultrasound to identify subclinical vascular disease and evaluate cardiovascular disease risk: a consensus statement from the American Society of Echocardiography Carotid Intima-Media Thickness Task Force. Endorsed by the Society for Vascular Medicine. J Am Soc Echocardiogr. 2008;21(2):93-111.

24. Touboul PJ, Hennerici MG, Meairs S, et al. Mannheim carotid intima-media thickness and plaque consensus (2004-2006-2011). An update on behalf of the advisory board of the 3rd, 4th and 5th watching the risk symposia, at the 13th, 15th and 20th European Stroke Conferences, Mannheim, Germany, 2004, Brussels, Belgium, 2006, and Hamburg, Germany, 2011. Cerebrovasc Dis. 2012;34(4):290-6.

25. Gómez-Vaquero C, Corrales A, Zacarías A, et al. SCORE and REGICOR function charts underestimate the cardiovascular risk in Spanish patients with rheumatoid arthritis. Arthritis Res Ther. 2013;15(4):R91.

26. Belinchon I, Vanaclocha F, De la cueva-dobao P et al. Metabolic syndrome in Spanish patients with psoriasis needing systemic therapy: Prevalence and association with cardiovascular disease in PSO-RISK, a cross-sectional study. J Dermatolog Treat 2015; 26: 318–325.

27. Miller IM, Ellervik C, Yazdanyar S, Jemec GB. Meta-analysis of psoriasis, cardiovascular disease, and associated risk factors. J Am Acad Dermatol 2013; 69: 1014–1024.

28. Curco N, Barriendos N, Barahona MJ et al. Factors influencing cardiometabolic risk profile in patients with psoriasis. Australas J Dermatol 2018; 59: e93–e98.

29. Jacobi A, Kupke C, Behzad M, Hertl M. Comorbidities, metabolic risk profile and health-related quality of life in German patients with plaquetype psoriasis: a cross-sectional prospective study. Int J Dermatol 2013; 52: 1081–1087.

30. Maleki A, Rashidi N, Aghaei meybodi H, et al. Metabolic syndrome and inflammatory biomarkers in adults: a population-based survey in Western region of iran. Int Cardiovasc Res J. 2014;8(4):156-60.

31. Leung WKC, Yu AP, Lai CWK, Siu PM. Association of Markers of Proinflammatory Phenotype and Beige Adipogenesis with Metabolic Syndrome in Chinese Centrally Obese Adults. J Diabetes Res. 2018;2018:8956509.

32. Snekvik I, Nilsen TIL, Romundstad PR, Saunes M. Psoriasis and cardiovascular disease risk factors: the HUNT Study, Norway. J Eur Acad Dermatol Venereol. 2018;32(5):776-782.

33. Argote A, Mora-Hernandez O, Milena Aponte L, et al. Cardiovascular Risk Factors and Carotid Intima-Media Thickness in a Colombian Population with Psoriasis. Actas Dermosifiliogr. 2017;108(8):738-745.

34. Glagov S, Weisenberg E, Zarins CK, Stankunavicius R, Kolettis GJ. Compensatory enlargement of human atherosclerotic coronary arteries. N Engl J Med. 1987;316(22):1371-5.

35. Spence JD. Carotid Ultrasound Phenotypes Are Biologically Distinct. Arterioscler Thromb Vasc Biol. 2015;35(9):1910-3.

36. Wang X, Li W, Song F, et al. Carotid Atherosclerosis Detected by Ultrasonography: A National Cross-Sectional Study. J Am Heart Assoc. 2018;7(8).

37. Blai Coll, Angels Betriu, Steve B. Feinstein, Jose M. Valdivielso, Jose L. Zamorano, Elvira Fernández.. (2013). Papel de la ecografía carotídea en la reclasificación del riesgo cardiovascular de sujetos de riesgo bajo-intermedio. Resvista Española de Cardiología, 66, 929-934.

38. Henrot P, Foret J, Barnetche T, et al. Assessment of subclinical atherosclerosis in systemic lupus erythematosus: A systematic review and meta-analysis. Joint Bone Spine. 2018;85(2):155-163.

39. Jagpal A, Navarro-millán I. Cardiovascular co-morbidity in patients with rheumatoid arthritis: a narrative review of risk factors, cardiovascular risk assessment and treatment. BMC Rheumatol. 2018;2:10.

40. Fernández-Torres R, Pita-fernández S, Fonseca E. Psoriasis and cardiovascular risk. Assessment by different cardiovascular risk scores. J Eur Acad Dermatol Venereol. 2013;27(12):1566-70.

41. El-Mongy S, Fathy H, Abdelaziz A, et al. Subclinical atherosclerosis in patients with chronic psoriasis: a potential association. J Eur Acad Dermatol Venereol. 2010;24(6):661-6.

42. Troitzsch P, Paulista markus MR, Dörr M, et al. Psoriasis is associated with increased intima-media thickness--the Study of Health in Pomerania (SHIP). Atherosclerosis. 2012;225(2):486-90.

43. Arias-Santiago S, Orgaz-Molina J, Castellote-Caballero L, et al. Atheroma plaque, metabolic syndrome and inflammation in patients with psoriasis. Eur J Dermatol. 2012;22(3):337-44.

44. García-Rodríguez S, Arias-Santiago S, Perandrés-López R, et al. Decreased plasma levels of clusterin in patients with psoriasis. Actas Dermosifiliogr. 2013;104(6):497-503.

45. Evensen K, Slevolden E, Skagen K, et al. Increased subclinical atherosclerosis in patients with chronic plaque psoriasis. Atherosclerosis. 2014;237(2):499-503.

46. Lise MLZ, Baptista TSA, Petersen LE, et al. Subclinical atherogenesis in patients with mild psoriasis: A role for IL-6?. Rev Assoc Med Bras (1992). 2017;63(9):747-752.

47. Gonzalez-Cantero A, Gonzalez-Cantero J, Sanchez-Moya AI, et al. Femoral artery ultrasound for improving the detection of atherosclerosis in psoriasis. J Am Acad Dermatol. 2018.

Tables:

Table 1. Cardiovascular risk factors in psoriasis and control group

Cardiovascular risk factors	Psoriasis	Controls	p
Age	47.10	48.40	0.574
Sex (men)	50%	52%	0.841
Obesity	17 (35.4%)	10 (23.3%)	0.205
Waist perimeter	30 (61.12%)	16 (34%)	0.008
Smoking habit	35 (70%)	23 (46%)	0.015, OR=2.74
Impaired fasting glucose	11 (22%)	7 (14%)	0.298
Altered HDL	21 (42%)	7 (14%)	0.002
Altered LDL	13 (26%)	17 (34%)	0.383
Hypercholesterolemia	1 (2%)	5 (10%)	0.092
Hypertriglyceridemia	14 (28%)	4 (8%)	0.009
Hypertension	8 (16%)	6 (12%)	0.564
Altered SBP	4 (8%)	3 (1%)	0.695
Altered DBP	1 (2%)	2 (4%)	0.558
MS	16 (32%)	4 (8%)	0.003, OR=5.04

Table 2. SCORE and REGICOR results in psoriasis and control population

Scale	Group	Mean value (min-max)	Risk classification	n (%)	Presence of atheromatous plaques
SCORE	Psoriasis	0.82 (0-6)	Low risk	40 (80.0%)	14 (35.0%)
			Medium-High risk	10 (20.0%)	9 (90.0%)
	Control	1.12 (0-7)	Low risk	40 (81.6%)	10 (25.0%)
			Medium-High risk	9 (18.4%)	7 (77.8%)
REGICOR	Psoriasis	3.14 (1-17)	Low risk	44 (88.0%)	18 (40.9%)
			Medium-High risk	6 (12.0%)	5 (83.3%)
	Control	3.16 (1-14)	Low risk	39 (79.6%)	9 (23.1%)
			Medium-High risk	10 (20.4%)	8 (80.0%)

Differences between psoriasis and control groups were not statistically relevant (SCORE: $p = 0.837$; REGICOR: $p = 0.256$)

Table 3. Carotid plaque prevalence in psoriasis and control groups in various studies

Publication	Number of psoriasis/control	Carotid plaque prevalence in psoriasis	Carotid plaque prevalence in controls	p
El-Mongy et. al. 2010 (Egypt)[41]	80/50	22 (27.8%)	7 (14%)	0.070
Troitzsch et. al. 2012 (Germany)[42]	72/1955	45 (63%)	1080 (55%)	0.175
Arias-Santiago et. al. 2012 (Spain)[43]	72/61	34.7%	8.2%	0.001
Garcia Rodriguez et. al. 2012 (Granada, Spain)[44]	21/11	7 (33%)		
Evensen et. al. 2014 (Norway)[45]	62/31	13 (21%)	1 (3%)	0.03
Lise et. al. 2017 (Brasil)[46]	65/64	23.8%	8.5%	0.045
Argote et. Al. 2017 (Colombia)[33]	40	6 (15%)		
Gonzalez-Cantero et. al. 2018 (Spain)[47]	51/51	21.6%	13.7%	<0.05
Our data	50/50	12 (24.0%)	9 (18.0%)	0.309

Fig 1 Prevalence of carotid and femoral atheromatosis and involvement of both territories in mild, moderate-severe psoriasis and control group

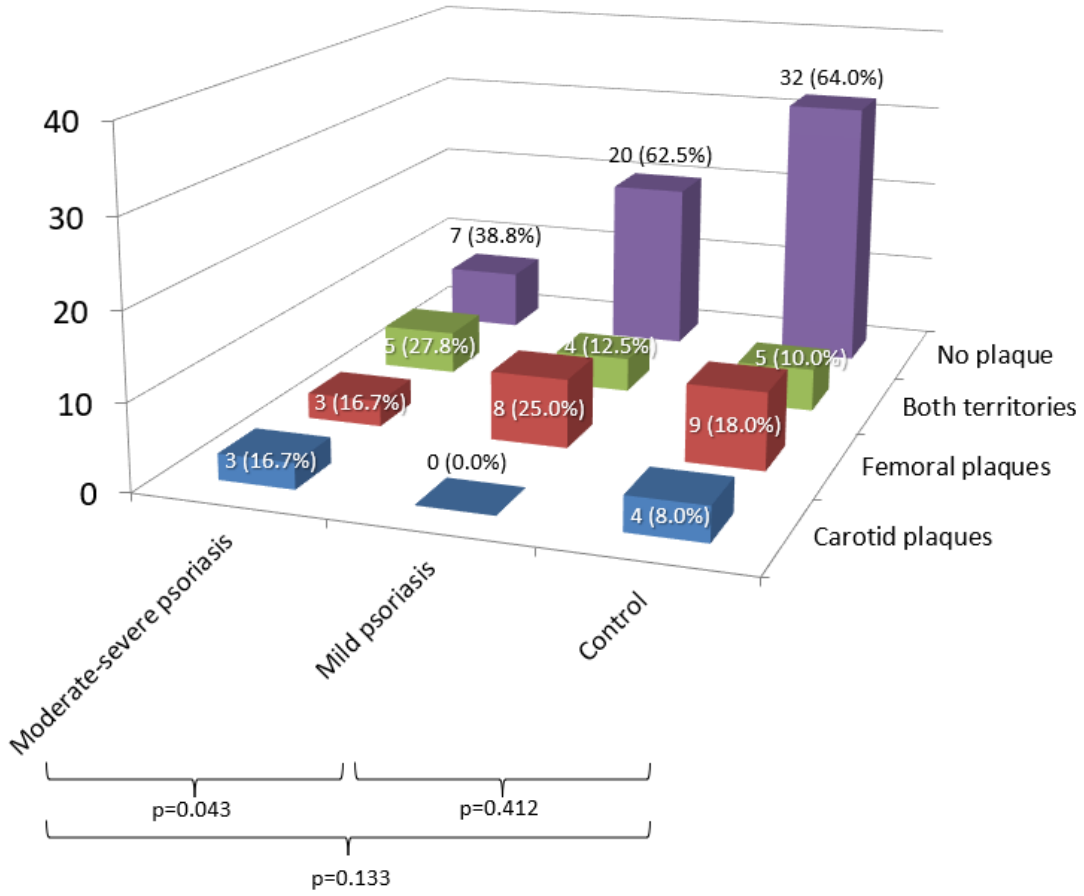
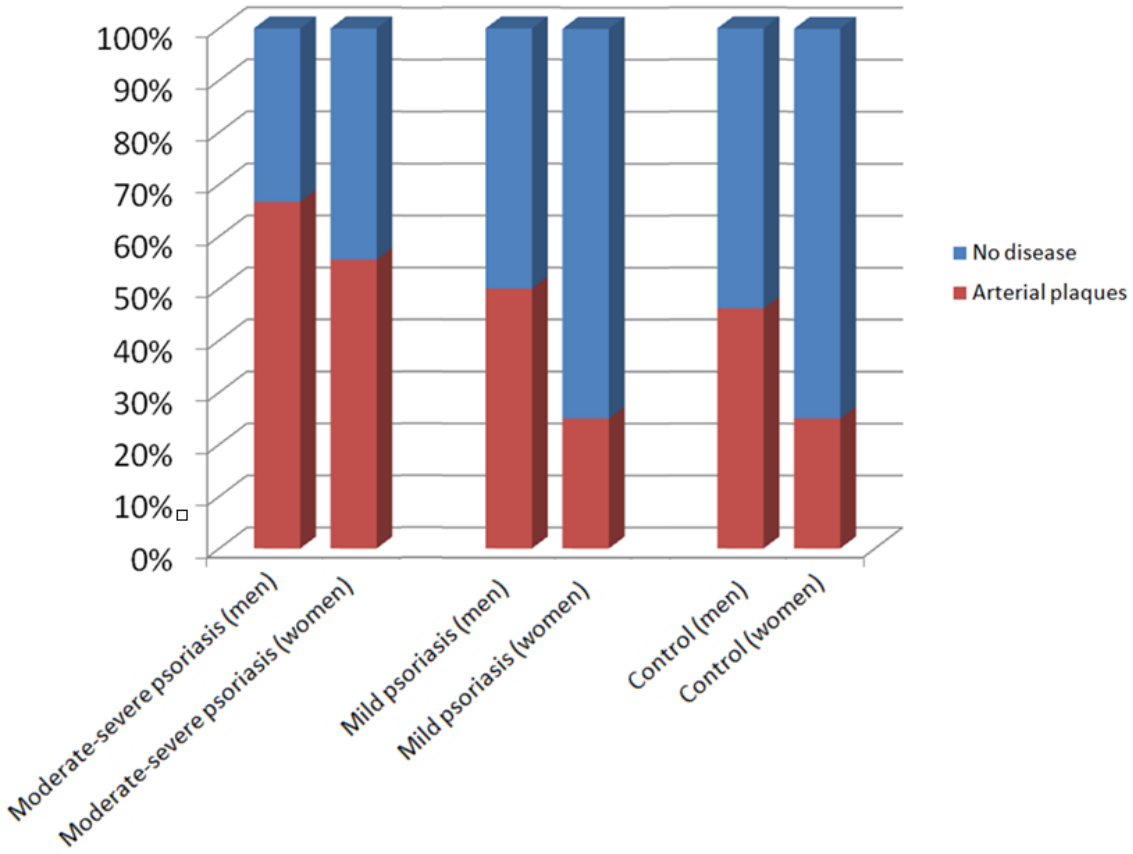


Fig 2 Prevalence of arterial atheromatosis in both sexes in mild, moderate-severe psoriasis and control group



Supplementary material

Supplementary table 1. Diagnostic criteria for cardiovascular risk factors and metabolic syndrome

Diagnostic criteria for cardiovascular risk factors and metabolic syndrome	
Impaired fasting glucose[a]	· Fasting glucose >100 mg/ml
Diabetes mellitus[a] (any of the following)	· Fasting blood glucose ≥126mg/dl · Random blood glucose ≥200 mg/dL in a patient with classic hyperglicemia (polyuria, polydipsia, polyphagy or weight loss) · Glicemia ≥200 mg/dL 2 hours after 75g oral glucose intake (glucose tolerance test) · HbA1c ≥ 6.5% · Registered diabetes mellitus diagnosis
Altered blood pressure	· Altered blood pressure (>140/90mm Hg) in a punctual medition without hypertension criteria
Hypertension[b] (any of the following)	· Altered blood pressure (>140/90mm Hg) in at least 3 separate occasions · Registered hypertension diagnosis
Dyslipidemia	· Hypercholesterolemia ± hypertriglyceridemia
Hypercholesterolemia[c] (any of the following)	· Total cholesterol ≥250mg/dl · Registered hypercholesterolemia diagnosis
Low HDL[c] (any of the following)	· HDL <40mg/dl in men · HDL <50mg/dl in women
High LDL[c] (any of the	· LDL ≥130mg/dl

following)	
Hypertriglyceridemia[c]	· Plasmatic triglycerides ≥150mg/dl
(any of the following)	· Registered hypertriglyceridemia diagnosis
High BMI[d]	· 25-29.9kg/m^2: Overweight · ≥30/m^2: Obesity
High waist perimeter	· Waist perimeter ≥102 cm in men or ≥88 cm in women
MS[e]	· Fasting glucose ≥100 mg/dL
(at least 3 criteria):	· Blood pressure ≥130/85 mm Hg · Triglycerides ≥150 mg/dL · HDL-C <40 mg/dL in men or <50 mg/dL in women · Waist circumference ≥102 cm (40 in) in men or ≥88 cm (35 in) in women; if Asian American, ≥90 cm (35 in) in men or ≥80 cm (32 in) in women

Extracted from: [a]American Diabetes Association, 2006; [b]Chobanian AV, 2003; [c]Diaz A, 2014; [d]National Institutes of Health (NIH), National Heart, Lung, and Blood Institute (NHLBI), 2000; [e]National Heart, Lung and Blood Institute (NHLKI) and American Heart Association (AHA), 2005.

Supplementary table 2. Average values of cardiovascular risk factors in psoriasis and control group

Cardiovascular risk factors	Psoriasis	Controls	p
Glucose in plasma	91.91	89.10	0.245
Cholesterol in plasma	190.98	187.73	0.611
HDL in plasma	49.80	55.12	0.021
LDL in plasma	117.80	117.05	0.890
Triglycerides in plasma	123.38	79.96	<0.001
Apo A1 in plasma	1.41	1.42	0.754
Apo B-100	0.98	0.91	0.090
Hs-CRP	4.83	1.78	0.013
ESR	13.58	11.25	0.332
HbA1c	5.34	5.81	0.444
SBP	120.84	121.19	0.915
DBP	68.83	73.19	0.132
BMI	28.38	26.93	0.230
Abdominal perimeter	99.98	91.71	0.005

Supplementary table 3. Prevalence of cardiovascular risk factors according to PASI in psoriasis group

Cardiovascular risk factor	PASI		p
	Mild	Moderate/severe	
Age	45.56	49.83	0.209
Sex (men)	50%	50%	1.000
Impaired basal glucose	6 (18.8%)	5 (27.8%)	0.459
Hypercholesterolemia	0 (0%)	1 (5.6%)	0.178
Hypertriglyceridemia	6 (18.8%)	8 (44.4%)	0.052
Altered HDL	15 (46.9%)	6 (33.3%)	0.352
Altered LDL	8 (25.0%)	5 (27.8%)	0.830
Hypertension	2 (6.3%)	6 (33.3%)	0.012
Altered SBP	1 (3.1%)	3 (16.7%)	0.090
Altered DBP	0 (0%)	1 (5.6%)	0.178
Obesity	9 (29.0%)	8 (47.1%)	0.212
Smoking habit	23 (71.9%)	12 (66.7%)	0.700
Altered waist circumference	19 (61.3%)	11 (61.1%)	0.990
MS	7 (21.9%)	9 (50.0%)	0.041

Supplementary table 4. Average values of cardiovascular risk factors in mild and moderate-severe psoriasis according to PASI

Cardiovascular risk factors	Psoriasis severity		p
	Mild	Moderate/severe	
Glucose in plasma	91.29	93.00	0.642
Cholesterol in plasma	186.84	198.33	0.241
HDL in plasma	49.69	50.00	0.930
LDL in plasma	116.05	120.89	0.546
Triglycerides in plasma	115.47	137.44	0.272
Apo A1 in plasma	1.39	1.44	0.433
Apo B-100	0.96	1.00	0.513
Hs-CRP	4.04	6.23	0.337
ESR	12.60	15.53	0.463
HbA1c	5.19	5.62	<0.001
SBP	118.87	124.35	0.298
DBP	68.18	70.00	0.694
BMI	27.11	30.69	0.044
Abdominal perimeter	97.26	104.67	0.097

TITLE PAGE:

TITLE: Adventitial carotid vasa vasorum study in patients with psoriasis

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ABSTRACT

Background and aims: An increased density of adventitial vasa vasorum can be observed in early stages of atheromatosis, even before the atheroma plaques are visible. Since atherosclerosis is more prevalent in patients with psoriasis, we believe it is interesting to study carotid vasa vasorum density in this population in order to detect atheromatosis in its initial stages.

Methods: It is an observational and cross-sectional study carried out in a single center. The study group of patients with psoriasis consisted of 50 patients with plaque

psoriasis and 50 individuals without this disease. A simple vascular ultrasonography and a contrast enhanced ultrasound examination were performed.

Results: A higher vasa vasorum density was associated with psoriasis, obesity and altered waist circumference. The density of vasa vasorum in the left common carotid artery in the psoriasis population was 0.682 as opposed to a density of 0.595 in controls (p = 0.008). Right common carotid artery vasa vasorum density was 0.693 in patients with psoriasis and 0.669 in the control sample (p=0.425).

Conclusions: It seems that the increase in density of vasa vasorum has a key role in the initial phases of atheromatosis and psoriasis acts as an independent factor in this pathogenesis.

INTRODUCTION

Psoriasis is a chronic inflammatory disease that affects the skin and joints. It is a very prevalent pathology in the population (1-3%) with a bimodal distribution pattern (early-onset around 35 and 44 years and late-onset around 65 and 74 years)[1]. Major cardiovascular events are the leading cause of death in patients with psoriasis and these events are more frequent in psoriatic patients than in general population (hazard ratio 1.21, 95% CI 1.13-1.3)[2-4]. Therefore, an early diagnosis of subclinical arterial disease, such as the presence of atheromatosis, is important. Our investigation group has already found a higher prevalence of carotid atheromatosis in patients with moderate-severe psoriasis compared to a control group (44.4% vs 18.0%, p = 0.026, OR=3.65, CI 1.12-11.76; pending publication). On the other hand, we know that atherosclerosis is a generalized disease triggered by dysfunction in the endothelium lining the blood vessel lumen[5]. Besides hypertension, diabetes mellitus, hypercholesterolemia, smorking and obesity, other atherosclerosis risk factors have been described, such as genetic and environmental factors and chronic inflammation. Many authors have linked systemic inflammatory diseases such as rheumatoid arthritis, systemic lupus erythematosus or inflammatory bowel disease with an

increased cardiovascular risk[6]. The need to describe early detectors of cardiovascular risk has encouraged the appearance of initial markers in the process of atherosclerosis.

The architecture of the vascular wall changes with age. At birth, the most internal layer consists only of an endothelial single layer covered by an internal elastic lamina. Medium layer has smooth muscular cells, connective tissue and elastic fibers. External layer or adventitial is composed by connective tissue rich in collagen, fibroblasts, perivascular nerves, pericytes, adipocytes and leukocytes[5].

Vascular inner layer becomes thicker with age, and it was believed that this phenomenon was associated with atherosclerosis. However, now it is known that it is a process associated with arterial growth. Diffusion of nutrients through wall vessels is usually sufficient in those with a diameter smaller than 0.5mm[7]. In greater vessels, conditions such as hypoxia and ischemia promote in the adventitial layer inflammatory cell activation (neutrophils, macrophages, lymphocytes) which produce proangiogenic molecules. These molecules (such as endothelial vascular growth factor and other cytokines) promote the formation of a new network of adventitial vasa vasorum, also called second order or pathological, which are oriented towards the vascular lumen in order to maintain the oxygenation of these vessels[5-8]. Vasa vasorum density is heterogeneously distributed with a higher density in proximal vessels[9] and many studies have evidenced a correlation between prevalence and severity of atherosclerosis and adventitial vasa vasorum density[5].

There are already established causes of adventitial neoangiogenesis such as age[10], hypercholesterolemia[11], arterial hypertension[12], diabetes type 1[13] and 2[14,15], obesity[16], chronic kidney disease[17], elevated levels of parathyroid hormone (PTH)[18], lower levels of vitamin D[19], anemia[20] and sleep apnea-hypopnea syndrome[15]. As described above, inflammation is known to be closely related in the process of neoangiogenesis. Therefore, since atherosclerosis is a disease with an inflammatory etiopathogenesis, as well as psoriasis, where patients are diagnosed at a young age and cardiovascular events are the leading cause of mortality, we believe it is really interesting to study cardiovascular risk factors in patients with psoriasis and the possibility of obtaining

data on early atheromatosis. This would allow us to take preventive measures to reduce cardiovascular risk and the associated morbidity and mortality.

Therefore, the main objectives of this study were:

1. To measure the density of the carotid adventitial vasa vasorum (which is an early subclinical atheromatosis detector) in a group of patients with psoriasis.
2. To compare these results with a control population.
3. To evaluate the association between vasa vasorum density and classic cardiovascular risk factors.

MATHERIAL AND METHODS

It is an observational and cross-sectional study carried out in a single center. The study group of patients with psoriasis consisted of 50 patients older than 18 years diagnosed with plaque psoriasis without previous cardiovascular events (infarction, stroke, peripheral arterial disease, heart failure or cardiac conduction disorders). Exclusion criteria for this group were: systemic treatment for psoriasis (acitretin, methotrexate, cyclosporine) in the last month, biological treatment for psoriasis (infliximab, adalimumab, etanercept, ustekinumab, secukinumab, ixekizumab, brodalumab) in the last 3 months, severe respiratory insufficiency, type 1 or 2 diabetes mellitus, renal insufficiency (glomerular filtration rate, CKD-EPI, <60), pregnancy or lactation or patients with contraindications for contrast administration (cardiac instability, type III or IV heart failure, recent coronary intervention in the last week, recent acute myocardial infarction, severe arterial hypertension, severe respiratory failure, pulmonary hypertension or previous allergic reaction to sulfur hexafluoride. Written informed consent was obtained from each patient included in the study. Furthermore, the study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki and it has been priorly approved by the “Hospital Arnau de Vilanova de Lleida ethics committee” (CEIC-1655).

The control group consisted of 50 patients older than 18 years without the diagnosis of psoriasis, and the subjects were usually relatives or cohabitants of psoriasis patients. Exclusion criteria for this group were the same as the psoriasis group.

Blood tests were performed on both groups, assessing HDL, LDL, total cholesterol, triglycerides, glucose, HbA1c, glomerular filtration, ultrasensitive C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR). Clinical and anthropometric data were collected: medical history and usual medication, weight (kg) and height (m) for calculation of body mass index (weight/m2), blood pressure and smoking habits. Diagnostic criteria for cardiovascular risk factors and metabolic syndrome are summarized in supplementary table A.

Vascular ultrasonography:

Vascular ultrasonography was performed following a method which was already described by Betriu et. al.[21]. B-mode ultrasound of the carotid and femoral arteries was performed using the Vivid BT09 apparatus (GE Healthcare, Waukesha, WI) equipped with a 6- to 13-MHz broadband linear array probe. An atheromatous plaque presence analysis was performed in 10 territories (internal, bulb, and common carotids and both common and superficial femoral arteries) by a single reader in blinded fashion using semiautomatic software (EchoPAC Dimension; GE Healthcare). To assess intraobserver reliability, a sample of 20 individuals was measured three to five times on different days. A κ-coefficient of one was obtained for plaque assessment, indicating excellent intraobserver reliability. The reader was unaware of patients' clinical histories.

Carotid intima-media thickness (cIMT) was only measured in common carotid regions without plaque and calculated as the average between left and right sides. The presence of atheromatous plaques was defined as a cIMT>1.5 mm protruding into the lumen according to the American Society of Echocardiography Consensus Statement[22] and the Mannheim cIMT Consensus[23].

Contrast-enhanced ultrasound (CEU) examinations were completed using a Siemens Sequoia 512 ultrasound system (equipped with a 15L8W linear array probe) and with ultrasound contrast software (Cadence contrast Pulse Sequencing technology). A phospholipidic shell containing sulphur hexafluoride served as a contrast agent

(Sonovue, Bracco Spa, Milan, Italy). Once the contrast was solubilized in 5 ml of saline, a 2.5 ml bolus was injected in the antecubital vein for each carotid artery explored (20-gauge needle to avoid microbubbles rupture). Adventitial VV content in the far adventitial layer was calculated as the average of the ratios of the intensities in the 2 mm above the intima-lumen boundary and the intensities of the 2 mm below the media-adventitia boundary of the common carotid artery 1 cm proximal to the bifurcation. The result (VV signal) was calculated as the average of 10 to 20 ratios calculated for each diastolic frame in which both the lumen intensity and the adventitial intensity was high and stable within a 1-minute video recording. Results are displayed on the right and left sides, and the mean VV signal of both sides is presented. As a ratio, VV signal has no units. All the studies were stored digitally for a posterior analysis by the same blinded investigator. Additionally, all participants underwent a B-mode ultrasound examination of the extra-cranial carotid arteries and the cIMT of the far wall of the common carotid artery was measured following the Mannheim consensus procedures[14].

RESULTS

The mean age of the psoriasis group was 47.10 years, with a standard deviation of 11.46 and 25 were men (50%). In the control group, the mean age was 48.40 years (SD 11.58) and 52.0% were men. The percentage of patients in both groups with classic cardiovascular risk factors is described in Table 1. It should be noted that a greater proportion of patients with smoking habit were found in the group with psoriasis (70 vs 46%, p = 0.015, OR = 2.74), altered waist circumference (61.22% vs 34%, p = 0.008), alteration of HDL in blood (42% vs 14%, p = 0.002), diagnosis of metabolic syndrome (32% vs 8%, p = 0.003, OR = 5.04) and hypertriglyceridemia (28% vs 8%, p = 0.009).

Prevalence of atheromatosis in individuals of both groups (psoriasis and controls) was 19.6% in individuals under 50 years of age and 68.2% in those over 50 years (p<0.001). Atheromatosis in men of both groups was 51.0% and in women 30.6% (p=0.029).

From the psoriasis group, 23 patients (46.0%) presented carotid or femoral plaques vs 18 individuals (36.0%) in the control group (p = 0.309). Other carotid and femoral ultrasound sub-analysis and results are disclosed in our previous publication.

Subsequently, a univariate analysis of the contrast-enhanced arterial ultrasound study was performed. Differences in carotid adventitial vasa vasorum density according to the diagnosis of psoriasis as well as other classic cardiovascular risk factors are summarized in table 2.

In our study, a higher vasa vasorum density was associated with psoriasis, obesity and altered waist circumference. The density of vasa vasorum in the left common carotid artery in the psoriasis population was 0.682 as opposed to a density of 0.595 in controls (p = 0.008). Right common carotid artery vasa vasorum density was 0.693 in patients with psoriasis and 0.669 in the control sample (p=0.425). The mean of the vasa vasorum results was also performed on both sides, finding an average of 0.686 in the patients with psoriasis and 0.636 in the controls (p = 0.056).

DISCUSSION

The prevalence of classic cardiovascular risk factors in patients with psoriasis, as well as the prevalence of carotid and femoral atheromatosis has been assessed and confirmed in multiple studies[24,25]. Our study provides more arguments in favor of psoriasis as a cardiovascular risk factor. However, these data have been published or presented in other publications, as well as the discussion of these results.

On the other hand, we present the first published study of vasa vasorum density in patients with psoriasis, and as it was believed in the formulation of the objectives, a higher density of adventitial vasa vasorum has been confirmed in patients with psoriasis. Since psoriasis and atheromatosis share a similar inflammatory etiopathogenesis and psoriasis is a chronic illness, the study of vasa vasorum density could be a promising technique in order to better assess vascular anatomy and prevent atheromatosis.

In addition we also found a higher density of adventitial vasa vasorum in the male group, although there was not a statistical significance. Considering that the prevalence of cardiovascular disease is higher in males and there is also a higher prevalence of atheromatosis in this population[26], our results in adventitial vasa

vasorum density are not unexpected. On the other hand, there are other studies that identify a higher density of vasa vasorum in women[15], and we believe that new studies should clarify this possible association.

We also found a higher density of adventitial vasa vasorum associated with altered waist circumference, a parameter involved in metabolic syndrome and obesity, both in the left and right carotid arteries. This association has already been published in other studies[16]. In fact, it has been confirmed that patients with obesity had lower vasa vasorum density after bariatric surgery. Similar studies could be useful in psoriatic patients after receiving systemic treatment for this cutaneous disease due to its possible repercussion in the progression of atheromatosis.

CONCLUSION

The relationship between psoriasis, cardiovascular risk factors and atheromatosis is currently clear and there are multiple studies which support this statement. Furthermore, it is becoming increasingly important to detect atherosclerosis in its earliest stages, especially in phases where this process could be reversible. Pathogenesis of psoriasis is better understood nowadays, and it seems that the increase in density of vasa vasorum has a key role in the initial phases. We believe that in pathologies such as psoriasis, where there is a significant burden of cardiovascular disease, it is important to make a good screening of these patients and thus avoid comorbidity and associated mortality.

CONFLICTS OF INTEREST

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

REFERENCES

1. Pezzolo E, Cazzaniga S, Colombo P, Chatenoud L, Naldi L. Psoriasis Incidence and Lifetime Prevalence: Suggestion for a Higher Mortality Rate in Older Age-classes among Psoriatic Patients Compared to the General Population in Italy. Acta Derm Venereol. 2019;99(4):400-403.
2. Springate DA, Parisi R, Kontopantelis E, Reeves D, Griffiths CE, Ashcroft DM. Incidence, prevalence and mortality of patients with psoriasis: a U.K. population-based cohort study. Br J Dermatol. 2017;176(3):650-658.
3. Takeshita J, Grewal S, Langan SM, et al. Psoriasis and comorbid diseases: Epidemiology. J Am Acad Dermatol. 2017;76(3):377-390.
4. Gelfand JM, Neimann AL, Shin DB, Wang X, Margolis DJ, Troxel AB. Risk of myocardial infarction in patients with psoriasis. JAMA. 2006;296(14):1735-41.
5. Boyle EC, Sedding DG, Haverich A. Targeting vasa vasorum dysfunction to prevent atherosclerosis. Vascul Pharmacol. 2017;96-98:5-10.
6. Sherer Y, Shoenfeld Y. Mechanisms of disease: atherosclerosis in autoimmune diseases. Nat Clin Pract Rheumatol. 2006;2(2):99-106.
7. E. Geiringer, Intimal vascularization and atherosclerosis, J. Pathol. Bacteriol. 63 (1951) 201–211. [4] H. Wolinsky, S. Glagov, Nature of species differences in the medial distribution of aortic vasa vasorum in mammals, Circ. Res. 20 (1967) 409–421.
8. Xu J, Lu X, Shi GP. Vasa vasorum in atherosclerosis and clinical significance. Int J Mol Sci. 2015;16(5):11574-608.
9. Sano M, Unno N, Sasaki T, et al. Topologic distributions of vasa vasorum and lymphatic vasa vasorum in the aortic adventitia--Implications for the prevalence of aortic diseases. Atherosclerosis. 2016;247:127-34.
10. Arcidiacono MV, Rubinat E, Borras M, et al. Left carotid adventitial vasa vasorum signal correlates directly with age and with left carotid intima-media thickness in individuals without atheromatous risk factors. Cardiovasc Ultrasound. 2015;13:20.
11. Herrmann J, Lerman LO, Rodriguez-porcel M, et al. Coronary vasa vasorum neovascularization precedes epicardial endothelial dysfunction in experimental hypercholesterolemia. Cardiovasc Res. 2001;51(4):762-6.
12. Kuwahara F, Kai H, Tokuda K, et al. Hypoxia-inducible factor-1alpha/vascular endothelial growth factor pathway for adventitial vasa vasorum formation in hypertensive rat aorta. Hypertension. 2002;39(1):46-50.
13. Rubinat E, Ortega E, Traveset A, et al. Microangiopathy of common carotid vasa vasorum in type 1 diabetes mellitus. Atherosclerosis. 2015;241(2):334-8.
14. Arcidiacono MV, Traveset A, Rubinat E, et al. Microangiopathy of large artery wall: a neglected complication of diabetes mellitus. Atherosclerosis. 2013;228(1):142-7.
15. López-Cano C, Rius F, Sánchez E, et al. The influence of sleep apnea syndrome and intermittent hypoxia in carotid adventitial vasa vasorum. PLoS ONE. 2019;14(2):e0211742.
16. Rius F, Sánchez E, Betriu À, et al. Influence of Morbid Obesity and Bariatric Surgery Impact on the Carotid Adventitial Vasa Vasorum Signal. Obes Surg. 2018;28(12):3935-3942.
17. Arcidiacono MV, Martinez-alonso M, Belart M, et al. High Levels of Hemoglobin Promote Carotid Adventitial Vasa Vasorum Neoangiogenesis in Chronic Kidney Disease. Mediators Inflamm. 2017;2017:3795142.

18. L.-L.Wang, D. Chen, J. Lee et al., "Mobilization of endogenous bone marrow derived endothelial progenitor cells and therapeutic potential of parathyroid hormone after ischemic stroke in mice," *PLoS ONE*, vol. 9, no. 2,Article ID e87284, 2014.
19. D. J.Mantell, P. E. Owens, N. J. Bundred, E. B.Mawer, and A. E. Canfield, "1α,25-Dihydroxyvitamin D3 inhibits angiogenesis in vitro and in vivo," *Circulation Research*, vol. 87, no. 3, pp. 214–220, 2000.
20. J. Dunst, A. Becker, C. Lautenschläger et al., "Anemia and elevated systemic levels of vascular endothelial growth factor (VEGF)," *Strahlentherapie und Onkologie*, vol. 178, no. 8, pp. 436–441, 2002.
21. Betriu A, Martinez-alonso M, Arcidiacono MV, et al. Prevalence of subclinical atheromatosis and associated risk factors in chronic kidney disease: the NEFRONA study. Nephrol Dial Transplant. 2014;29(7):1415-22.
22. Stein JH, Korcarz CE, Hurst RT, et al. Use of carotid ultrasound to identify subclinical vascular disease and evaluate cardiovascular disease risk: a consensus statement from the American Society of Echocardiography Carotid Intima-Media Thickness Task Force. Endorsed by the Society for Vascular Medicine. J Am Soc Echocardiogr. 2008;21(2):93-111.
23. Touboul PJ, Hennerici MG, Meairs S, et al. Mannheim carotid intima-media thickness and plaque consensus (2004-2006-2011). An update on behalf of the advisory board of the 3rd, 4th and 5th watching the risk symposia, at the 13th, 15th and 20th European Stroke Conferences, Mannheim, Germany, 2004, Brussels, Belgium, 2006, and Hamburg, Germany, 2011. Cerebrovasc Dis. 2012;34(4):290-6.
24. Arias-Santiago S, Orgaz-molina J, Castellote-Caballero L, et al. Atheroma plaque, metabolic syndrome and inflammation in patients with psoriasis. Eur J Dermatol. 2012;22(3):337-44.
25. Gonzalez-Cantero A, Gonzalez-Cantero J, Sanchez-Moya AI, et al. Femoral artery ultrasound for improving the detection of atherosclerosis in psoriasis. J Am Acad Dermatol. 2018.
26. Zhao W, Wu Y, Shi M, et al. Sex Differences in Prevalence of and Risk Factors for Carotid Plaque among Adults: A Population-based Cross-Sectional Study in Rural China. Sci Rep. 2016;6:38618.

FIGURES AND TABLES

Table 1. Prevalence of classic cardiovascular risk factors

Cardiovascular risk factor	Psoriasis group	Control group	p
Impaired fasting glucose	11 (22%)	7 (14%)	p=0.298
Decreased hdl	21 (42%)	7 (14%)	p=0.002
Increased ldl	13 (26%)	17 (34%)	p=0.383
Hypercholesterolemia	1 (2%)	5 (10%)	p=0.092
Hypertriglyceridemia	14 (28%)	4 (8%)	p=0.009
Arterial hypertension	8 (16%)	6 (12%)	p=0.564
Impaired systolic blood pressure	4 (8%)	3 (1%)	p=0.695
Impaired diastolic blood pressure	1 (2%)	2 (4%)	p=0.558
Obesity	17 (35.4%)	10 (23.3%)	p=0.205
Altered waist circumference	30 (61.12%)	16 (34%)	p=0.008
Metabolic syndrome	16 (32%)	4 (8%)	p=0.003, or=5.04
Smoking habit	35 (70%)	23 (46%)	p=0.015, or=2.74

Table 2. Vasa vasorum density according to different cardiovascular risk factors

Parameter	Categories	LCVV Density (SD)	p	RCVV Density (SD)	p	MCVV Density (SD)	p
Sex	Men	0.662 (0.159)	0.223	0.710 (0.174)	0.066	0.687 (0.121)	0.057
	Women	0.621 (0.154)		0.653 (0.142)		0.638 (0.117)	
Age	Under 50 years	0.649 (0.159)	0.553	0.691 (0.164)	0.438	0.669 (0.133)	0.579
	50 years or older	0.629 (0.156)		0.667 (0.113)		0.654 (0.099)	
Altered basal glycemia	No	0.641 (0.160)	0.969	0.681 (0.152)	0.841	0.662 (0.124)	0.821
	Yes	0.643 (0.142)		0.690 (0.110)		0.671 (0.103)	
Hypercholesterolemia	No	0.647 (0.157)	0.217	0.681 (0.148)	0.774	0.665 (0.122)	0.516
	Yes	0.557 (0.155)		0.700 (0.119)		0.629 (0.099)	
Altered HDL	No	0.628 (0.151)	0.208	0.684 (0.158)	0.827	0.657 (0.120)	0.483
	Yes	0.674 (0.168)		0.677 (0.119)		0.677 (0.123)	
Altered LDL	No	0.655 (0.164)	0.187	0.681 (0.159)	0.882	0.667 (0.134)	0.616
	Yes	0.606 (0.135)		0.686 (0.109)		0.652 (0.078)	
Hypertriglyceridemia	No	0.630 (0.162)	0.163	0.691 (0.156)	0.228	0.124 (0.129)	0.897
	Yes	0.691 (0.124)		0.642 (0.081)		0.667 (0.076)	
Altered Systolic Blood Pressure	No	0.638 (0.160)	0.462	0.681 (0.148)	0.783	0.661 (0.122)	0.462
	Yes	0.687 (0.103)		0.698 (0.122)		0.693 (0.103)	
Altered Diastolic Blood Pressure	No	0.643 (0.159)	0.604	0.684 (0.147)	0.374	0.665 (0.122)	0.373
	Yes	0.584 (0.017)		0.591 (0.001)		0.587 (0.008)	
Altered BMI	No	0.617 (0.166)	0.020	0.657 (0.127)	0.007	0.639 (0.112)	0.020
	Yes	0.706 (0.128)		0.751 (0.170)		0.729 (0.128)	
Smoking habit	Non-smokers	0.638 (0.138)	0.836	0.673 (0.67)	0.597	0.657 (0.129)	0.670
	Smokers or ex-smokers	0.645 (0.645)		0.689 (0.120)		0.668 (0.115)	
Altered waist circumference	No	0.589 (0.151)	0.001	0.677 (0.124)	0.506	0.634 (0.101)	0.008
	Yes	0.707 (0.149)		0.698 (0.165)		0.704 (0.133)	
Metabolic syndrome	No	0.629 (0.164)	0.145	0.685 (0.153)	0.717	0.658 (0.127)	0.443
	Yes	0.691 (0.113)		0.671 (0.118)		0.683 (0.088)	
Psoriasis	No	0.595 (0.160)	0.008	0.669 (0.171)	0.425	0.636 (0.136)	0.056
	Yes	0.682 (0.144)		0.693 (0.122)		0.686 (0.102)	

Legend: LCVV (Left Carotid Vasa Vasorum), SD (Standard Deviation), RCVV (Right Carotid Vasa Vasorum), MCVV (Mean Carotid Vasa Vasorum), BMI (Body Mass Index).

Supplementary table A. Diagnostic criteria for cardiovascular risk factors and metabolic syndrome

Diagnostic criteria for cardiovascular risk factors and metabolic syndrome	
Impaired fasting glucose[a]	· Fasting glucose >100 mg/ml
Diabetes mellitus[a] (any of the following)	· Fasting blood glucose ≥126mg/dl · Random blood glucose ≥200 mg/dL in a patient with classic hyperglicemia (polyuria, polydipsia, polyphagy or weight loss) · Glicemia ≥200 mg/dL 2 hours after 75g oral glucose intake (glucose tolerance test) · HbA1c ≥ 6.5% · Registered diabetes mellitus diagnosis
Altered blood pressure	· Altered blood pressure (>140/90mm Hg) in a punctual medition without hypertension criteria
Hypertension[b] (any of the following)	· Altered blood pressure (>140/90mm Hg) in at least 3 separate occasions · Registered hypertension diagnosis
Dyslipidemia	· Hypercholesterolemia ± hypertriglyceridemia
Hypercholesterolemia[c] (any of the following)	· Total cholesterol ≥250mg/dl · Registered hypercholesterolemia diagnosis
Low HDL[c] (any of the following)	· HDL <40mg/dl in men · HDL <50mg/dl in women
High LDL[c] (any of the following)	· LDL ≥130mg/dl

Hypertriglyceridemia[c]	· Plasmatic triglycerides ≥150mg/dl
(any of the following)	· Registered hypertriglyceridemia diagnosis
High BMI[d]	· 25-29.9kg/m^2: Overweight
	· ≥30/m^2: Obesity
High waist perimeter	· Waist perimeter ≥102 cm in men or ≥88 cm in women
MS[e]	· Fasting glucose ≥100 mg/dL
(at least 3 criteria):	· Blood pressure ≥130/85 mm Hg
	· Triglycerides ≥150 mg/dL
	· HDL-C <40 mg/dL in men or <50 mg/dL in women
	· Waist circumference ≥102 cm (40 in) in men or ≥88 cm (35 in) in women; if Asian American, ≥90 cm (35 in) in men or ≥80 cm (32 in) in women

Extracted from: [a]American Diabetes Association, 2006; [b]Chobanian AV, 2003; [c]Diaz A, 2014; [d]National Institutes of Health (NIH), National Heart, Lung, and Blood Institute (NHLBI), 2000; [e]National Heart, Lung and Blood Institute (NHLKI) and American Heart Association (AHA), 2005.

5. Discusión global de los resultados.

La prevalencia de psoriasis en la provincia de Lleida fue del 1.72%. Este dato se encuentra dentro del rango obtenido en dos estudios previos nacionales (1.43% en 2001[3] y 2.31% en 2013[4]). En el caso de estos estudios previos, se obtuvieron los datos mediante encuestas telefónicas y con una población aproximada de unas 12.000 personas, cifra muy inferior a la estudiada en nuestro trabajo (398.701). Así pues creemos que nuestra población es representativa y los resultados obtenidos de este estudio tienen validez. Así mismo nuestros resultados de prevalencia de psoriasis difieren parcialmente de otros publicados en series italianas (2.9%)[45], francesas (5.2%)[46], inglesas (2.8%)[47] y alemanas (2.78%)[48] aun usando la misma metodología. Pueden haber influido las diferencias en la metodología aplicada y las características de la población (fototipo, envejecimiento de la población, etc).

Teniendo en cuenta el tratamiento pautado, en nuestra población, el 7.27% tenían una psoriasis moderada-severa. Estos datos son muy inferiores a la prevalencia descrita en otras series como la de *Takeshita et. al*. en Estados Unidos (27.3%)[43] y la de *Yeung et. al.* en Reino Unido (38.2%)[49]. Creemos que la metodología usada en nuestro trabajo podría ser una de las causas de esta disparidad en los resultados (aunque en el trabajo de *Takeshita et. al.* también se usó este método) ya que los médicos de atención primaria no utilizan las escalas de severidad de la psoriasis más frecuentemente usadas (BSA y PASI) y no existe en el eCAP un campo para registrarla. Por otra parte, la dieta y otros factores ambientales (irradiación solar, estilos de vida al aire libre) podrían tener un efecto protector y evitar el empeoramiento de pacientes con psoriasis[50]. Ahora bien, nuestros datos son similares a los encontrados en un estudio poblacional hecho en Noruega utilizando la misma metodología (prevalencia de psoriasis moderada-severa del 8.67%)[51]. Ello también podría indicar que en lugares donde el acceso al dermatólogo es difícil por motivos de distancia, los pacientes con psoriasis moderada-grave no podrían recibir tratamiento con fototerapia ni tratamientos sistémicos y por tanto estarían infradiagnosticados usando esta metodología. Igualmente, podríamos sugerir que el fácil acceso a tratamientos inmunomoduladores, como el uso continuado de corticoides tópicos potentes[52], sobre todo bajo cura oclusiva[53,54], corticoides sistémicos[55], o de inmunosupresores clásicos o biológicos como el infliximab[56], efalizumab[57], alefacept[58] o el brodalumab[59,60] podrían favorecer el desarrollo de una psoriasis más inestable y grave, por un efecto rebote, como también sucede en otras enfermedades inflamatorias cutáneas como la dermatitis atópica[61-63].

La edad media de la población general fue de 42.34 años, cifra bastante inferior a la media del grupo con psoriasis (52.08 años), hecho que evidencia que se trata de una enfermedad que suele iniciarse en la adolescencia o en adultos jóvenes. En relación a la distribución de los pacientes con psoriasis según los grupos de edad, el porcentaje mayor de pacientes tenía entre 51 a 60 años (19.66% de la población con psoriasis) y la prevalencia máxima de esta enfermedad se observó en el grupo de edad entre 61 y 70 años (2.90% del total de la población de este grupo). Estos datos

son comparables con la mayoría de estudios donde se aprecia un aumento en la prevalencia de psoriasis directamente proporcional a la edad hasta los 60-70 años, momento en que la frecuencia disminuye[4,64]. Esto refleja el hecho de que se trata de una enfermedad crónica y que los pacientes que van debutando con la enfermedad se van acumulando con los años. En otros trabajos también se ha descrito un patrón de incidencia bimodal (el primer pico entre 35 y 44 años y el segundo entre 65 y 74 años)[65] que no encontramos en nuestro estudio. En relación a la psoriasis en menores de 18 años, encontramos una prevalencia del 0.30%, datos también similares a los publicados en Italia (0.22%)[66] y Alemania (0.45%)[67], y no determinados previamente en España.

En nuestro estudio el sexo masculino resultó ser un factor de riesgo asociado a psoriasis (1.88% vs 1.56%, OR: 1.21, 95% IC: 1.15-1.27). Aunque muchos otros trabajos también encuentran una mayor frecuencia de hombres con psoriasis[4,48], existe aún controversia respecto a la asociación entre psoriasis y sexo, donde se han publicado también datos de psoriasis asociada al sexo femenino[68] u otros donde no se han encontrado diferencias[69,70]. Creemos que otros factores podrían interferir en esta asociación y se requeriría un mayor estudio de factores de confusión.

En relación a los factores de riesgo cardiovascular en nuestro estudio epidemiológico, encontramos una mayor prevalencia de diabetes mellitus 2, dislipemia, hipertensión y obesidad. Así mismo encontramos una mayor proporción de pacientes diagnosticados de síndrome metabólico en el grupo con psoriasis respecto a la población control, así como también de todos los criterios de este síndrome por separado (glicemia alterada en ayunas, tensión arterial alterada, HDL bajo, hipertrigliceridemia y perímetro alterado de cintura). Igualmente pudimos diseñar un modelo predictivo de la probabilidad de síndrome metabólico donde la edad, el sexo masculino y el diagnóstico de psoriasis presentaron una relación no linear significativa con la presencia de este síndrome.

En nuestro estudio no pudimos detectar diferencias estadísticamente significativas entre la prevalencia de factores de riesgo cardiovascular clásicos y la severidad de la psoriasis, y solamente se obtuvo un aumento (aunque no significativo) de la prevalencia de síndrome metabólico en el grupo con psoriasis moderada-severa. En estudios previos del norte de Europa se evidenció un aumento en la prevalencia de síndrome metabólico en pacientes con psoriasis moderada-severa usando una metodología similar a la nuestra[51], así que creemos que factores culturales o geográficos podrían explicar estas diferencias. Nuestros datos corroboran también la asociación entre la psoriasis y los eventos cardiovasculares mayores, tanto infarto de miocardio como enfermedad cerebrovascular.

La confirmación de que la psoriasis, también en nuestro medio, se asocia a factores de riesgo cardiovascular y a eventos cardiovasculares mayores (accidente cerebrovascular e infarto agudo de miocardio) indica que el abordaje de la misma debe ser multidisciplinar y que se deben implementar de forma activa medidas preventivas, diagnósticas y terapéuticas, que tengan en cuenta este hecho (eliminación de factores de riesgo conductuales como el tabaquimo o el

alcoholismo, modificaciones en la dieta, ejercicio moderado para reducir el peso, estudio analítico de dislipemia y diabetes).

En nuestro trabajo sobre ateromatosis y *vasa vasorum* adventiciales incluimos una población mucho menor a la del estudio epidemiológico, por lo que los datos de prevalencia de factores de riesgo cardiovascular clásicos no obtiene tanta significación como en el estudio previo. Igualmente cabe destacar que en el estudio de ateromatosis analizamos algunos factores nuevos como el tabaquismo, donde encontramos una mayor proporción de fumadores y exfumadores en el grupo con psoriasis. Además también se encontró un aumento estadísticamente significativo en los niveles de PCR ultrasensible, hecho que podría argumentarse por la inflamación producida por la psoriasis así como también por su asociación a obesidad y otros factores de riesgo cardiovascular clásicos, considerados hoy en día como procesos inflamatorios *per se*[71,72].

A pesar de la escasa muestra estudiada (50 pacientes con psoriasis y 50 controles) encontramos una mayor frecuencia de síndrome metabólico, hipertensión, aumento de la hemoglobina glicosilada y del índice de masa corporal en el grupo de psoriasis moderada-severa con respecto al PASI. Creemos que el hecho de encontrar diferencias en este estudio y no en el anterior, aun teniendo mucha menos población, pone de manifiesto que en estos estudios, el uso de escalas como el PASI permitiría valorar la severidad de la psoriasis de una forma más ajustada.

El grosor de la íntima-media carotídea ha sido usado para determinar el perfil de riesgo cardiometabólico en los pacientes con psoriasis[24,73], obteniendo mayores cifras en el grupo con esta enfermedad. De todas formas, existen diferentes fenotipos evidenciados en el estudio ecográfico carotídeo, y ciertos autores concluyen que la presencia de placa de ateroma es un mejor predictor de riesgo cardiovascular que el grosor íntima-media[74,75]. Teniendo en cuenta estos datos, la presencia de placa de ateroma fue el método usado en nuestro estudio para determinar la presencia de ateromatosis subclínica.

La prevalencia de placas de ateroma fue mayor en el grupo de individuos mayores de 50 años, así como también en los hombres, como se ha descrito previamente[76]. Centrándonos en las diferencias de ateromatosis respecto a la presencia de psoriasis, encontramos un porcentaje elevado de ateromatosis en ambos grupos a nivel carotídeo y/o femoral (46% en el grupo con psoriasis y 36% en el grupo control) aunque no encontramos diferencias estadísticamente significativas entre los dos grupos.

Respecto a la ateromatosis carotídea, encontramos enfermedad arterial en el 24% de los individuos con psoriasis respecto al 18% en el grupo control. Existen estudios similares al nuestro que encontraron un aumento estadísticamente significativo de placas de ateroma en la población con psoriasis[77,78]. En estos estudios vemos como la prevalencia de ateromatosis fue similar a la nuestra en el grupo psoriásico, pero mucho menor en el grupo control, hecho que podría explicar que no hayamos encontrado diferencias.

También es relevante la alta prevalencia de ateromatosis femoral que fue del 40% en la población con psoriasis y del 28% en controles aunque no se encontraron diferencias significativas. Sí se detectaron en el estudio de *González et. al.* en el que la prevalencia de ateromatosis femoral fue del 45.1% en los pacientes con psoriasis y del 19.6% en controles ($p<0.05$)[78]. Aunque no detectamos significación estadística, vimos una mayor prevalencia de ateromatosis en el grupo de psoriasis, y creemos que aumentar la muestra en nuestro estudio ayudaría a confirmar estas diferencias, lo que nos proponemos en un futuro estudio multicéntrico para el que hemos calculado una "n" de 400 pacientes y 400 controles.

Finalmente quisimos valorar las diferencias en la prevalencia de ateromatosis respecto a la severidad de la psoriasis. Los valores de ateromatosis en cualquier territorio (carotídeo o femoral) fue del 36.0% en controles, 37.5% en psoriasis leve y del 61.1% en psoriasis moderada-severa ($p=0.108$). En este caso evidenciamos una diferencia clara en la prevalencia de ateromatosis en el grupo de psoriasis más severa y un aumento de la muestra podría ayudar a encontrar la significación. Es interesante destacar que la prevalencia obtenida en controles y psoriasis leve fue similar. Así mismo cuando se realizó el análisis por separado de cada territorio comparando el grupo con psoriasis moderada-severa con el grupo control a nivel carotídeo sí que encontramos diferencias estadísticamente significativas (44.4% vs 18.0%, $p=0.026$, OR=3.65). Por lo tanto parece que la severidad de la psoriasis aumenta el riesgo de ateromatosis y en nuestro estudio la población con psoriasis leve se comportó como la población control en relación a este factor estudiado.

Dentro del grupo de psoriasis, un 80% presentó un riesgo bajo según la escala SCORE. Es interesante destacar que un 35% de estos pacientes presentó placas carotídeas o femorales en el momento del estudio. En el grupo control el 81.6% obtuvo un riesgo bajo según SCORE y de estos un 25% presentaba placas en algún territorio. La evaluación del riesgo cardiovascular según SCORE y su reclasificación mediante ecografía carotídea ya había sido estudiada previamente en una población sin psoriasis[79], encontrando un 25.1% de placas de ateroma a nivel carotídeo en la población identificada como de riesgo bajo, datos similares a nuestra población control. En relación al REGICOR, el 88% de los pacientes con psoriasis se clasificó como de bajo riesgo y un 40% de éstos presentaron placas de ateroma, así como también un 23.1% del 79.6% identificado como de bajo riesgo en el grupo control.

Presentar ateromatosis subclínica en individuos clasificados como de riesgo bajo según SCORE y REGICOR reclasifica a estos pacientes a un riesgo mayor de un evento cardiovascular. Nuestro estudio revela que un alto porcentaje de pacientes con psoriasis tendría una infraestimación de su riesgo cardiovascular si se siguiesen solamente estas escalas en pacientes con esta enfermedad. Además, no se encontraron diferencias significativas entre las cifras de REGICOR y SCORE entre los grupos con psoriasis y control. Teniendo en cuenta que el grupo con psoriasis presentaba una mayor prevalencia de ateromatosis podemos concluir que el estudio predictivo del riesgo

cardiovascular en los pacientes con psoriasis debería incluir este diagnóstico para así no infraestimar el riesgo cardiovascular. Hasta la fecha pocos autores han usado SCORE y REGICOR para evaluar el riesgo cardiovascular en los pacientes con psoriasis[17]. Sin embargo, estos trabajos no cuentan con una población control, así que sería difícil obtener conclusiones al respecto y serían necesarios más estudios.

Estos datos aconsejan introducir la realización de una ecografía simple carotídea y femoral al resto de medidas recomendadas en el abordaje del paciente con psoriasis, al menos en los casos graves, aunque esperamos confirmarlos con un estudio multicéntrico que comenzaremos próximamente.

Finalmente, presentamos el primer estudio publicado de densidad de vasa vasorum adventicial en pacientes con psoriasis, y como se intuía formulando las hipótesis del trabajo, encontramos una mayor densidad de estos vasa vasorum en los pacientes con psoriasis. Puesto que la psoriasis y la ateromatosis comparten una etiopatogenia inflamatoria común y la psoriasis es una enfermedad crónica, el estudio de densidad de vasa vasorum podría ser una técnica prometedora con el objetivo de mejorar la evaluación de enfermedad vascular en nuestros pacientes y prevenir el proceso de ateromatosis.

Además también encontramos una mayor densidad de vasa vasorum en la población masculina, aún sin encontrar significación. Considerando que la prevalencia de factores de riesgo cardiovascular clásicos es mayor en el sexo masculino y que hay una mayor presencia de ateromatosis en este grupo[80], los resultados de vasa vasorum son esperables. Por otro lado hay otros estudios que han identificado una mayor densidad de vasa vasorum adventiciales en mujeres[36] y creemos que nuevos estudios serían necesarios para clarificar este tema.

En nuestro trabajo confirmamos la asociación entre el aumento de densidad de los vasa vasorum adventiciales carotídeos y el perímetro alterado de cintura, un parámetro involucrado en el síndrome metabólico. Así mismo también encontramos una mayor densidad de vasa vasorum adventiciales en pacientes con obesidad, tanto en carótida común izquierda como derecha. Esta asociación ya ha sido publicada en otros estudios[37]. De hecho se ha evidenciado una disminución en la densidad de los vasa vasorum carotídeos en pacientes con obesidad posterior a una intervención de cirugía bariátrica. Estudios similares podrían ser útiles en pacientes con psoriasis una vez tratados con fármacos sistémicos o biológicos para valorar su posible repercusión en la progresión de la ateromatosis.

6. Conclusiones finales

Los resultados de nuestro estudio aportan mayor evidencia a la importante asociación entre la psoriasis y las comorbilidades cardiovasculares aunque a su vez en algunos puntos pueden suscitar controversia.

Los datos de prevalencia de psoriasis en la población general y según edad y sexo fueron bastante equiparables a los de la mayor parte de los estudios. Ahora bien obtuvimos una prevalencia de psoriasis moderada-severa bastante inferior a la de muchos de los estudios epidemiológicos de psoriasis publicados hasta ahora y que han usado la misma metodología, aunque similar a la de otros como el trabajo noruego de *Snekvik et. al*.[51]. El hecho de encontrar estas grandes diferencias podría deberse quizás a la menor utilización de fototerapia y tratamientos sistémicos en nuestra población (y en la de *Snekvik et. al*) al representar un área donde existen largas distancias entre los pacientes y los hospitales o centros de referencia. Esto indicaría que en realidad queda una población con psoriasis grave desatendida lo que debiera corregirse acercando el dermatólogo a esta población dado el elevado deterioro en la calidad de vida que podría comportar para estos pacientes. Ahora bien, también podría deberse a una menor utilización de inmunomoduladores como el uso continuado de corticoides tópicos potentes especialmente en cura oclusiva, ciclosporina o fármacos biológicos que podrían favorecer en algunos casos la aparición de una psoriasis inestable y más grave (por un efecto rebote).

Por otra parte, nuestro estudio confirma la estrecha asociación que existe entre la psoriasis y los factores de riesgo cardiovascular clásicos, así como también evidencia un mayor riesgo de ateromatosis en estos pacientes. En nuestro trabajo realizamos un estudio epidemiológico de una población relativamente grande en comparación con el resto de trabajos publicados en la literatura y del que creemos que se pueden obtener unas conclusiones veraces y a su vez poner de manifiesto las diferencias ambientales o dietéticas que podrían existir en relación a otras regiones. Teniendo en cuenta que muchos de los pacientes con psoriasis pueden ser solamente visitados por el dermatólogo[2], creemos que sería interesante un cribado de estos factores de riesgo cardiovascular ya sea por un dermatólogo especializado como por atención primaria. Igualmente objetivamos un aumento en la prevalencia de ateromatosis en los pacientes con psoriasis. Aun necesitando una mayor muestra para confirmar con más peso nuestros resultados, el estudio ecográfico vascular rutinario en nuestros pacientes con psoriasis sería útil para clasificarlos correctamente según su riesgo de presentar un evento cardiovascular futuro.

Creemos que el abordaje de un paciente con psoriasis debe ser multidisciplinar. Además del tratamiento de la piel debe solicitarse el estudio de las comorbilidades incluyendo factores de riesgo cardiovascular e implementar medidas preventivas y terapéuticas dirigidas a reducir el tabaquismo y el alcoholismo, modificar la dieta y fomentar la reducción de peso con el ejercicio.

Así mismo, pudimos evidenciar por vez primera que en la psoriasis, al igual que en otros factores de riesgo cardiovascular clásicos asociados a ateromatosis, existen también procesos neoangiogénicos adventiciales carotídeos previos a la formación de la placa de ateroma. Aunque este método diagnóstico todavía se encuentra en fases experimentales, en un futuro se podría usar de rutina para detectar más precozmente el daño vascular y así evitar mayor morbimortalidad en nuestros pacientes con intervenciones dirigidas.

7. Bibliografía

1. Michalek IM, Loring B, John SM. A systematic review of worldwide epidemiology of psoriasis. J Eur Acad Dermatol Venereol. 2017;31(2):205-212.
2. Takeshita J, Grewal S, Langan SM, et al. Psoriasis and comorbid diseases: Epidemiology. *J Am Acad Dermatol*. 2017. doi:10.1016/j.jaad.2016.07.064
3. Ferrándiz C, Bordas X, García-patos V, Puig S, Pujol R, Smandía A. Prevalence of psoriasis in Spain (Epiderma Project: phase I). J Eur Acad Dermatol Venereol. 2001;15(1):20-3.
4. Ferrándiz C, Carrascosa JM, Toro M. Prevalence of psoriasis in Spain in the age of biologics. Actas Dermosifiliogr. 2014;105(5):504-9.
5. Sirje Kaur, Külli Kingo, Mihkel Zilmer. (Agosto 2017). Psoriasis and Cardiovascular Risk- Do promising new biomarkers have clinical impact?. 2018, de Hindawi. Mediators of Inflamation Sitio web: https://www.hindawi.com/journals/mi/2017/7279818
6. Zachariae R, Zachariae C, Ibsen HHW, Mortensen JT, Wulf HC. Psychological symptoms and quality of life of dermatology outpatients and hospitalized dermatology patients. *Acta Derm Venereol*. 2004. doi:10.1080/00015550410023284
7. Ibrahim G, Waxman R, Helliwell PS. The prevalence of psoriatic arthritis in people with psoriasis. Arthritis Rheum. 2009;61(10):1373-8.
8. Kumar S, Han J, Li T, et al. Obesity, waist circumference, weight change and the risk of psoriasis in US women. J Eur Acad Dermatol Venereol. 2013;27:1293-1298.
9. Ma C, Harskamp CT, Armstrong EJ, et al. The association between psoriasis and dyslipidaemia: a systematic review. Br J Dermatol. 2013;168:486-495.
10. Armstrong AW, Harskamp CT, Armstrong EJ. Psoriasis and the risk of diabetes mellitus: a systematic review and meta-analysis. JAMA Dermatol. 2013;149:84-91.
11. Armstrong AW, Harskamp CT, Armstrong EJ. The association between psoriasis and hypertension: a systematic review and meta-analysis of observational studies. J Hypertens. 2013;31: 433-442.
12. Singh S, Young P, Armstrong AW. An update on psoriasis and metabolic syndrome: A meta-analysis of observational studies. PLoS ONE. 2017;12(7):e0181039.
13. Correia B, Torres T. Obesity: a key component of psoriasis. Acta Biomed. 2015;86:121-9.
14. Gelfand JM, Neimann AL, Shin DB, et al. Risk of myocardial infarction in patients with psoriasis. JAMA. 2006;296: 1735-1741.

15. Samarasekera EJ, Neilson JM, Warren RB, Parnham J, Smith CH. Incidence of cardiovascular disease in individuals with psoriasis: a systematic review and meta-analysis. J Invest Dermatol. 2013;133:2340-6.
16. Gelfand J.M., Troxel A.B., Lewis J.D., Kurd S.K., Shin D.B., Wang X., Margolis D.J., Strom B.L. The risk of mortality in patients with psoriasis: Results from a population-based study. Arch. Dermatol.2007;143:1493–1499.
17. Fernández-Torres R, Pita-fernández S, Fonseca E. Psoriasis and cardiovascular risk. Assessment by different cardiovascular risk scores. J Eur Acad Dermatol Venereol. 2013;27(12):1566-70.
18. Hu SC, Lan CE. Psoriasis and Cardiovascular Comorbidities: Focusing on Severe Vascular Events, Cardiovascular Risk Factors and Implications for Treatment. Int J Mol Sci. 2017;18(10)
19. Castañeda S, Nurmohamed MT, González-Gay MA. Cardiovascular disease in inflammatory rheumatic diseases. Best Pract Res Clin Rheumatol. 2016;30(5):851-869.
20. Ayman Elgendy, Eslam Alshawadfy, Abdelaziz Altaweel and Ahmed Elsaidi. (Enero 2016). Cardiovascular and Metabolic Comobordities of Psoriasis. 2018, de Dermatology Case Reports Sitio web: https://www.omicsonline.org/open-access/cardiovascular-and-metabolic-comorbidities-of-psoriasis-DMCR-1000106.pdf
21. Boyle EC, Sedding DG, Haverich A. Targeting vasa vasorum dysfunction to prevent atherosclerosis. Vascul Pharmacol. 2017;96-98:5-10.
22. Sherer Y, Shoenfeld Y. Mechanisms of disease: atherosclerosis in autoimmune diseases. Nat Clin Pract Rheumatol. 2006;2(2):99-106.
23. Shaharyar S, Warraich H, Mcevoy JW, et al. Subclinical cardiovascular disease in plaque psoriasis: association or causal link?. Atherosclerosis. 2014;232(1):72-8.
24. Dinić M, Zečević RD, Hajduković Z, et al. Psoriasis is the independent factor for early atherosclerosis: A prospective study of cardiometabolic risk profile. Vojnosanitetski pregled. 2016; 73(12):1094-1101.
25. Santilli S, Kast DR, Grozdev I, et al. Visualization of atherosclerosis as detected by coronary artery calcium and carotid intima-media thickness reveals significant atherosclerosis in a cross-sectional study of psoriasis patients in a tertiary care center. J Transl Med. 2016;14(1):217.
26. Bańska-kisiel K, Haberka M, Bergler-czop B, Brzezińska-wcisło L, Okopień B, Gąsior Z. Carotid intima-media thickness in patients with mild or moderate psoriasis. Postepy Dermatol Alergol. 2016;33(4):286-9.
27. Eder L, Joshi AA, Dey AK, et al. Association of Tumor Necrosis Factor Inhibitor Treatment With Reduced Indices of Subclinical Atherosclerosis in Patients With Psoriatic Disease. Arthritis Rheumatol. 2018;70(3):408-416.

28. Lerman JB, Joshi AA, Chaturvedi A, et al. Coronary Plaque Characterization in Psoriasis Reveals High-Risk Features That Improve After Treatment in a Prospective Observational Study. Circulation. 2017;136(3):263-276.
29. E. Geiringer, Intimal vascularization and atherosclerosis, J. Pathol. Bacteriol. 63 (1951) 201–211. [4] H. Wolinsky, S. Glagov, Nature of species differences in the medial distribution of aortic vasa vasorum in mammals, Circ. Res. 20 (1967) 409–421.
30. Xu J, Lu X, Shi GP. Vasa vasorum in atherosclerosis and clinical significance. Int J Mol Sci. 2015;16(5):11574-608.
31. Arcidiacono MV, Rubinat E, Borras M, et al. Left carotid adventitial vasa vasorum signal correlates directly with age and with left carotid intima-media thickness in individuals without atheromatous risk factors. Cardiovasc Ultrasound. 2015;13:20.
32. Herrmann J, Lerman LO, Rodriguez-porcel M, et al. Coronary vasa vasorum neovascularization precedes epicardial endothelial dysfunction in experimental hypercholesterolemia. Cardiovasc Res. 2001;51(4):762-6.
33. Kuwahara F, Kai H, Tokuda K, et al. Hypoxia-inducible factor-1alpha/vascular endothelial growth factor pathway for adventitial vasa vasorum formation in hypertensive rat aorta. Hypertension. 2002;39(1):46-50.
34. Rubinat E, Ortega E, Traveset A, et al. Microangiopathy of common carotid vasa vasorum in type 1 diabetes mellitus. Atherosclerosis. 2015;241(2):334-8.
35. Arcidiacono MV, Traveset A, Rubinat E, et al. Microangiopathy of large artery wall: a neglected complication of diabetes mellitus. Atherosclerosis. 2013;228(1):142-7.
36. López-Cano C, Rius F, Sánchez E, et al. The influence of sleep apnea syndrome and intermittent hypoxia in carotid adventitial vasa vasorum. PLoS ONE. 2019;14(2):e0211742.
37. Rius F, Sánchez E, Betriu À, et al. Influence of Morbid Obesity and Bariatric Surgery Impact on the Carotid Adventitial Vasa Vasorum Signal. Obes Surg. 2018;28(12):3935-3942.
38. Arcidiacono MV, Martinez-alonso M, Belart M, et al. High Levels of Hemoglobin Promote Carotid Adventitial Vasa Vasorum Neoangiogenesis in Chronic Kidney Disease. Mediators Inflamm. 2017;2017:3795142.
39. L.-L.Wang, D. Chen, J. Lee et al., “Mobilization of endogenous bone marrow derived endothelial progenitor cells and therapeutic potential of parathyroid hormone after ischemic stroke in mice,” *PLoS ONE*, vol. 9, no. 2,Article ID e87284, 2014.
40. D. J.Mantell, P. E. Owens, N. J. Bundred, E. B.Mawer, and A. E. Canfield, “1α,25-Dihydroxyvitamin D3 inhibits angiogenesis in vitro and in vivo,” *Circulation Research*, vol. 87, no. 3, pp. 214–220, 2000.

41. J. Dunst, A. Becker, C. Lautenschläger et al., “Anemia and elevated systemic levels of vascular endothelial growth factor (VEGF),” *Strahlentherapie und Onkologie*, vol. 178, no. 8, pp. 436–441, 2002.
42. Grundy SM, Cleeman JI, Daniels SR, et al. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. Circulation. 2005;112(17):2735-52.
43. Takeshita J, Gelfand JM, Li P, et al. Psoriasis in the US medicare population: Prevalence, treatment, and factors associated with biologic use. *J Invest Dermatol*. 2015. doi:10.1038/jid.2015.296.
44. Touboul PJ, Hennerici MG, Meairs S, et al. Mannheim carotid intima-media thickness and plaque consensus (2004-2006-2011). An update on behalf of the advisory board of the 3rd, 4th and 5th watching the risk symposia, at the 13th, 15th and 20th European Stroke Conferences, Mannheim, Germany, 2004, Brussels, Belgium, 2006, and Hamburg, Germany, 2011. Cerebrovasc Dis. 2012;34(4):290-6.
45. Saraceno R, Mannheimer R, Chimenti S. Regional distribution of psoriasis in Italy. *J Eur Acad Dermatology Venereol*. 2008. doi:10.1111/j.1468-3083.2007.02423.x
46. Wolkenstein P, Revuz J, Roujeau JC, Bonnelye G, Grob JJ, Bastuji-Garin S. Psoriasis in France and associated risk factors: results of a case-control study based on a large community survey. *Dermatology*. 2009. doi:10.1159/000182258
47. Springate DA, Parisi R, Kontopantelis E, Reeves D, Griffiths CEM, Ashcroft DM. Incidence, prevalence and mortality of patients with psoriasis: a U.K. population-based cohort study. *Br J Dermatol*. 2017. doi:10.1111/bjd.15021
48. Radtke MA, Schäfer I, Glaeske G, Jacobi A, Augustin M. Prevalence and comorbidities in adults with psoriasis compared to atopic eczema. *J Eur Acad Dermatology Venereol*. 2017. doi:10.1111/jdv.13813
49. Yeung H, Takeshita J, Mehta NN, et al. Psoriasis severity and the prevalence of major medical comorbidity: A population-based study. *JAMA Dermatology*. 2013.
50. Barrea L, Balato N, Di Somma C, et al. Nutrition and psoriasis: Is there any association between the severity of the disease and adherence to the Mediterranean diet? *J Transl Med*. 2015. doi:10.1186/s12967-014-0372-1.
51. Snekvik I, Nilsen TIL, Romundstad PR, Saunes M. Psoriasis and cardiovascular disease risk factors: the HUNT Study, Norway. J Eur Acad Dermatol Venereol. 2018;32(5):776-782.

52. Farber EM, Peterson JB. Variations in the natural history of psoriasis. Calif Med. 1961; 95:6-11
53. Mommers JM, van Erp PE, van De Kerkhof PC. Clobetasol under hydrocolloid occlusion in psoriasis results in a complete block of proliferation and in a rebound of lesions following discontinuation. Dermatology. 1999; 199:323-7.
54. Theeuwes M, Bright R. Use of a hydrocolloid dressing in combination with a topical steroid in plaque psoriasis. Cutis. 1996; 57:48-50.
55. Mrowietz U, Domm S. Systemic steroids in the treatment of psoriasis: what is fact, what is fiction?. J Eur Acad Dermatol Venereol. 2013; 27:1022-5.
56. Teixeira MZ. Biological therapies (immunomodulatory drugs), worsening of psoriasis and rebound effect: new evidence of similitude. Homeopathy. 2016; 105:344-355.
57. Kop EN, Körver JE, Van Ruysevelt D, De Jong EM, Van der Valk PG, Van de Kerkhof PC. Erythroderma in two patients with psoriasis upon discontinuation of efalizumab treatment. J Dermatolog Treat. 2009; 20:67-9.
58. Sánchez-Regaña M, Dilmé E, Puig L, Bordas X, Carrascosa JM, Ferran M, Herranz P, García-Bustinduy M, López Estebaranz JL, Alsina M, Rodríguez MA, Ribera M, Fernández-López E, Moreno JC, Belinchón Romero I, Vidal D; Grupo Español de Psoriasis de la Academia Española. [Adverse reactions during biological therapy for psoriasis: results of a survey of the Spanish Psoriasis Group]. Actas Dermosifiliogr. 2010; 101:156-63.
59. Khemis A, Cavalié M, Montaudié H, Lacour JP, Passeron T. Rebound pustular psoriasis after brodalumab discontinuation. Br J Dermatol. 2016; 175:1065-1066
60. Masson Regnault M, Konstantinou MP, Khemis A, Poulin Y, Bourcier M, Amelot F, Bulaï Livideanu C, Paul C. Early relapse of psoriasis after stopping brodalumab: a retrospective cohort study in 77 patients. J Eur Acad Dermatol Venereol. 2017; 31:1491-1496.
61. Forte WC, Sumita JM, Rodrigues AG, Liuson D, Tanaka E. Rebound phenomenon to systemic corticosteroid in atopic dermatitis. Allergol Immunopathol (Madr). 2005; 33:307-11.
62. Siegfried EC, Jaworski JC, Kaiser JD, Hebert AA. Systematic review of published trials: long-term safety of topical corticosteroids and topical calcineurin inhibitors in pediatric patients with atopic dermatitis. BMC Pediatr. 2016; 16:75.
63. Yu SH, Drucker AM, Lebwohl M, Silverberg JI. A systematic review of the safety and efficacy of systemic corticosteroids in atopic dermatitis. J Am Acad Dermatol. 2018; 78:733-740.

64. Danielsen K, Olsen AO, Wilsgaard T, Furberg AS. Is the prevalence of psoriasis increasing? A 30-year follow-up of a population-based cohort. *Br J Dermatol*. 2013. doi:10.1111/bjd.12230.
65. Pezzolo E, Cazzaniga S, Colombo P, Chatenoud L, Naldi L. Psoriasis Incidence and Lifetime Prevalence: Suggestion for a Higher Mortality Rate in Older Age-classes among Psoriatic Patients Compared to the General Population in Italy. Acta Derm Venereol. 2019;99(4):400-403.
66. Cantarutti A, Don D, Visentin F, et al. Epidemiology of Frequently Occurring Skin Diseases in Italian Children from 2006 to 2012: A Retrospective, Population-Based Study. *Pediatr Dermatol*. 2015. doi:10.1111/pde.12568.
67. Augustin M, Radtke MA, Glaeske G, et al. Epidemiology and Comorbidity in Children with Psoriasis and Atopic Eczema. *Dermatology*. 2015. doi:10.1159/000381913.
68. Stern RS, Nijsten T, Feldman SR, Margolis DJ, Rolstad T. Psoriasis is common, carries a substantial burden even when not extensive, and is associated with widespread treatment dissatisfaction. *J Investig Dermatology Symp Proc*. 2004. doi:10.1046/j.1087-0024.2003.09102.x
69. Seminara NM, Abuabara K, Shin DB, et al. Validity of The Health Improvement Network (THIN) for the study of psoriasis. *Br J Dermatol*. 2011. doi:10.1111/j.1365-2133.2010.10134.x
70. Gelfand JM, Weinstein R, Porter SB, Neimann AL, Berlin JA, Margolis DJ. Prevalence and treatment of psoriasis in the United Kingdom: A population-based study. *Arch Dermatol*. 2005. doi:10.1001/archderm.141.12.1537.
71. Maleki A, Rashidi N, Aghaei meybodi H, et al. Metabolic syndrome and inflammatory biomarkers in adults: a population-based survey in Western region of iran. Int Cardiovasc Res J. 2014;8(4):156-60.
72. Leung WKC, Yu AP, Lai CWK, Siu PM. Association of Markers of Proinflammatory Phenotype and Beige Adipogenesis with Metabolic Syndrome in Chinese Centrally Obese Adults. J Diabetes Res. 2018;2018:8956509.
73. Argote A, Mora-Hernandez O, Milena Aponte L, et al. Cardiovascular Risk Factors and Carotid Intima-Media Thickness in a Colombian Population with Psoriasis. Actas Dermosifiliogr. 2017;108(8):738-745.
74. Glagov S, Weisenberg E, Zarins CK, Stankunavicius R, Kolettis GJ. Compensatory enlargement of human atherosclerotic coronary arteries. N Engl J Med. 1987;316(22):1371-5.
75. Spence JD. Carotid Ultrasound Phenotypes Are Biologically Distinct. Arterioscler Thromb Vasc Biol. 2015;35(9):1910-3.

76. Wang X, Li W, Song F, et al. Carotid Atherosclerosis Detected by Ultrasonography: A National Cross-Sectional Study. J Am Heart Assoc. 2018;7(8).
77. Arias-Santiago S, Orgaz-Molina J, Castellote-Caballero L, et al. Atheroma plaque, metabolic syndrome and inflammation in patients with psoriasis. Eur J Dermatol. 2012;22(3):337-44.
78. Gonzalez-Cantero A, Gonzalez-Cantero J, Sanchez-Moya AI, et al. Femoral artery ultrasound for improving the detection of atherosclerosis in psoriasis. J Am Acad Dermatol. 2018.
79. Blai Coll, Angels Betriu, Steve B. Feinstein, Jose M. Valdivielso, Jose L. Zamorano, Elvira Fernández.. (2013). Papel de la ecografía carotídea en la reclasificación del riesgo cardiovascular de sujetos de riesgo bajo-intermedio. Resvista Española de Cardiología, 66, 929-934.
80. Zhao W, Wu Y, Shi M, et al. Sex Differences in Prevalence of and Risk Factors for Carotid Plaque among Adults: A Population-based Cross-Sectional Study in Rural China. Sci Rep. 2016;6:38618.