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ANALISYS OF EXTRASKELETAL FUNCTION OF VITAMIN D AND CARDIOVASCULAR RISK FACTORS IN PATIENTS WITH PSORIASIS.

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Fdo. Miguel Ángel Arrabal Polo

ANÁLISIS DE FUNCIONES EXTRAESQUELÉTICAS DE LA VITAMINA D Y FACTORES DE RIESGO CARDIOVASCULAR EN PACIENTES CON PSORIASIS.

"La ciencia es la progresiva aproximación del hombre al mundo real".

Max Planck*Físico Alemán (1858-1947)*

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ABSTRACT

INTRODUCTION

In recent years there has been described an increased prevalence of cardiovascular disease associated with increased mortality in patients with psoriasis. Psoriasis is a chronic inflammatory disease pathogenically characterized by an unbalanced immune expression in favor of a predominant Th1 response. Moreover, cardiovascular disease today is defined as a chronic inflammatory disease with pathogenic phenomena similar to those observed in plaque psoriasis.

Moreover, a lower level of vitamin D has been described in connection with certain chronic inflammatory diseases, such as multiple sclerosis, lupus or rheumatoid arthritis. Also, it has been noted an inverse relationship between serum vitamin D and the prevalence and mortality associated with cardiovascular diseases.

On this basis, we decided to conduct a study to compare cardiovascular riskfactors(through assessment of the presence of MS and carotid atheroma) in psoriatic patients compared with a control group and evaluate this cardiovascular riskwith clinical parameters of psoriasis and inflammatory parameters.

Moreover, in the literature there is a lack of studies on vitamin D in patients with psoriasis and their relationship with cardiovascular risk. Therefore, we

evaluated the serum concentration of vitamin D in patients with psoriasis compared with a control group and its relationship with SM and carotid atheromatosis.

PATIENTS AND METHOD

This study included 480 individuals, corresponding to 403 participants (180 controls, 159 patients with psoriasis without arthritis and 64 patients with psoriatic arthritis). Differences between number of inclusions and number of participants are due to an overlapping of patients with psoriasis and psoriatic arthritis, some of which have participated in different studies. All patients came from outpatient clinic of Dermatology and Rheumatology Departments. Controls were also recruited from the same outpatient clinics.

Anamnesis and physical exploration and blood samples were performed in both patients and controls evaluating clinical parameters related to psoriasis (family history, PASI, BSA, time with psoriasis), biochemical parameters and variables related with metabolic syndrome (based on ATP III criteria), acute phase reactants or 25-hydroxyvitamin D. Carotid intima-media thickness and atheromatous plaque was measured by ultrasound examination, 1 cm proximal to carotid bulb.

As a particular aspect, studies which vitamin D was evaluated the interval time was very important. So, controls were recruited and evaluated strictly in the same week that their corresponding individual case.

RESULTS

A higher prevalence of MS and carotid intima-media thickness was found in patients with psoriasis compared with a control group. Furthermore, clinical parameters of psoriasis, such as PASI and time with psoriasis, were directly associated withcarotidintima-media thickness. All components of metabolic syndrome (waist circumference, systolic blood pressure, diastolic blood pressure, triglycerides, and fasting glucose) were directly and significantly associated with clinical parameters of psoriasis (PASI, BSA, and time with psoriasis), except fasting glucose for PASI and triglycerides and HDL-c for time with psoriasis. HDL-c was inversely correlated with clinical parameters of psoriasis. Acute phase parameters (CRP, fibrinogen, D-dimer, ESR) showed asignificant higher value in psoriasis than controls. All this parameters were significant and positively correlated with PASI and BSA; all except ESR showed a higher value in patients with atheroma plaques; CRP showed a positive and significant correlation with waist circumference, triglycerides and negatively with HDL-c; fibrinogen showed a positive and significant correlation with waist circumference, triglycerides and systolic and diastolic blood pressure; D-dimer showed a positive and significant correlation with waist circumference, triglycerides and systolic blood pressure and inversely correlated with HDL-c.

Moreover, we found a significant deficiency of 25-OHD in patients with psoriasis compared to a control group after controlling for potential confounders.Age, body mass index, and CRP were inverse and independently associated with a

lower level of 25-hydroxyvitamin D. In patients with psoriasis, BMI>27 kg/m^2 showed a higher risk of vitamin D deficiency.

Serum concentration of 25-hydroxyvitamin D has been inversely correlated with the presence of MS and its components in patients with psoriasis; association not found in controls. Analog relationship has been found between concentration of 25-hydroxyvitamin D and subclinical atheromatosis (measured as maximal intima-media thickness) in patients with psoriasis.

Finally, it must be signaled that the inverse relationship found between vitamin D and metabolic parameters in patients with psoriasis without arthritis has not been found in patients with psoriatic arthritis.

CONCLUSIONS

Psoriasis is a disease showing a systemic involvement that goes beyond the cutaneous level, with increased cardiovascular risk (measured as the presence metabolic syndrome and degree of subclinical carotid atheromatosis), an increase in inflammatory parameter values. This inflammatory underground correlated directly with components of metabolic syndrome and subclinical atheromatosis, suggesting a pathogenic association. Therefore, emphasis should be placed on the management of cardiovascular risk in this group of patients and include this approach in the treatment of inflammatory disease, past or psychological morbidity associated cutaneous psoriasis.

Moreover, a deficit on serum 25-hydroxyvitamin D concentration has been found in patients with psoriasis *vs* a control group. The serum 25-OHD

concentration has been inversely correlated with cardiovascular risk (measured as presence of metabolic syndrome and degree of subclinical carotid atheromatosis). This inverse association has not been found in control group. These studies suggest that psoriasis could be an ideal condition for evaluating the benefit of vitamin D supplementation at dermatological and cardiovascular level.

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III.2 Deficiency of serum concentration of 25-hydroxyvitamin D in psoriatic patients: A case-control study. **J Am Acad Dermatol. 2012; 67 (5): 931-8.**

III.3 Association of 25-hydroxyvitamin D with metabolic syndrome in patients with psoriasis: A case-control study. **Acta Derm Venereol.** (pendiente de referencia).

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I. INTRODUCCIÓN

I. INTRODUCCIÓN

I.1 INMUNOPATOGENIA DE LA PSORIASIS

La psoriasis es una enfermedad inflamatoria crónica manifestada habitualmente como placas eritemato-descamativas y en menor proporción como erupción pustulosa o eritrodermia. Además la artritis psoriásica, presente en el 7-30%de los pacientes con psoriasis (Zachariae H, 2003), puede manifestarse antes, simultáneamente o tiempo después de la clínica cutánea. Estas manifestaciones son el resultado de una alteración en el equilibrio inmunológico cuya causa desencadenante y condiciones favorecedoras (del propio paciente) no son bien conocidas en este momento. En cualquier caso, independientemente de la condición primaria, actualmente se describe cada día mejor el proceso inmunológico que conduce a la expresión clínica de la psoriasis. Se trata de un proceso complejo en el que participa el sistema inmune innato y adquirido (Lowes MA y cols, 2007).

Inicialmente parecen activarse elementos del sistema innato, como los queratinocitos y las células dendríticas (CDs). Así, se ha descrito que distintas circunstancias, como traumatismo, infecciones, medicamentos pueden desencadenar una respuesta patológica, provocando la activación de los queratinocitos que liberan distintas citoquinas (IL-1, TNFα) y proteínas de choque térmico. Por otra parte, las CDs pueden ser activadas por medio de la unión a distintos antígenos mediante la unión a sus receptores *"toll-like".* Las citoquinassecretadas por los queratinocitos favorecen la activación de las CDsde

la dermis y epidermis, que a su vez son capaces de producir nuevas sustancias (Lowes MA y cols, 2007; Menter A y cols, 2008; Nickoloff BJ & Nestle FO, 2004; Mackenzie B y cols, 2006; Guttman-Yassky y cols, 2007). Una vez que las CDs son activadas procesan un antígeno (ambiental o endógeno, aún no determinado) y migran a los ganglios regionales para presentarlos a los linfocitos T (LT). En este momento es cuando la inmunidad adquirida comienza a participar. Con el desarrollo de la sinapsis inmunológica se produce la activación de los linfocitos, que en el caso de la psoriasis se asocia principalmente a una participación de de los LTCD4+ tipo 1 (LTh1: productores de INF-γ, TNF-α e IL-2) y tipo 17 (Th17: productores de IL-17, TNF-α, IL-6 e IL-22) y LTCD8+ tipo 1 (LTc1: productor de TNF-α, INF-γ, perforinas and granzima B) [Lowes MA y cols, 2007; Menter A y cols, 2008; Nickoloff BJ & Nestle FO, 2004; Mackenzie B y cols, 2006; Guttman-Yassky y cols, 2007].

Los linfocitos activados migran hacia la piel en virtud de la expresión de moléculas de adhesión en su membrana plasmática (CLA –antígeno leucocitario cutáneo- y LFA-1 –antígeno 1 asociado a la función leucocitaria-) y las moléculas de adhesión expresadas en la membrana plasmática de las células endoteliales activadas (E-selectina e ICAM-1 –molécula de adhesión intercelular 1-) (Lowes MA y cols, 2007; Menter A y cols, 2008; Nickoloff BJ& Nestle FO, 2004). Cuando los linfocitos alcanzan la dermis interaccionan con las CDs, formando nuevas sinapsis inmunológicas, generando nuevas citoquinas que conducen a la amplificación y mantenimiento del proceso inflamatorio (Lowes MA y cols, 2007; Menter A y cols, 2008; Nickoloff BJ& Nestle FO, 2004). Entre

estas citoquinas hay que destacar la IL-12 y la IL-23 (Mackenzie B y cols, 2006). Mientras que la IL-12 favorece la proliferación de LTh1 la IL-23 favorece la proliferación de LTh17 (Mackenzie B y cols, 2006; Guttman-Yassky y cols, 2007). La proliferación de LTh1 y LTh17 se atribuye también a la reducción de los LT reguladores (Lowes MA y cols,2007; Guttman-Yassky y cols, 2007; Sugiyama H y cols, 2005). Por tanto, se puede resumir que el resultado final es una respuesta inmunológica desequilibrada, con predominio de los subtipos celulares Th1 y Th17, con un déficit de la función de los LT reguladores.

I.2 ENFERMEDAD CARDIOVASCULAR

I.2.ASÍNDROME METABÓLICO

El síndrome metabólico (SM) se podría definir como un desorden metabólico que conduce a la presencia de múltiples factores de riesgo cardiovascular en una misma persona. Esta confluencia de factores de riesgo cardiovascular (FRCV)se da en el SM en una proporción mayor de lo que se esperaría de la incidencia de cada uno de estos FRCV por separado en la población general. Esta confluencia mayor de lo esperada sugiere la idea de que existe un elemento patogénico común que daría consistencia a toda esta constelación como síndrome. Además, el SM parece ser algo más que una simple confluencia de FRCV puesto que se ha mostrado que supone un riesgo en el desarrollo de enfermedad cardiovascular (ECV) mayor que cada uno de sus elementos componentes actuando por separado (Gisondi P y cols, 2007).

El elemento patogénico clave ha sido en los últimos años centrado en la resistencia a la insulina, aunque la cuantificación de la insulina *in vivo* no está siempre fuertemente correlacionada con la presencia del SM (Hanley AJ y cols, 2003). Así, Unger RH (Unger RH, 2003) sugiere una alternativa patogénica: la resistencia a la leptina. El déficit o resistencia a leptina se ha asociado con acúmulo visceral de triglicéridos (hígado, músculo o páncreas) [Unger RH, 2003] o con un estado de hiperinsulinemia (Seufert J, 2004).

Existen criterios diagnósticos elaborados por distintas sociedades y academias científicas ampliamente conocidos, como los criterios de la OMS (Alberti KGMM& Zimmet PZ, 1998), los criterios EGIR (Balkau B & Charles MA, 1999) o los criterios NCEP-ATP-III 2005 (Grundy SM y cols, 2005). Es importante aclarar que estos son criterios que tienen un valor clínico, práctico, que tienen como fin identificar de una manera sencilla, por medio de parámetros fácilmente objetivables, aquellos individuos con mayor probabilidad de estar padeciendo un SM. No obstante, hoy día sabemos que el SM, como condición asociada a un incremento de riesgo cardiovascular es mucho más que un incremento de perímetro abdominal o de la glucosa. Así, actualmente se acepta la asociación entre el SM y un estado pro-inflamatorio (Sutherland J y cols, 2004). Entre las citoquinas pro-inflamatorias existe un incremento de la interleuquina 6 (IL-6), la resistina, TNFα y proteína C reactiva (PCR), reflejando un aumento de su producción por el tejido adiposo en exceso (Trayhurn P & Wood IS, 2004). Se sugiere que la resistencia a la insulina encontrada en hígado, músculo y tejido adiposo pueda estar asociada al menos en parte con la producción de citoquinas pro-inflamatorias provenientes de los macrófagos residentes en el tejido adiposo (Weisberg SP y cols, 2003; Xu H y cols, 2003). Es más, según algunos estudios esta resistencia podría ser resultado directo de esta carga de citoquinas pro-inflamatorias (Neuschwander-Tetri BA &Caldwell SH, 2003). Por tanto, se centraría la atención patogénica del SM en su naturaleza inflamatoria, siendo la principal fuente generadora el tejido adiposo actuando como "órgano endocrino".

I.2.BINMUNOPATOGENIA DE LA ATEROMATOSIS

Las placas de ateroma pueden ser definidas desde un punto de vista estrictamente morfológico como engrosamientos focales y asimétricos de la capa más interna de la pared vascular, la íntima. Desde un punto de vista citopatológico se puede componer, dependiendo del estadio evolutivo, del propio endotelio vascular de la íntima, músculo liso, lípidos y de manera importante tanto desde el punto de vista cuantitativo como funcional de células inflamatorias (Hansson GK, 2005). La importancia del conocimiento de la placa de ateromatosis, como lesión elemental, es su implicación patogénica en las distintas manifestaciones de la enfermedad cardiovascular (isquemia cardíaca, isquemia cerebral, arterial periférica, renal…).

La hipercolesterolemia es un factor de riesgo clásicamente conocido. Así, se sabe que los ratones utilizados normalmente en el laboratorio no desarrollan placas de ateromatosis. Sin embargo, delecciones específicas del gen de la apolipoproteína E ("apoE knockout mice") generan hipercolesterolemia que conduce al desarrollo de placas de ateroma en estos ratones; lo mismo ocurre en ratones que no expresan los receptores para LDL(Zadelaar S y cols, 2007). No obstante, se sabe que la hipercolesterolemia no actúa en el proceso de ateromatosis por simple depósito físico, sino que la retención e infiltración de la íntima por partículas de LDL desencadena una respuesta inflamatoria en la pared de la arteria (Skålén K y cols, 2002; Leitinger N, 2003). Además, la modificación de las partículas de LDL por oxidación y procesado enzimático puede dar lugar a la liberación de fosfolípidos, que activan las células

endoteliales (Leitinger N, 2003). Por otra parte, determinados patrones de flujo con grandes variaciones u oscilaciones de tensión son capaces también de facilitar la activación endotelial, estimulando el incremento de expresión de moléculas de adhesión y genes relacionados con la inflamación (Dai y cols, 2004). De esta manera, estos dos elementos (el depósito de lípidos y la tensión hemodinámica) son dos elementos iniciales en el desarrollo de la ateromatosis, estimulando una actividad de tipo inflamatoria.

El primer elemento forme procedente de la sangre periférica es la plaqueta, capaz de unirse a la superficie de la íntima por medio de las glicoproteínas Ib y IIb/IIIa. La asociación a la superficie endotelial puede a su vez favorecer la activación endotelial.Dentro del proceso inflamatorio desencadenado el macrófago es una célula clave. Durante el comentado proceso de activación endotelial, se libera desde la íntima una citoquina conocida como factor estimulante de colonias de macrófagos, que permite la diferenciación de los monocitos circulantes en la sangre periférica en macrófagos capaces de integrarse en la placa de ateromatosis en desarrollo (Smith JD y cols, 1995). Estas células presentan dos receptores de especial importancia, los *"scavenger receptors"* (o literalmente los "receptores basureros") y los receptores tipo *Toll-like*. Los primeros reconocen distintas partículas, entre ellas las partículas de LDL modificadas (oxidadas) a las que previamente hemos hecho referencia. Conforme el colesterol procedente de las partículas fagocitadas de LDL se acumula, los macrófagos evolucionan hacia el tipo morfológico conocido como *"foam cells"* (o "células espumosas"), tipo celular característico de la

ateromatosis. Los otros receptores, los tipo *Toll-like* se pueden unir también a distintas partículas pero a diferencia de los *"scavenger receptors"* son capaces de producir la activación del macrófago (Peiser L y cols, 2002), convirtiéndolo en una fuente de citoquinas inflamatorias (que producen un efecto de potenciación inflamatoria), proteasas y radicales de oxígeno y nitrógeno citotóxicos. Efectos similares se producen en otras células que contienen receptores tipo *Toll-like*, como células dendríticas, mastocitos o células endoteliales (Edfeldt K y cols, 2002). La importancia del sistema de los receptores tipo *toll-like* ha sido puesta de manifiesta en modelos animales (ratones *"apoE-knockout"*), en los que la inhibición de la vía de señalización de estos receptores ha conducido a la inhibición de la aterosclerosis en estos animales (Bjorkbacka H y cols, 2004). En este contexto, nuestro grupo de investigación ha encontrado una expresión genética de receptores tipo *toll-like* tipo 2 y 4 significativamente mayor en pacientes con psoriasis respecto a un grupo control.En el subgrupo de pacientes con placas de ateroma esta expresión fue significativamente mayor que en los controles y mostró una correlación positiva y estadísticamente significativa respecto al nivel plasmático de TNF-α (García-Rodriguez S y cols, 2013).

Además de células del sistema innato, participa también la defensa adquirida, con un patrón tipo Th1. Se han mostrado poblaciones linfocitarias específicas frente a antígenos relacionados con las partículas LDL,proteínas de choque térmico 60 *("heat-shock protein 60")* y proteínas de chlamydia (Xu Q, 2002; Stemme S y cols1995; de Boer OJ y cols, 2000). La unión de los linfocitos a su

correspondiente antígeno conduce a la producción y liberación de distintas citoquinas inflamatorias, expresión de moléculas de superficie y enzimas. La activación del patrón Th1 conduce a la activación de macrófagos, favoreciendo el círculo vicioso inflamatorio (Szabo SJ y cols, 2003).

No todas las citoquinas tienen un papel pro-inflamatorio. Así, existen otras citoquinas con carácter contrarregulador, como la IL-10 y el factor de crecimiento transformador-β (TGF-β). De esta manera, la inhibición de estas sustancias mediante métodos farmacológicos o genéticos conduce a una exacerbación del proceso de ateromatosis en modelos animales (Mallat Z y cols, 1999; Pinderski LJ y cols, 2002; Caligiuri G y cols, 2003; Robertson AKL y cols, 2003).

En resumen, desde los factores iniciadores (lípidos y tensión hemodinámica) se produce un mecanismo patogénico que implica el desarrollo de una red inflamatoria que favorece la llegada de nuevas células inflamatoriasque, a su vez, perpetúan e incrementan el proceso inflamatorio y generan la migración de músculo liso y el acúmulo de lípidos y células inflamatorias desde sangre periférica.De esta manera, la ECV puede ser concebida desde el punto de vista patogénico como una enfermedad inflamatoria crónica, al igual que otras enfermedades autoinmunes como la artritis reumatoide, la diabetes mellitus tipo 1 o la psoriasis. El paralelismo patogénico existente entre aquélla y éstas podría justificar, al menos en parte, el incremento de riesgo cardiovascular descrito respecto a la población general.

I.3 VITAMINA D

I.3.A CONCEPTOS FISIOLÓGICOS CLÁSICOS: SÍNTESIS Y HOMEOSTASIS

El término "vitamina" fue acuñado por el bioquímico polaco Casimir Funk (1884-1967). En el siglo XIX ya era conocido que el cuerpo humano necesitaba proteínas, carbohidratos, grasa y sal para un normal funcionamiento. No obstante, Funk se planteaba que existían enfermedades por déficit nutricional y que no era debido a estos componentes ya conocidos. Él, como otros investigadores, se planteaba que la incidencia de determinadas enfermedades en marineros embarcados durante mucho tiempo debía corresponder a la carencia de algún tipo de elemento necesario obtenido del exterior y que era necesario para una normal fisiología. Señaló que las poblaciones que consumían arroz integral eran menos tendentes a desarrollar beri-beri y en 1912 publicó su libro "Teoría de las Vitaminas". Su hipótesis fue comprobada al descubrir en la cáscara del arroz una sustancia que prevenía el beriberi, la vitamina B1 o tiamina (descubierta por el doctor Robert Williams en 1936).

El término "vitamina" proviene del latín "vita" (vida) y "amina" (sustancia química); no obstante, hoy se sabe que no todas las vitaminas están formadas por aminas. Desde el punto de vista funcional, la vitamina concuerda en gran medida con lo planteado por Funk: sustancia exógena que no puede ser sintetizada por el propio organismo y que, en mínimas concentraciones, es necesaria para el normal funcionamiento del organismo.

El complejo vitamina D son un conjunto de esteroles, íntimamente relacionados estructuralmente con la molécula de colesterol. Desde el punto de vista funcional, la vitamina D activa (1,25-dihidroxivitamina D3 o colecalciferol) es una hormona. Aunque la vitamina D se puede obtener por medio de la dieta, en forma de ergocalciferol (D2), también puede ser sintetizada por la piel mediante exposición a radiación ultravioleta B (siendo éste el mecanismo más importante desde el punto de vista cuantitativo para obtener vitamina D -Holick MF, 1994; Holick MF, 2003-). Por tanto, según este último dato difiere del conceptode vitamina.

Son pocos los alimentos que contienen de forma natural cantidades significativas de vitamina D2 y D3. No obstante, a lo largo de la primera mitad del siglo XX, con el descubrimiento de la asociación entre vitamina D y raquitismo se fue popularizando cada vez más la leche enriquecida en vitamina D.No obstante, como se ha comentado, la exposición solar es el medio más eficiente para la obtención de vitamina D. Esto justifica que las primeras grandes epidemias de raquitismo fueran documentadas en el norte de Europa durante la Revolución Industrial. Se generaron grandes núcleos de urbanización, con viviendas próximas las unas a las otras que, junto a la combustión de carbón y madera que contaminaba la atmósfera, dificultaban la exposición directa de los niños a la radiación solar. Estos niños mostraban retraso del crecimiento y alteraciones esqueléticas, manifestaciones propias del raquitismo (Holick MF, 1994).Sniadecki publicó en 1822 sus observaciones, mostrando un incremento de prevalencia de raquitismo entre aquellos niños

que vivían en el interior de las ciudades, respecto a niños que vivían en áreas rurales (MF Holick, 2004). Siguiendo la hipótesis de que la falta de exposición podía ser el origen del raquitismo, distintos autores iniciaron estudios orientados a evaluar el beneficio de la exposición solar (Palm TA, 1890; Huldschinsky K, 1919) u observaron el beneficio de la exposición solar sobre el raquitismo, como Hess y Unger (Hess AF& Unger LJ, 1921), que confirmaron el beneficio de la exposición solar en niños expuestos a la misma en el techo del hospital en la ciudad de New York. Así, de una manera progresiva se fue conformando la importancia de la exposición solar en relación con esta enfermedad y condujo a algunos autores a exponer distintos sustancias, incluidas grasas y aceites vegetales a radiación solar, mostrando que dichas sustancias adquirían poder antirraquítico (Hess AF & Weinstock M, 1924; Steenbock H & Black A, 1924), conduciendo posteriormente a la fortificación de alimentos que tuvo un gran impacto en aquellos países que lo implantaron.

Actualmente se sabe que la exposición solar, concretamente a la radiación ultravioleta B (RUVB) -290-315 nm-, conduce a la fotólisis del 7-dehidrocolesterol, presente en la membrana plasmática de los queratinocitos y fibroblastos dérmicos (Holick MF y cols, 1995). La absorción de la radiación por los enlaces dobles del anillo B del 7-dehidrocolesterol conduce a su apertura generando la previtamina D3. Una vez formada la previtamina D3, aun integrada en la membrana plasmática celular, se produce una transformación de los dobles enlaces del anillo B de la estructura molecular conduciendo a una forma termodinámicamente más estable (isomerización térmica), la vitamina

D3, que es vertida al espacio extracelular (Holick MF y cols, 1995). A nivel capilar, la proteína fijadora de vitamina D3 tiene una especial afinidad por la vitamina D3 y la transporta a la circulación general (Holick MF y cols, 1995; Haddad JG y cols, 1993).

El siguiente paso en la activación de la vitamina D es la hidroxilación del carbón 25 a nivel hepático. Se han planteado distintas enzimas como posibles candidatas, de las cuales tres fueron excluidas: CYP2C11, puesto que no es expresada en humanos (Sareem K y cols, 1984); CYP27A1, puesto que en modelos "knockouts" se encontraron niveles normales de vitamina D (Rosen H y cols, 1998); y CYP3A4, que no ejerce hidroxilación de la vitamina D3 (Gupta y cols, 2004). Sin embargo, CYP2R1parece ser un buen candidato. Así, Cheng JB y cols publicaron la mutación del gen 2R1, identificado en un paciente con bajo nivel de 25-OHD y raquitismo (Chen JB y cols, 2004).

El siguiente paso para obtener la forma activa de la vitamina D consiste en la hidroxilación 1α, dando lugar a la 1,25-(OH)2D3. Este paso tiene lugar a nivel renal por medio de la 1α-hidroxilasa (Fraser DR & Kodicek E, 1970). La actividad de la 1α-hidroxilasa a nivel renal está altamente regulada. La ingesta diaria de calcio puede regular la actividad de dicha enzima de dos maneras, directamente a partir de los cambios producidos en la concentración sérica de calcio e indirectamente al influir en la secreción de hormona paratiroidea (PTH) (Omdahl JL y cols, 1972). No obstante, hay que decir que este efecto es mayoritariamente realizado a través de su influencia sobre la PTH (Garabedian M y cols, 1972).

I.3.BFACTORES IMPLICADOS EN LA CONCENTRACIÓN SÉRICA DE VITAMINA D

Existen distintos y variados factores externos que influencian el nivel sérico de vitamina D. La dieta influye directamente en la concentración sérica de 25-OHD (Holick MF, 1981). Pocos son los alimentos naturalmente ricos en vitamina D, entre los cuales destacan el pescado azul, como el atún, la caballa, la sardina o el salmón, los champiñones o el huevo; otro pequeño grupo de alimentos están enriquecidos artificialmente como la leche, el zumo de naranja y algunos cereales (tabla de equivalencias de vitamina D enZhang R & Naughton DF, 2010). No obstante, la principal variable externa en relación con la concentración sérica de vitamina D proviene de la exposición solar (Holick MF, 1994; Holick MF, 2003). Evidentemente, su influencia varía directamente en función del tiempo de exposición, de manera que a mayor tiempo de exposición mayor concentración sérica de vitamina. No obstante, este incremento no es lineal a lo largo del tiempo, de manera que en exposiciones mantenidas el incremento de concentración sérica es progresivamente menor, lo cual tiene valor evitando la intoxicación por vitamina D. Esto ocurre porque la pre-vitamina D3 y la vitamina D3 que no alcanzan la circulación y son sobreexpuestos a la RUVB, absorben esta energía dando lugar a distintos foto-productos con una menor actividad sobre el metabolismo del calcio (Holick MF, 1994; Holick MF, 1995; Holick MF, 2003).

Por otra parte, hay tres factores relacionados con la perpendicularidad de la incidencia de la radiación respecto a la Tierra que influyen de manera determinante, como son el horario de exposición (siendo más eficientes las horas centrales del día, por presentar la radiación solar una mayor perpendicularidad), la latitud geográfica y la estación del año. Finalmente, en relación con el grado de dispersión de la radiación solar a su paso por la atmósfera también influyen otros factores como la altitud y características atmosféricas relacionadas con la nubosidad, contaminación y partículas en suspensión (Holick MF, 1994; Holick MF, 2003; Webb AR y cols, 1988).

Siendo los elementos externos importantes, hay que decir que dos personas expuestas exactamente a los mismos elementos externos no tendrán la misma concentración sérica de vitamina D, puesto que hay caracteres fenotípicos, propios del individuo, que influyen en la síntesis cutánea de vitamina D. De esta manera, a mayor edad menor capacidad de síntesis cutánea de vitamina D, comportándose como una variable inversamente relacionada con la concentración sérica de vitamina D. Este factor es especialmente relevante en edades avanzadas de la vida. Esto es así porque la cantidad de 7-dehidrocolesterol se encuentra en concentraciones relativamente constantes a lo largo de toda la vida, hasta alcanzar la edad avanzada en que la concentración decrece (Holick MF y cols, 1989;MacLaughlin J y cols, 1985). Por otra parte, el fototipo es otro elemento a tener en cuenta, puesto que la melanina cumple una función protectora esencial absorbiendo los fotones de RUVB. Así, aquellos individuos con un fototipo más alto presentan una mayor

dificultad para la síntesis cutánea de vitamina D y a igual exposición la síntesis de vitamina D es menor (Clemens TL y cols, 1982). Desde un punto de vista antropológico este hecho es fácilmente entendible: la mayor cantidad de melanina sintetizada por pacientes con fototipo alto tiene un papel protector frente a la radiación solar, aunque ello conlleve una menor fotólisis de la 7-dehidrocolesterol para iniciar la síntesis de vitamina D. No obstante, no supone un problema cuando estos individuos se encuentran en áreas geográficas con un importante grado de radiación diaria. No obstante, actualmente individuos con un fototipo mayor en latitudes geográficas altas están más predispuestos a un menor nivel de vitamina D. Por el mismo principio, los fotoprotectores solares dificultan la síntesis de vitamina D de forma significativa, de manera que un producto con un factor de protección solar del 8 bien utilizado conduce a una reducción en la síntesis de vitamina D > 98% (Matsuola LY, 1987).

Finalmente, el índice de masa corporal se relaciona de manera indirecta con la concentración sérica de vitamina D. Al tratarse la vitamina D de una sustancia lipofílica, queda retenida en el panículo adiposo siendo su biodisponibilidad menor que la de una persona con iguales condiciones que él pero con menor nivel de IMC (Botella-Carretero JI y cols, 2007).

En un tercer nivel se puede decir que dos personas expuestas a las mismas condiciones ambientales y exactamente con las mismas características fenotípicas comentadas presentarán distinta concentración sérica de vitamina D en función de distintos caracteres genéticos relacionados con la síntesis y el metabolismo de la vitamina. Así, como ha sido recientemente descrito en el

estudio de Wang TJ y cols (Wang TJ y cols, 2010),queda demostrada la determinación genética de la concentración de vitamina D. Analizan el nivel sérico de 25-OHDen un grupo poblacional y encontraron una asociación estadísticamente significativa entre algunos polimorfismos de nucleótido único (SNP) localizados en los *loci* 4p12, 11q12 y 11p15 y una concentración significativamente menor de 25-OHD respecto a los individuos que no presentan dichos SNP. El polimorfismo situado en el locus 4p12 (rs2282679) se localiza en la proximidad del gen GC (proteína fijadora de vitamina D); el polimorfismo del 11q12 (rs7944926) se localiza próximo al gen DHCR7 (7-dehidrocolesterol reductasa); y el polimorfismo del 11p15 (rs10741657) se encuentra cerca del CYP2R1 (enzima 25-hidroxilasa). Por tanto, demostraron variaciones genéticas en *loci* sensibles en el metabolismo de la vitamina D que determinan diferencias en el nivel sérico de 25-OHD.

Como vemos, la concentración sérica de 25-OHD es influenciada por múltiples variables externas e intrínsecas, lo que la convierte en una variable controvertida desde el punto de vista metodológico. Para alcanzar una adecuada validez interna en un estudio tienen que ser controlados la mayor cantidad de variables posibles en el momento de diseñar el estudio, con una adecuada estratificación de las variables en los grupos a estudiar y/o mediante su incorporación en los análisis estadísticos multivariantes posteriores.

Actualmente sabemos que el mejor parámetro para evaluar el estatus de vitamina D en el organismo es la 25-OHD. Esto es así por tratarse de una sustancia con una vida media de 2-3 semanas [a diferencia de la 1,25-

(OH)2D3, con una vida media de6 horas] y por encontrarse en un paso de la regulación por PTH "previo". Es decir, la 1,25-(OH)2D3 se mantiene en unos niveles más o menos regulares gracias a la regulación por la PTH. De esta manera, si el nivel de 1,25-(OH)2D3 es bajo se produce un incremento de la PTH que estimula la 1α-hidroxilasa renal aumentando los niveles de 1,25-(OH)2D3 en plasma a partir de 25-OHD; al contrario, cuando los niveles de 1,25-(OH)2D3 presenta unos niveles incrementados se produce la inhibición de la acción de la PTH de manera que no se produce más 1,25-(OH)2D3. Por tanto, la regulación fisiológica permite mantener unos niveles estables de forma activa de vitamina D independientemente del estatus de vitamina D del organismo. En cambio los niveles de 25-OHD, sustancia "previa" a la síntesis de 1,25-(OH)2D3, mantiene un nivel coherente con el estatus de vitamina D del organismo. Así, si el estatus de vitamina D es bajo, la 25-OHD presenta un nivel bajo en plasma (incrementando la conversión en 1,25-(OH)2D3 por la PTH), mientras que si el estatus de vitamina D es alto la 25-OHD presenta un nivel elevado en plasma (cese de conversión a 1,25-(OH)2D3 por la PTH).

En resumen podemos decir que existen dos formas principales de vitamina D, la D2 (ergocalciferol) sintetizada por las plantas y no producida por el cuerpo humano, y la D3 (colecalciferol) que puede ser producida por el cuerpo humano. En cualquier caso, tras la producción por el cuerpo (D3) o su ingesta (D2 o D3), la vitamina D es transformada en 25-OHD (calcidiol) circulante en plasma y susceptible de ser transformada por el riñón en 1,25-(OH)2D3 (calcitriol), que es la forma biológicamente activa de la vitamina D. La

reducciónde 1,25-(OH)2D3 es el estímulo que da lugar a la secreción de PTH, hormona que aumenta la producción de 1,25-(OH)2D3 al activar a 1α-hidroxilasa renal. La 1,25-(OH)2D3 se encarga de aumentar la absorción de calcio en los intestinos favoreciendo el metabolismo anabólico óseo. El propio aumento de la 1,25-(OH)2D3 es el encargado de actuar como retroalimentación negativa para reducir su síntesis a partir de 25-OHD.

I.3.C NUEVAS PERSPECTIVAS: LOCALIZACIONES DEL RECEPTOR DE VITAMINA D Y POTENCIALES FUNCIONES EXTRAESQUELÉTICAS

Hoy día, en los países occidentales, difícilmente podríamos pensar en la asociación de la vitamina D con el raquitismo de una manera tan evidente como ocurrió en la época de la Revolución industrial. En cambio a partir de entonces y en los primeros años del siglo XX se fijaron algunos conceptos que hoy son conceptos clásicos de la fisiología. No obstante, la vitamina D parece algo más que la "hormona del hueso"; distintas localizaciones para el receptor de la vitamina D (RVD) y enzimas del metabolismo de la vitamina D (como la 1α-hidroxilasa) (Hewison M y cols, 2004) se fueron progresivamente descubriendo en distintos tejidos no relacionados con el metabolismo fosforo-cálcico. La fuerza de los años de evolución han hecho que cada elemento de nuestra economía tenga una razón, un porqué o como decía mi profesor de anatomía (Dr. Luis Álvarez): "en el cuerpo humano las cosas no están puestas ahí por el ayuntamiento". Por tanto, pensando en la significación biológica y clínica que puedan tener la presencia de elementos del metabolismo y la fisiología de la vitamina D en lugares no propios del metabolismo fosforo-cálcico ha abierto una puerta a la investigación sobre las "funciones extraesqueléticas" de la vitamina D.

Sin ser el objetivo de la presente tesis, los médicos en general y los dermatólogos en particular conocen la utilidad clínica del uso tópico del

calcipotriol en el tratamiento de la psoriasis, como ejemplo de función extraesquelética de la vitamina D. Los queratinocitos tienen RVD y la exposición a 1,25-(OH)D2 mostró una marcada acción antiproliferativa, estimulando la diferenciación de los queratinocitos (Smith EL y cols, 1986). El beneficio clínico de la 1,25-(OH)D2 se reflejó en una mejoría de la descamación, el eritema y el espesor de las placas (Smith EL y cols, 1988; Perez A y cols, 1995; Holick MF, 1998).

Influencia inmunorreguladora de la vitamina D

Múltiples descubrimientos han ido progresivamente apoyando la hipótesis de la vitamina D como sustancia con carácter inmunorregulador, como la presencia de receptores de vitamina D en macrófagos, CDs y linfocitos T y B activados, la capacidad de expresar25OHD-1α-hydroxylasa (CYP27B1), enzima productora de 1,25-(OH)2D3 a partir de 25-OHD, o la propia capacidad de 1,25-(OH)2D3 de regular la función y proliferación de estas células.

Aunque el riñón es reconocido como la principal fuente de 1,25-(OH)2D3, esta forma activa de vitamina D puede ser sintetizada también a nivel extrarrenal. CYP27B1, que como hemos dicho se encarga de la conversión de 25-OHD en 1,25-(OH)2D3, es una oxidasa mitocondrial perteneciente al sistema citocromo P450 (CYP450) localizada en su membrana interna. La expresión de CYP27B1 es mayor a nivel de los queratinocitos epidérmicos (Fu GK y cols, 1997; Liu PT y cols, 2007), pero se expresa de manera importante también en otros órganos,

como la próstata, pulmones, intestino, mama, así como en los macrófagos, CDs, linfocitos T y B (Chen S y cols, 2007; Sigmundsdottir H y cols, 2007). En relación con las células del sistema inmune hay que nombrar dos hechos reseñables. La primera es que esta enzima se expresa en las células del sistema inmune sólo cuando están activadas. En segundo lugar, mientras que es bien reconocido que los principales reguladores de la producción de 1,25-(OH)2D3 a nivel renal son la hormona paratiroidea (PTH), el FGF23, el calcio, el fosfato y la propia 1,25-(OH)2D3, interesantemente la actividad de CYP27B1 viene regulado por citoquinas como INF-Y o TNF-α de manera más efectiva que por PTH (la cual no presenta receptores en dichas células) y otros factores de regulación (Bikle DD& Pillai S, 1993).

Las células presentadoras de antígenos, como las CDs y los macrófagos, son las encargadas de iniciar la respuesta adaptativa, activando a las células centrales del sistema: los linfocitos T y B. Hay que señalar que el tipo de célula T activada (CD4 o CD8) o el tipo de T *"helper"* o colaborador (Th1, 2, 17) depende en parte de características ambientales en el momento que se produce la presentación del antígeno. De manera general, se puede decir que la vitamina D cumple una función inhibidora en la expresión del sistema inmune adaptativo. Así, la 1,25-(OH)2D3 reduce la maduración de las CDs al inhibir la expresión de moléculas co-estimuladoras, como HLA-DR, CD40, CD80 y CD86, de manera que se reduce la capacidad de presentación antigénica y activación linfocitaria (van Etten E& Mathieu C, 2005). Por otra parte, en un paso posterior inhibe la respuesta Th1 (patrón productor de INF-Y e IL-2) y la respuesta Th17

(productor de IL-17), mediante la supresión de las IL-12 y la 23 y 6 (Daniel C y cols, 2008). Además, la supresión de la IL-12 favorece el desarrollo de un patrón de respuesta inmune Th2, incrementando la producción de las IL-4, 5 y 13, las cuales a su vez inhiben el patrón Th1 (Daniel C y cols, 2008). Finalmente, el tratamiento de CDs con 1,25-(OH)2D3 puede estimular el desarrollo de células T reguladoras CD4+/25+ (Treg) (Gregori S y cols, 2001), células productoras de IL-10 y que constituyen un elemento clave en la inducción de tolerancia inmunológica (Sakaguchi S y cols, 2008). Además, 1,25-(OH)2D3 es capaz de inhibir de manera directa la producción de importantes citoquinas, como el INF-Y y el TNF-α, a través de elementos de respuesta para la vitamina D localizados en la zona promotora de síntesis de dichas sustancias (Bouillon R y cols, 2008).

Estos argumentos pueden justificar los resultados encontrados en distintas publicaciones en las que se describe un nivel significativamente menor de vitamina D en enfermedades autoinmunes respecto a un grupo control. Es decir, el déficit de vitamina D puede conducir a un disbalance inmunitario a favor de una respuesta Th1, Th17 (características de la respuesta inmune en la psoriasis y la ateromatosis) y a un déficit en la capacidad inmunorreguladora por parte de las Treg (Jeffery LE y cols, 2012).

Influencia a nivel metabólico de la vitamina D

Como ha sido comentado previamente, el RVD se ha localizado en distintos tejidos relacionados con el metabolismo y los parámetros relacionados con el SM. Por tanto, desde el punto de vista epidemiológico y clínico tiene sentido explorar el estado de vitamina D, su correlación y su influencia sobre distintos aspectos relacionados con el estado metabólico y cardiovascular.

En relación con el metabolismo de la glucosa se ha evidenciado la presencia del RVD y la enzima 1α-hidroxilasa en las células β del páncreas (Christakos S y cols, 1979; Johnson JA y cols, 1994; Bland R y cols, 2004). Se ha visto que el déficit de vitamina D está en relación con un deterioro de la secreción de insulina inducida por glucosa y arginina en estudios ex vivo con páncreas perfundidos de ratas (Norman AW y cols, 1980; Kadowaki S & Norman AW, 1984). En estudios in vivo en ratas se han corroborado resultados en el mismo sentido (Cade C y cols, 1986). Todos estos resultados concuerdan con el beneficio mostrado por el suplemento con vitamina D en el perfil glucémico de animales diabéticos (de Souza Santos R y cols, 2005). Además, la vitamina D influye en el metabolismo de la insulina, de manera que el déficit de vitamina D se asocia con menor capacidad de síntesis de insulina y reduce la conversión de pro-insulina en insulina (Bourlon PM y cols, 1999; Ayesha I y cols, 2001).

En cuanto a la relación de la vitamina D con la tensión arterial, los RVD se encuentran en distintas células humanas que pueden contribuir a modificar la misma, como los cardiomiocitos, músculo liso vascular, células endoteliales y células productoras de renina (Li YC y cols, 2002; Li YC, 2003; Zitterman A

&Koerfer R, 2008). Así, podría influir en la modulación de la tensión arterial mediante la intervención sobre la proliferación, inflamación (Mitsuhashi T y cols, 1991) o trombosis (Aihara K y cols, 2004). Además, en estudios experimentales se ha mostrado una función reguladora para la 1,25-(OH)2D3 sobre el eje de la renina-angiotensina mediante la supresión de la expresión del gen de la renina (Li YC y cols, 2002; Li YC, 2003; Zitterman A & Koerfer, 2008; Mitsuhashi T y cols, 1991; Rigby WF y cols, 1987; Aihara K y cols, 2004; Xiang W y cols, 2005); así, se puede producir una sobreexpresión de renina en ratones mediante la inhibición farmacológica de la síntesis de vitamina D (Li YC y cols, 2002). En modelos animales se ha demostrado el beneficio del suplemento de la vitamina D sobre la presión arterial tanto en humanos como en ratas (Lind L y cols, 1989; Lind L y cols, 1987; Pfeifer M y cols, 2001; Wong MS y cols, 2010).

II. JUSTIFICACIÓN Y OBJETIVOS

II. JUSTIFICACIÓN Y OBJETIVOS

II.1JUSTIFICACIÓN E HIPÓTESIS DE TRABAJO

La enfermedad cardiovascular es la primera causa de mortalidad en los países Occidentales con una previsión de incremento de su incidencia.Aunque distintos estudios han descrito la prevalencia de comorbilidades y eventos cardiovasculares en pacientes con psoriasisen relación con un grupo control, pocos estudios han examinado el proceso de aterosclerosis y el SM en pacientes con psoriasis y su relación con niveles de homocisteína, insulina y parámetros inflamatorios.

Por otra parte, diversos estudios han mostrado una relación inversa entre distintas enfermedades inflamatorias crónicas y nivel sérico de vitamina D. La psoriasis es una enfermedad inflamatoria crónica caracterizada por un disbalance inmunológico a favor de un patrón de respuesta tipo Th1. En virtud de la función inmunorreguladora de la vitamina D, dicha relación inversa encontrada en otras enfermedades podría encontrarse en la psoriasis. Ante la falta de estudios evaluando esta hipótesis decidimos iniciar un estudio en este sentido. Por tanto, ¿presentarán los pacientes con psoriasis un déficit de vitamina D respecto a un grupo control?

Por otra parte, se ha señalado una relación inversa entre nivel sérico de vitamina D y mortalidad por causa cardiovascular, con el síndrome metabólico y con el proceso de ateromatosis. La fisiología íntima y los factores que influyen

en las funciones extraesqueléticas de la vitamina D no son aún bien entendidos. La enfermedad cardiovascular se considera actualmente una enfermedad inflamatoria desde el punto de vista patogénico. La placa de psoriasis presenta un importante paralelismo a nivel celular y humoral con la placa de ateromatosis. Si los pacientes con psoriasis presentan un estatus deficitario de vitamina D ¿se presentará la descrita correlación inversa entre el nivel sérico de 25-OHD y el proceso de ateromatosis? ¿los pacientes con psoriasis presentarán diferencias en el grado de dicha correlación comparando con un grupo control?

De manera análoga al planteamiento previo en relación con el SM ¿se presentará una relación inversa entre el nivel de 25-OHD y el SM en los pacientes con psoriasis?¿si se presentará dicha relación, el grado de correlación será mayor que en un grupo control?

II.2 OBJETIVOS PRIMARIOS GENERALES

1.Comparar la prevalencia de SM en pacientes con psoriasis grave respecto a un grupo control.

2. Comparar la prevalencia de placas de ateroma y el grosor de íntima-media en pacientes con psoriasis grave respecto a un grupo control.

3. Comparar el estado de vitamina D en los pacientes con psoriasis con respecto a un grupo control.

4. Evaluar la relación entre vitamina D y síndrome metabólico y ateromatosis carotidea subclínica en pacientes con psoriasis.

II.3 OBJETIVOS SECUNDARIOS

1. Evaluar la relación entre distintos parámetros inflamatorios(PCR, homocisteína, fibrinógeno, dímero-D y VSG) y la presencia de SM y con parámetros clínicos de psoriasis.

2. Evaluar la relación entre distintos parámetros inflamatorios(PCR, homocisteína, fibrinógeno y VSG) y el grado de ateromatosis (grosor de íntima-media).

3. Evaluar la relación entre distintos parámetros clínicos de la psoriasis y la presencia de SM: PASI, BSA, años de evolución de la psoriasis.

4. Evaluar la relación entre distintos parámetros clínicos de la psoriasis y el proceso de ateromatosis carotídea: PASI, BSA, años de evolución de la psoriasis.

5. Evaluar la relación entre el nivel sérico de 25-OHD y distintas variables clínicas del paciente, como edad, sexo, IMC, PASI, BSA, tiempo con psoriasis.

6. Comparación del nivel de 25-OHD entre pacientes con psoriasis sin artritis y artritis psoriásica y la relación de 25-OHD y parámetros metabólicos en pacientes con artritis psoriásica.

II.4 SUJETOS DE ESTUDIO

Los sujetos del presente estudio corresponden a pacientes de las consultas de Dermatología y Reumatología del Hospital Universitario San Cecilio. Los controles fueron seleccionados entre aquellos pacientes que acudían a nuestras consultas por dermatosis no inflamatorias (mayoritariamente tumoraciones benignas como queratosis seborreicas, quistes epidérmicos o nevus) y sin antecedentes de patologías inflamatorias crónicas.

En esta tesis se han incluido 480 muestras,que corresponden con403 individuos (180 controles, 159 pacientes con psoriasis vulgar y 64 pacientes con artritis psoriásica).La diferencia entre el número de muestra o inclusiones en estudio y el número total de individuos se debe a que distintos pacientes con artritis psoriásica y psoriasis vulgar han participado en distintos estudios.

II.5 PROBLEMAS ÉTICOS

Todos los pacientes incluidos en el presente estudio fueron informados por escrito y verbalmente de los objetivos del estudio, los beneficios que se podían extraer para el futuro y riesgos que implicaba su inclusión en el estudio. Estos riesgos derivan de los propios de las pruebas complementarias realizadas (extracción sanguínea y en un grupo de pacientes ecografía carotidea).

El estudio de la posible implicación de la vitamina D como factor patogénico contributivo en el desarrollo de la psoriasis y la enfermedad cardiovascular tiene un eminente interés clínico, al tratarse de condiciones que generan alta morbilidad y, en el caso de la enfermedad cardiovascular, también alta mortalidad.

III. PUBLICACIONES

III. PUBLICACIONES

En este apartado se exponen los distintos trabajos que componen esta tesis. El primer trabajo (Publicación I), publicado en la revista *European Journal of Dermatology*, es un estudio caso-control en el que se evalúa el riesgo cardiovascular en pacientes con psoriasis respecto a un grupo control. Se comprueba un incremento de la prevalencia de ateromatosis y síndrome metabólico en el grupo de pacientes con psoriasis respecto al grupo control. Por otra parte, se evalúa la relación entre ateromatosis y síndrome metabólico y distintos parámetros inflamatorios y clínicos relacionados con la psoriasis.

En el segundo trabajo (Publicación II), publicado en la revista *Journal of the American Academy of Dermatology*, se realiza un estudio caso-control comparando el nivel sérico de 25-OHD entre pacientes con psoriasis y un grupo control; además, se evalúa la relación entre el nivel sérico de 25-OHD y distintos parámetros clínicos y de laboratorio.Este trabajo recibió el Primer Premio del Colegio de Médicos de Almería concedido por la Real Academia de Medicina y Cirugía de Andalucía Oriental (2012).

El tercer trabajo (aceptado para publicación en la revista *Acta Dermato-Venereologica*),es un estudio caso-control que evalúa la relación entre vitamina D y los criterios individuales de SM según la NCEP-ATP III y la propia presencia de SM en un grupo de pacientes con psoriasis y en un grupo control.

El cuarto trabajo (enviado en el momento de escribir la presente tesis doctoral a la revista the *European Journal of Dermatology*) evalúa la relación entre el nivel sérico de 25-OHD y el grado de ateromatosis carotidea (medido como grosor máximo de íntima-media) tanto en pacientes con psoriasis como en un grupo control. Este último trabajo ha recibido el premio a la mejor comunicación en la Sección Territorial Andaluza de la Academia Española de Dermatología del año 2012 (Córdoba), premio a la mejor comunicación del grupo de Epidemiología de la Academia Española de Dermatología (Oviedo 2012) y un Accésit Honorífico de la Real Academia de Medicina y Cirugía de Galicia (2013).

El quinto trabajo(revisado en el momento de escribir la presente tesis doctoral en la revista *Journal of the American Academy of Dermatology*), es un estudio comparativo entre el nivel de 25-OHD en pacientes con psoriasis sin artritis respecto a pacientes con artritis psoriásica y la relación que presenta el nivel de 25-OHD con distintos parámetros metabólicos en cada uno de los dos grupos estudiados.

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Atheroma plaque, metabolic syndrome and inflammation in patients with psoriasis

Background: Chronic inflammation plays an important role in the development of cardiovascular risk factors. Although the prevalence of comorbidities and cardiovascular events has been described in patients with psoriasis, few studies have examined subclinical atherosclerosis in psoriasis patients. *Objective:* Our objective was to investigate the prevalence of atheroma plaques in patients with severe psoriasis compared with control subjects and to analyze the association with metabolic syndrome, homocysteine levels and inflammatory parameters. *Patients and Methods:* This case-control study included 133 patients, 72 with psoriasis and 61 controls consecutively admitted to the outpatient clinic in Dermatology Departments (Granada, Spain.) *Results:* Carotid atheroma plaques were observed in 34.7% of the psoriatic patients *versus* 8.2% of the controls ($p=0.001$) and metabolic syndrome was diagnosed in 40.3% of the psoriatic patients versus 13.1% of the controls ($p<0.001$). Significantly higher mean values of insulin, aldosterone, homocysteine and acute phase parameters (fibrinogen, D-dimer, C reactive protein and erythrocyte sedimentation rate) were found in psoriatic patients. Binary logistic regression showed a strong association between psoriasis and atheroma plaque and metabolic syndrome after controlling for confounding variables. *Limitations:* The absence of longitudinal quantification of metabolic syndrome parameters and intima-media thickness in psoriatic patients. *Conclusion:* The chronic inflammation and hyperhomocysteinemia found in psoriatic patients may explain the association with atheroma plaque and metabolic syndrome. Cardiovascular screening by metabolic syndrome criteria assessment and carotid ultrasound in psoriasis may be useful to detect individuals at risk and start preventive treatment against the development of cardiovascular disease.

Key words: Psoriasis, atherosclerosis, cardiovascular risk factors, metabolic syndrome, comorbidity

Abbreviations:

ATP-III	Adult Treatment Panel III
BSA	Body Surface Area
BMI	Body mass index
BP	Blood pressure
CI	Confident interval
CRP	C reactive protein
ESR	Erythrocyte sedimentation rate
HDL-C	High density lipoprotein Cholesterol
HOMA-IR	homeostasis model assessment of insulin resistance
IMT	Intima-media thickness
LDL-C	Low density lipoprotein Cholesterol
MS	Metabolic syndrome
OR	Odds ratio
PASI	Psoriasis Area and Severity Index

Psoriasis is a chronic, immune-mediated inflammatory skin disease that affects 2-3% of the general population [1]. Psoriasis involves the innate and acquired immune systems with an imbalance Th1/Th2 in favor of a Th1 pattern. Recent advances in immunopathogenesis and the genetics of psoriasis have shifted the focus from a single organ disease confined to the skin to a systemic inflammatory condition. Similarly to other immune disorders, patients with psoriasis have an increased risk of developing cardiovascular disease and metabolic syndrome [2]. Recent research has shown that chronic and systemic inflammation plays a major role in the development of atherosclerosis [3] and there are striking similarities between the molecular and inflammatory pathways in psoriasis and atherosclerosis [4].

Although the prevalence of comorbidities and cardiovascular events has been described in patients with psoriasis *versus* control populations [5, 6], few studies have examined subclinical atherosclerosis in patients with psoriasis [7, 8]. The end point of these studies was to analyze carotid

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artery intima-media thickness (IMT) in patients without risk factors and also it has been suggested that the carotid artery IMT does not always correlate with atherosclerosis, particularly in relatively young individuals with chronic inflammatory disease [9]. Some authors even found that myocardial infarction was more closely correlated with atheroma plaque than with the intima-media thickness [10].

The relative impact of systemic inflammation related to psoriasis on vascular lesions and cardiovascular risk nonetheless remains poorly understood. The end point of this case-control study was to investigate the prevalence of carotid atheromatosis (atheroma plaque) in patients with severe psoriasis in comparison with control subjects and to analyze the association with metabolic syndrome (MS), homocysteine levels and inflammatory parameters.

Material and methods

Patients and controls

This case-control study included 133 outpatients, 72 with severe psoriasis (PASI and BSA>10) and 61 controls with other dermatological diseases other than psoriasis (mainly nevi, seborrheic keratosis, actinic keratosis or verruca, as reported in other similar studies [11]) from the Dermatology Department of San Cecilio University Hospital, Granada (Spain). Psoriatic and control groups were enrolled during the same time period. No significant differences were recorded according to sex of patients or controls (p=0.70). Diagnosis of psoriasis was based on clinical findings. Inclusion criteria were: age >18 years for males and females, presence of plaque or erythrodermic severe psoriasis with PASI and BSA higher than 10, without systemic treatment in the last 2 months and signing of informed consent to study participation. Exclusion criteria were: cutaneous lymphomas or other cancers except for non-melanoma skin cancer. Inclusion criteria for controls were: age >18 years for males and females and signing of informed consent to study participation. Exclusion criteria for controls were the same as described above and the presence of psoriasis. The study was approved by the Ethics Committee of San Cecilio University Hospital and written informed consent was obtained from all patients and controls, according to Helsinki Declaration.

Clinical and laboratory parameters and Doppler ultrasound examination

The severity of psoriasis was determined by application of the Psoriasis Area Severity Index (PASI) and the Body Surface Area (BSA). The weight, height and abdominal circumference of subjects were measured, and their body mass index (BMI, kg/m^2) was calculated. Systolic and diastolic blood pressure (BP) was measured after a 5-min rest and again 10 min later, recording the mean value. Serum aldosterone, triglycerides, HDL-C, LDL-C, total cholesterol, blood glucose, insulin, D-dimer, fibrinogen, erythrocyte sedimentation rate (ESR), C reactive protein (CRP), homocysteine and folic acid levels were studied in samples drawn between 8 and 9 am after a rest period of ≥30 min. The homeostasis model assessment of insulin resistance (HOMA-IR index, μU/mg) was calculated (fasting insulin×fasting glucose/22.5). Data were also gathered on age, sex, personal or family history of early cardiovascular disease (<55 yrs in father and <65 yrs in mother), personal history of psoriatic arthritis or nail psoriasis, mean time with psoriasis, alcoholism (>40 g/day), smoking (>5 cigarettes/day), sedentarism (physical exercise <30 min/day), diet (sodium intake) and drug intake (antihypertensives, diuretics, hypocholesterolemics or oral antidiabetics). Prevalence of metabolic syndrome was calculated according to ATP-III criteria; MS was defined by the presence of three of the following [12]: abdominal circumference >102 cm in males and >88 cm in females; hypertriglyceridaemia >150 mg/dL, HDL-cholesterol <40 mg/dL in males and <50 mg/dL in females, blood pressure >130/85 mmHg or blood glucose >110 mg/dL.

Subjects underwent Doppler ultrasound examination with Acuson Antares equipment (Siemens, Berlin, Germany), using 5-10 MHZ transducer with supra-aortic trunk programme and recording with M mode the presence of atheroma plaques (intima-media thickness >1.5 cm) in common carotids, carotid bulb and internal and external carotids. The bilateral common carotids were scanned longitudinally to measure the intima-media thickness (IMT). Images were obtained from the distal portion of the common carotid artery, 1 to 2 cm proximal to the carotid bulb recording a mean value in left and right side. The two bright echogenic lines in the arterial wall were identified as the intima and media lines. The IMT was measured as the distance from the main edge of the lumen-intima interface to the media-adventitia interface of the carotids (*figure 1*). Patients and controls were examined in supine or semi-supine position, with the neck extended and the chin turned contralateral to the side being examined. The Doppler system was also used to detect carotid flow anomalies. All ultrasonographic measurements were obtained by a single radiologist and all images of the carotid arteries were recorded on the hard disk of the ultrasound system for subsequent analysis and evaluated by an independent

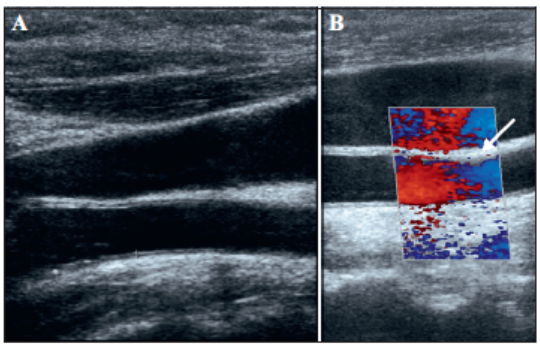

Figure 1. Doppler ultrasound examination.
A) The two bright echogenic lines in the arterial wall were identified as the intima and media lines. The IMT was measured as the distance from the main edge of the lumen-intima interface to the media-adventitia interface of the carotids. **B)** Atheroma plaque in a patient with psoriasis (arrow).

investigator who was unaware of the subjects' clinical status. None of the psoriasis patients or healthy control subjects refused testing.

Statistical analysis

Student's t test was applied to compare mean values of quantitative variables, the Shapiro-Wilk test to examine the normality of their distribution and the Levene test to study the variance. The Mann Whitney U test was used if the variables were not normally distributed. Qualitative variables were analysed with chi-square test or Fisher's exact test if at least one cell had an expected count <5. Correlations among variables were studied by using the Pearson coefficient and binary logistic regression models (Wald method), obtaining estimate-adjusted ORs and their 95% confidence intervals (CI), and were used to measure the association between psoriasis and metabolic syndrome criteria or atheroma plaque in a multivariate analysis. Multiple linear regression analysis was used to predict the independent predictors of IMT. The outcome variable was IMT and the significant predictors in bivariate correlation (age, PASI Score and duration of psoriasis) were included in the model. Standardized coefficient of determination was calculated. Differences were considered significant at $P \leq 0.05$ and nearly significant at $P \leq 0.1$. The SPSS 17.0 programme was used for the data analyses (SPSS, Inc, Chicago, IL).

Results

We studied 72 outpatients (39 male and 33 female) with severe psoriasis (all of them with generalized plaques), all Caucasians. The mean time with psoriasis was 17.64 yrs in the males and 18.72 in the females (p=0.66). The mean PASI value was 19.25 (17.26 *vs* 21.63, p=0.12 for males and females respectively) and BSA was 22.77 (21.86 *vs* 22.87, p=0.97 for males and females respectively). 56.9% of psoriasis patient presented nail psoriasis (56.4% *vs* 57.6%, p=0.91, for males and females) and 34.7% psoriatic arthritis (33.3% *vs* 36.5%, p=0.78 for males and females). Mean age, weight, height, BMI, tobacco, and sedentarism are summarized in *table 1*. No differences in alcohol consumption or diet (sodium intake) were found between groups. The male and female psoriatic groups did not differ in above parameters, while the females showed a lower height (172.87 *vs* 163.60 cm p<0.0001), weight (90.53 *vs* 74.90 kg, p<0.0001) and alcohol consumption (46.2% *vs* 1.2%, p=0.012). No patients or control subjects had previous history of myocardial infarction or cerebrovascular disease.

The control group was formed by 61 outpatients (31 male and 30 female) with other dermatological diseases and without psoriasis. No significant differences were found in antihypertensives (19.4% *vs* 14.7% p=0.31), anticholesterolemics (13.8% *vs* 8.1% p=0.22) or oral antidiabetic intake (12.5% *vs* 6.5% p=0.19) between psoriatic patients and controls respectively. 48.6% of psoriatic patients had a family history of psoriasis *versus* 8.2% of the controls (p<0.0001, OR=10.59 95% CI: 3.80-29.52). 17.4% of the patients with psoriasis presented family history of early cardiovascular disease (<55 yrs in males and <65 yrs in females) *versus* 13.1% of the controls (p=0.32, OR=1.59 95% CI: 0.62-4.11). No significant differences were found in the family histories of early cardiovascular disease between male and female patients with psoriasis (12.8% *vs* 21.2% respectively, p=0.26).

Metabolic syndrome

ATP-III criteria for MS were met by 40.3% of the patients with psoriasis *versus* 13.1% of the controls (p<0.001, OR=4.46 95% CI: 1.85-10.72). The OR for MS was 6.49 (95% CI: 1.68-25.06) for the psoriatic males and 3.25 (95% CI: 1.09-10.62) for the psoriatic females. MS was not significantly more frequent (p=0.88) in the psoriatic males (41%) than in females (39.4%) but was significantly more frequent in the psoriatic patients than in the controls (41% *vs* 9.7% for males, p=0.003 and 39.4% *vs* 16.7% for females p=0.046). Significant differences in MS parameters between psoriatic patients and controls are listed in *table 2*. Male and female psoriatic groups did not significantly differ in the presence of any MS variable or lipid value, with the exception of the abdominal perimeter (p=0.01), LDL-C (p=0.09) and LDL-C/HDL-C (p=0.03), which were higher in the males. Positive significant correlation between MS variables and PASI, BSA and mean time with psoriasis are found in *table 3*. Patients with psoriatic arthritic did not present higher prevalence of MS than patients without psoriatic arthritic (p=0.33). Multivariate studies with binary logistic regression, showed a strong association between

Table 1. Mean (standard deviation, SD) weight, height, age, BMI, mean time with psoriasis, tobacco (%), sedentarism (%) and alcohol consumption (%) in men and women with psoriasis and their respective controls.

	Men		P value	Women		P value
	Psoriasis	Controls		Psoriasis	Controls	
Weight (kg)	90.53 (17.02)	80.25 (11.80)	0.006	74.90 (15.80)	64.66 (13.09)	0.007
Height (cm)	172.87 (9.45)	171.54 (7.40)	0.52	163.60 (7.42)	160.80 (5.21)	0.91
Age (yrs)	46.87 (13.68)	43.54 (12.03)	0.29	45.42 (12.92)	48.43 (8.47)	0.28
BMI (kg/m^2)	30.48 (6.31)	27.25 (3.65)	0.014	28.16 (6.43)	24.95 (4.59)	0.028
Mean time with psoriasis (yrs)	18.64 (10.77)	-	-	18.72 (10.54)	-	-
Tobacco (%)	38.5%	22.6%	0.15	36.4%	10%	0.014
Sedentarism (%)	61.5%	64.5%	0.79	78.8%	60%	0.105
Alcohol (%)	46.2%	29%	0.14	18.2%	10%	0.35

Table 2. Analysis of the ATP-III metabolic syndrome criteria (mean, SD) in men and women with psoriasis and their respective controls. Also LDL-C, total cholesterol, Total Cholesterol/HDL and LDL-C/HDL-C values are listed.

	Men		P value	Women		P value
	Psoriasis	Controls		Psoriasis	Controls	
Abdominal perimeter (cm)	109.28 (16.25)	97.48 (9.6)	0.01	96.66 (12.80)	85.16 (14.37)	0.001
Triglycerides (mg/dL)	130.46 (52.64)	114.16 (57.39)	0.221	43.50 (7.57)	47.07 (8.59)	0.190
HDL-C (mg/dL)	48.82 (13.23)	49.61 (11.24)	0.791	53.33 (15.90)	63.76 (21.91)	0.033
Systolic BP (mmHg)	143.12 (19.67)	123.80 (12.46)	0.0001	139.67 (22.77)	112.0 (12.70)	0.0001
Diastolic BP (mmHg)	87.71 (13.46)	77.03 (9.44)	0.0001	83.45 (11.54)	64.33 (11.04)	0.0001
Blood glucose (mg/dL)	97.56 (26.97)	88.90 (17.17)	0.125	84.15 (13.87)	88.80 (12.20)	0.165
LDL-C (mg/dL)	127.69 (40.08)	117.67 (34.43)	0.273	104.33 (32.39)	112.80 (32.29)	0.304
Total cholesterol(mg/dL)	198.41 (43.91)	186.09 (40.53)	0.232	180.24 (40.98)	191.13 (36.25)	0.148
Total Cholesterol/HDL	4.31 (1.36)	3.95 (1.38)	0.287	3.71 (1.49)	4.71 (6.44)	0.41
LDL-C/HDL-C	2.79 (1.09)	2.50 (1.05)	0.273	2.18 (1.24)	2.87 (4.45)	0.42

Table 3. Correlation (r coefficient and p value, in brackets) between metabolic syndrome variables and PASI, BSA and mean time with psoriasis (N.S.: no significant differences).

	Abdominal perimeter	Triglycerides	HDL-C	Systolic BP	Diastolic BP	Blood glucose
PASI	0.35 (0.0001)	0.19 (0.03)	-0.23 (0.008)	0.36 (0.0001)	0.32 (0.0001)	N.S.
BSA	0.27 (0.002)	0.24 (0.05)	-0.27 (0.02)	0.31 (0.0001)	0.26 (0.002)	0.25 (0.004)
Time with psoriasis	0.33 (0.0001)	N.S.	N.S.	0.42 (0.0001)	0.37 (0.0001)	0.28 (0.001)

psoriatic patients and MS, even after additional adjustment for age, sex, weight, height, tobacco, sedentarism and alcohol consumption (OR=3.45 95% CI: 1.28-9.27, p<0.014, *table 4)*. The MS criteria most frequently recorded in male and female psoriatic groups were abdominal obesity and systolic and diastolic hypertension *(table 5)*.

Carotid atheromatosis

Carotid atheroma plaque was detected in 34.7% of the psoriatic patients *versus* 8.2% of the controls (p=0.001, OR=4.46, 95% CI: 1.85-10.72). It was recorded in 38.5% (OR=9.06 95% CI: 1.81-46.6) of the psoriatic males *versus* 6.5% of male controls (p=0.002) and in 30.3% (OR=3.91, 95% CI: 1.60-15.94) of psoriatic females *versus* 10% of female controls (p=0.047). There was no significant difference in atheroma plaque between male and female psoriatic patients (38.5% *vs* 30.3%, P=0.60). In the group of patients with psoriasis, 45.3% of the plaques were described as fibro-adipose (hyper-hypoechoic) and the remainder as calcified (hyperechogenic). Carotid blood flow abnormalities were detected in only two male patients. The odds ratio for atheroma plaque in patients with psoriasis and metabolic syndrome was 3.53 (95% CI: 1.28-9.76, p=0.013). Patients with atheroma plaque had significantly higher mean abdominal circumference (104.06 *vs* 96.16 cm, p=0.017), hypertriglyceridemia (137.66 *vs* 106.98 mg/dL, p=0.04), systolic BP (146.23 *vs* 126.23 mmHg, P=0.0001) and diastolic BP (87.73 *vs* 76.32 mmHg, p=0.0001). Patients with psoriatic arthritis did not present higher prevalence of atheroma plaques than patients without psoriatic arthritis (p=0.86). Binary logistic regression showed a strong association between psoriatic patients and atheroma plaque, even after additional adjustment for age, sex, weight, height, metabolic syndrome, tobacco, sedentarism and alcohol consumption (OR=7.32 95% CI: 2.00-26.84, p<0.003, *table 6)*.

Patients with psoriasis presented significantly higher carotid intima-media thickness (0.72 *vs* 0.64 mm, p=0.013 for right IMT and 0.72 *vs* 0.65 mm, p=0.042 for left IMT for patients and controls, respectively). There was a positive significant correlation between left and right IMT (r=0.86, p<0.0001). Patients with atheroma plaques presented significantly higher IMT (p=0.003). Males with psoriasis presented significantly higher mean IMT than females with psoriasis (0.77 *vs* 0.67 mm, p=0.049). PASI was positively correlated with right IMT (r=0.19, p=0.029)

Table 4. Binary logistic regression model for metabolic syndrome. The presence of psoriasis and weight were independent factors associated with MS.

Variable	OR	95%CI	P-value
Psoriasis (*vs* control)	3.45	1.28-9.27	0.014
Male sex (*vs* female)	1.58	0.49-5.06	0.44
Age (per year)	1.01	0.96-1.05	0.58
Weight (per kg)	1.05	1.01-1.08	0.01
Height (per m)	0.95	0.89-1.01	0.16
Tobacco	1.56	0.58-4.17	0.37
Sedentarism	0.54	0.19-1.49	0.23
Alcohol consumption	0.79	0.27-2.31	0.67

Table 5. Prevalence of metabolic syndrome criteria (%) in men and women with psoriasis and their respectively controls.

	Men		P value	Women		P value
	Psoriasis	Controls		Psoriasis	Controls	
Abdominal perimeter	61.5%	29%	0.07	75.8%	40%	0.004
Triglycerides	43.6%	22.%	0.066	27.3%	16.7%	0.31
HDL-C	33.3%	22.6%	0.32	30.3%	16.7%	0.20
Systolic BP	66.7%	6.5%	0.0001	60.6%	6.7%	0.0001
Diastolic BP	59%	16.1%	0.0001	42.4%	1.8%	0.0001
Glucose levels	15.4%	9.7%	0.47	3%	10%	0.25

and left IMT (r=0.19, p=0.032). Systolic BP was positively correlated with right (r=0.33, p=0.005) and left IMT (r=0.33, p=0.005). Mean time with psoriasis correlated with right (r=0.22, p=0.009) and left IMT (r=0.25, p=0.003), also age of the patients correlated with right (r=0.58, p=0.0001) and left IMT (r=0.63, p=0.0001). Multiple linear regression analysis showed that age and PASI predicted 0.42 (model R^2) of IMT changes (standardized β for age: 0.62, p=0.0001 and standardized β for PASI: 0.14, p=0.032).

Hormonal study

Patients with psoriasis presented significantly higher mean values of insulin (12.91 *vs* 9.61 μU/mL, p=0.037), aldosterone (267.58 *vs* 205.78 pg/mL, p=0.048) and homocysteine (15.43 *vs* 11.87 μmol/l, p=0.038) for patients and controls, respectively. No significant differences were found in folic acid (11.16 *vs* 10.43 ng/mL, p=0.43), or HOMA-IR index (5.31 *vs* 4.25 μU/mg, p=0.22). Hyperinsulinemia, defined as an insulin level >10.0 μU/mL, was significantly higher in psoriatic patients than in controls (68.1% *vs* 27.9%, p=0.0001, OR=5.51, 95CI%: 2.61-11.64). Psoriatic males and females did not differ in mean values of these hormones (data not shown). Patients with metabolic syndrome presented significantly higher insulin levels than patients without MS (16.45 *vs* 9.48 μU/mL p=0.004). Patients with atheroma plaque presented significantly higher insulin values *versus* those without (14.79 *vs* 10.41 μU/mL p=0.019). There was a significant correlation between insulin levels and all the MS parameters: abdominal obesity (r=0.29, p=0.001), triglycerides (r=0.33, p=0.0001), HDL-C (r=-0.34, p=0.0001), systolic BP (0.23, p=0.04), diastolic BP (0.30, p=0.001), blood glucose (r=0.34, p=0.0001) and aldosterone (r=0.52, p=0.0001). PASI correlated positively with insulin (r=0.23, p=0.008), homocysteine (r=0.34, p=0.02) and negatively with folic acid (r=-0.26, p=0.03).

Table 6. Binary logistic regression model for atheroma plaque. The presence of psoriasis, age and metabolic syndrome were independent factors associated with atheroma plaque.

Variable	OR	95%CI	P-value
Psoriasis (vs control)	7.32	2.00-26.84	0.003
Male sex (vs female)	0.77	0.19-3.05	0.71
Age (per year)	1.11	1.05-1.18	0.0001
Metabolic syndrome	6.83	2.07-22.47	0.002
Weight (per kg)	1.94	0.92-1.98	0.26
Height (per m)	1.08	0.70-1.17	0.35
Tobacco	1.22	0.38-3.88	0.730
Sedentarism	1.29	0.40-4.16	0.667
Alcohol consumption	0.81	0.23-2.81	0.749

Acute phase reactants

Table 7 shows the mean fibrinogen, D-dimer, ESR and CRP values in the study groups. Elevated levels of CRP, fibrinogen and D-dimer were noted in male patients with psoriasis and elevation of all the parameters in females with psoriasis. Female psoriatic patients presented significantly higher values of all these parameters than male psoriatic patients: CRP (1.14 *vs* 0.31 mg/dL p=0.025), ESR (26.7 *vs*7.21 mm/h p=0.0001), fibrinogen (416 *vs* 343.5 mg/dL p=0.005) and D-dimer (236.5 *vs* 131.8 ng/mL, p=0.03). Fibrinogen (383.9 *vs* 319.8 mg/dL P=0.002), D-dimer (233.6 *vs* 109.1 ng/mL, P=0.006), ESR (19.5 *vs* 11.1 mm/h, P=0.04) and CRP (1.04 *vs* 0.22 mg/dL, P=0.016) values were significantly higher in patients with MS than in those without. CPR values (0.93 *vs* 0.31 mg/dL, p=0.007), fibrinogen (372.4 *vs* 327.22 mg/dL p=0.03) and D-dimer (218.6 *vs* 121.3 ng/mL p=0.05) were significantly higher in patients with atheroma plaque than in those without. Elevated CRP values were positively correlated with abdominal obesity (r=0.19, p=0.026), triglycerides (r=0.17, p=0.04), systolic BP (r=0.21, p=0.018) and negatively with HDL-C (r=-0.29, p=0.001). Fibrinogen was positively correlated with abdominal obesity (r=0.26, P=0.003), triglycerides (r=0.19, p=0.027), systolic BP (r=0.24, p=0.007) and diastolic BP (r=0.25, p=0.004). D-dimer was positively correlated with abdominal obesity (r=0.23, p=0.009), triglycerides (r=0.21, p=0.016) and systolic BP (r=0.33, p=0.0001), diastolic BP (r=0.20, p=0.021) and negatively with HDL-C (r=-0.33, p=0.0001). PASI and BSA were positively correlated with all acute phase parameters (p=0.0001). Right and left IMT correlated positively with CRP (r=0.23, p=0.014). Insulin was positively correlated with CRP (r=0.57, p<0.0001) and ESR (r=0.41, p<0.0001).

Discussion

The results of this study confirm the association between severe psoriasis and a higher cardiovascular risk in both male and female groups. We found a higher prevalence of

Table 7. Mean (SD) of CRP, fibrinogen, D-dimer, ESR in men and women with psoriasis and their respectively controls.

	Men		p value	Women		p value
	Psoriasis	Controls		Psoriasis	Controls	
CRP (mg/dL)	0.316 (0.2)	0.125 (0.1)	0.002	1.14 (0.8)	0.16 (0.1)	0.009
Fibrinogen (mg/dL)	343.58 (61.1)	274.17 (83.6)	0.0001	416 (126.3)	303.3 (73.9)	0.0001
D-Dimer (ng/mL)	131.83 (84.1)	94.31 (33.2)	0.018	236.5 (55.4)	100.7 (39.4)	0.005
ESR (mm/hour)	7.77 (4.4)	7.21 (3.5)	0.56	26.7 (13.8)	12.5 (8.7)	0.03

subclinical carotid atheromatosis (atheroma plaques) and MS (ATP-III criteria) in patients with psoriasis than in control subjects. Binary logistic regression showed a strong association between psoriasis and atheroma plaque and metabolic syndrome after controlling for confounding variables. The prevalence of these cardiovascular risk factors differs slightly between male and female patients with psoriasis.

Metabolic syndrome

Many studies have demonstrated an increased risk for all the components of metabolic syndrome among patients with psoriasis, based on huge computerized medical databases and this may be problematic due to information bias regarding documentation of the diagnosis of psoriasis and its comorbidities [13]. A recent study showed that only 57% of patients with a registered diagnosis of psoriasis in the computerized medical records had a true diagnosis of psoriasis [14] and most computerized medical records do not compel the physician to input data regarding some parameters such as obesity, body mass index or smoking habits.

We found a higher prevalence of MS in patients with psoriasis than in their respective control groups. Few studies have analyzed the prevalence of MS not based on computerized medical databases [11, 15]. Comparison of published prevalence for different populations is difficult if different diagnostic criteria are used. Studies have reported a MS prevalence of 7.5-20% in the general population [16], within the range observed in our controls.

The importance of metabolic syndrome is that it may confer a cardiovascular risk higher than the individual components, subjects who met ATP-III MS criteria had a 2.59-fold greater likelihood (OR=2.59) of a cardiovascular event in the next 10 yrs [17]. In our study, patients with MS had a 3.5-fold higher risk (OR=3.5, 95% CI: 1.2 - 9.7) of the presence of atheroma plaque. A higher mortality risk for arterial and venous thrombosis and a higher risk of myocardial infarction, especially in young patients with severe psoriasis, has been described [18].

In the present study, a higher mean BMI and abdominal circumference were found in psoriatic patients than in controls. This indicates that psoriatic patients undergo an abdominal redistribution of fat, which is considered an important cardiovascular risk factor and was associated in our study with higher insulin resistance, a key element in the MS. We did not find differences between cases and controls regarding mean levels of blood glucose or lipid levels. In contrast to our findings, others studies showed that diabetes mellitus type 2 and an atherogenic lipid profile ocurred significantly more frequently in patients with psoriasis than in controls [15, 19]. Despite the fact that the association with hypertension has not been completely supported by all of the current literature [1], we found that patients with psoriasis presented higher mean levels of systolic and diastolic BP.

Carotid atheromatosis

We found a significantly higher prevalence of carotid atheromatosis in the male and female psoriatic patients than in controls. The prevalence of atheroma plaque as a marker of subclinical atherosclerosis has not been properly studied in patients with psoriasis. Most studies directly analyse cardiovascular events, e.g., myocardial infarction [20, 21], with the potential bias of only considering those who survive heart disease. The presence of the majority of parameters that constitute MS were positively related to the presence of atheroma plaque in this study. Only two reports analyzed the prevalence of carotid atheroma plaque and IMT in patients with psoriasis, excluding patients with risk factors, without finding significant differences [7, 8]. Impaired endothelial function and increased IMT of the carotid arteries in psoriatic arthritis have also been reported [22]. In this study psoriasis was associated with atheroma plaque even after controlling for confounding parameters and metabolic syndrome in a multivariate analysis. IMT was also significantly higher in patients with psoriasis and correlated with psoriasis activity (PASI) and age in multiple linear regression analysis. So, older patients with severe psoriasis need frequent follow-up to reduce cardiovascular morbidity.

Detection of subclinical atherosclerosis and identification of patients at risk for developing atherosclerosis are important for the prevention of cardiovascular disease. Systemic inflammation has been associated with the development of atherosclerosis, which suggests that psoriatic patients may have a higher risk for cardiovascular disease, also metabolic syndrome parameters and treatments may contribute to the development of atherosclerosis in these patients. Both diseases share common inflammatory cytokine profiles, locally and systemically [23]. The metabolic aspects of chronic Th-1 and Th-17 inflammation in psoriasis have the potential to impact other conditions, such as risk factors and atherosclerosis but inflammatory cytokines and hormones produced in conditions such as obesity, insulin resistance or atherosclerosis may also promote a pro-inflammatory state.

Hormonal study

Patients with psoriasis presented significantly higher insulin levels and hyperinsulinemia, defined as an insulin

level >10.0 μU/mL, was significantly higher in psoriatic patients than in controls. However, the HOMA-IR index did not show differences between the groups, maybe because glucose levels were very similar in patients and in controls. Given that a proportion of patients with psoriasis are obese and abdominal obesity is strongly associated with the development of metabolic syndrome, the relationship between psoriasis and insulin resistance is not unexpected. No differences in blood glucose were found, presumably because of the number of patients involved in the study, but hyperinsulinemia may reflect a trend to develop glucose intolerance in the future. Also, insulin levels correlated positively with all the metabolic syndrome parameters, aldosterone and PASI. Aldosterone, a mineralocorticoid hormone classically involved in sodium balance regulation and hypertension [24], is increased in patients with metabolic syndrome [25-28] associated with insulin resistance, as found in the present study.

Patients with psoriasis presented significantly higher levels of plasma homocysteine without differences in folic acid. Homocysteine correlated positively with psoriasis activity (r=0.34, p=0.02), inflammation (CRP, r=0.29, p=0.01) and mean IMT (r=0.28, p=0.036). Clinical and epidemiological studies have provided strong evidence that plasma homocysteine is an independent risk factor for atherosclerotic diseases including coronary artery disease, stroke and peripheral vascular disease [29]. There have been several studies that investigated homocysteine levels in psoriasis patients with different results. Reduced plasma folate levels in patients with psoriasis, which results from reduced absorption from the gut or increased vitamin utilization in the skin, have been one of several explanations for this hyperhomocysteinemia found in patients with psoriasis [30-33]. In the present case, folic acid correlated negatively with PASI, but no significant differences were found between patients and controls. The mechanisms of hyperhomocysteinemia for the development of atherothrombosis are endothelial injury, increased platelet turnover, enhanced platelet activation with increased thromboxane synthesis, oxidative modification of low-density lipoproteins and endothelial-leucocyte interactions [34]. Dietary supplementation with folic acid and vitamins B6 and B12 appears to be a reasonable and safe therapeutic option in these patients [30].

Acute phase reactants

Mean CRP, fibrinogen, D-dimer and ESR (only in females) values were significantly higher in psoriatic patients *versus* their controls, and these parameters were related to MS and carotid atheromatosis. PASI, BSA and IMT were positively correlated with all acute phase parameters. Chronic inflammation was found to play an important role in the development of insulin resistance, endothelial dysfunction and cardiovascular disease [35] and other studies report that plasma acute-phase protein levels (C-reactive protein or fibrinogen) were significantly elevated in patients with psoriasis compared with healthy controls [36]. The Th-1 and Th-17 pro-inflammatory situation underlying psoriasis, and shown by higher mean values of acute phase reactants, may have a potential impact in other conditions, such as obesity, diabetes, thrombosis, or atherosclerosis.

Although case-control studies can show a possible selection bias, the distribution of the potentially confounding factors as age, sex, tobacco use, sedentarism and drug intake were homogeneous in the two groups. In the present study, the binary logistic regression model showed a higher risk for MS and atheroma plaque in patients with psoriasis, after controlling for multiple confounding factors. Also, case-control studies do not allow the directionality of the association to be ascertained, so more prospective studies with larger numbers of patients are required to analyze the pathogenic mechanisms underlying the increase in cardiovascular risk in patients with psoriasis.

In conclusion, the results obtained indicate an association between psoriasis in males and females and the cardiovascular risk factors of MS and carotid atheromatosis. Our data show that the presence of psoriasis was an independent risk factor for subclinical atherosclerosis (atheroma plaque and higher IMT) and metabolic syndrome, possibly due to chronic inflammation and hyperhomocysteinemia. Cardiovascular screening by MS criteria assessment and carotid ultrasound in males or females with psoriasis may be useful to detect individuals at risk and start preventive treatment against the development of cardiovascular disease. ■

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Deficiency of serum concentration of 25-hydroxyvitamin D in psoriatic patients: A case-control study

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Background: Some autoimmune conditions have been associated with reduced vitamin D levels, including systemic lupus erythematosus, rheumatoid arthritis, diabetes mellitus, and multiple sclerosis.

Objective: The main objective of this study was to analyze the 25-hydroxyvitamin D (OHD) status of patients with psoriasis in comparison with control subjects without this disease.

Methods: This case-control study included 86 patients (43 with psoriasis and 43 age- and sex-matched control subjects) from the outpatient clinic of our hospital dermatology department in Granada, Spain. All patients and control subjects were studied during one 4-week period to avoid seasonal variations in vitamin D levels.

Results: Serum 25-OHD levels were significantly lower in psoriatic patients than in control subjects even after adjusting for confounding factors in a multivariate analysis (odds ratio 2.89, 95% confidence interval 1.02-7.64, $P < .03$ for vitamin D insufficiency). Low 25-OHD levels were negatively associated with C-reactive protein (inflammatory activation marker) and body mass index in multiple linear regression analysis. Psoriatic patients with body mass index greater than or equal to 27 kg/m^2 had a higher risk of 25-OHD insufficiency (sensitivity of 82.3% and specificity of 51.7%).

Limitations: Further studies with larger numbers of patients are required to analyze the pathogenic mechanisms underlying the relationship between 25-OHD deficiency and psoriasis.

Conclusions: The 25-OHD values are significantly lower in psoriatic patients than in control subjects. Low 25-OHD levels are negatively associated with C-reactive protein, an inflammatory activation marker, and with obesity. Psoriatic patients with a body mass index of 27 or more are likely to have vitamin D insufficiency. (J Am Acad Dermatol 2012;67:931-8.)

Key words: autoimmunity; body mass index; C-reactive protein; psoriasis; Psoriasis Area and Severity Index; 25-hydroxyvitamin D.

Psoriasis is a chronic inflammatory disease that involves the innate immunologic system (keratinocytes, dendritic cells, histiocytes, mastocytes, and endothelial cells) and acquired immunologic system (T lymphocytes).[1] Once the innate immune system is activated, dendritic cells present an antigen (not yet defined) to lymphocytes. Finally, a response is generated that leads to an expansion and activation of lymphocytes with a Th1/Th2 imbalance in favor of Th1.[2]

Vitamin D performs different functions besides its well-known role in calcium-phosphorus metabolism, as indicated by the presence of vitamin D receptors (VDRs) and CYP271B (enzyme responsible for 25-hydroxyvitamin D [25-OHD] synthesis) in different tissues.[3-6] An important regulatory role for vitamin D in

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the immune system is suggested by the presence of VDRs on activated T lymphocytes,[7,8] the suppressive or inhibiting effect of 1,25-dihydroxyvitamin D in different autoimmune diseases, and in vitro and in vivo findings of vitamin D–induced changes in immune functions.[9] Furthermore, dermatologists and other physicians have observed the effectiveness of vitamin D analogs to treat psoriasis plaques in daily clinical practice.[10]

Autoimmune conditions associated with reduced vitamin D levels include rheumatoid arthritis (RA), insulin-dependent diabetes mellitus (IDDM), and multiple sclerosis (MS),[11-13] which share some immunologic features with psoriasis, such as Th1/Th2 dysregulation. With this background, we compared 25-OHD levels between patients with psoriasis and control subjects without psoriasis. All patients and control subjects were studied in one 4-week period to avoid seasonal variations in vitamin D levels.

CAPSULE SUMMARY

- Some autoimmune conditions that share immunologic and genetic features with psoriasis have been associated with reduced vitamin D levels.
- In the current study, patients with psoriasis had significantly lower levels of 25-hydroxyvitamin D than control subjects, even after adjusting for confounding factors in a multivariate analysis.
- Low 25-hydroxyvitamin D levels are negatively associated with markers of inflammatory activation (C-reactive protein) and obesity. Patients with psoriasis and a body mass index greater than or equal to 27 are likely to have vitamin D insufficiency.

METHODS

Patients and control subjects

This case-control study included 86 outpatients: 43 patients with psoriasis randomly selected from among patients of the psoriasis unit and 43 randomly selected age- and sex-matched control subjects (28 male and 15 female in each group) with nonphotosensitive dermatologic diseases other than psoriasis (mainly nevi, seborrheic keratosis, or verruca) from the Dermatology Department of San Cecilio University Hospital, Granada, Spain. Randomization was conducted using randomized number tables. All patients were studied during the same period (from May 16 to June 17, 2011) to avoid seasonal variations in vitamin D levels.[14,15] All individuals were from the metropolitan area of Granada to avoid geographic differences in sun exposure and vitamin D levels. No patients or control subjects refused participation in the study.

Diagnosis of psoriasis was based on clinical findings (generalized psoriasis plaques). Inclusion criteria were: age between 18 and 65 years, the presence of plaque psoriasis not treated systemically or topically in the previous month, and the absence of vitamin D supplementation or current phototherapy treatment or the presence of chronic inflammatory disease such as MS, inflammatory bowel disease, RA, IDDM, lupus erythematosus, cutaneous lymphoma, nonmelanoma skin cancer, or any other cancer. Inclusion criteria for control subjects were the same as for cases except for the absence of psoriasis. The study was approved by the Ethics Committee of San Cecilio University Hospital, and written informed consent was obtained from all patients and control subjects in accordance with the Helsinki Declaration.

Clinical and laboratory parameters

The severity of psoriasis was assessed according to the Psoriasis Area and Severity Index (PASI) and body surface area. The weight, height, and abdominal circumference of subjects were measured, and their body mass index (BMI) (kg/m^2) was calculated. Systolic and diastolic blood pressure (BP) was measured after a 5-minute rest and again after a 10-minute interval, and the mean values were recorded. Data were also gathered on: age, sex, mean time with psoriasis, personal history of psoriatic arthritis or nail psoriasis, family history of psoriasis, Fitzpatrick skin type, estimate of time spent outdoors (sum of estimated hours per weekday and weekend day), tobacco (cigarettes per day), and daily and weekend alcohol intake (grams per day). C-reactive protein (CRP), erythrocyte sedimentation rate, triglycerides, high-density lipoprotein cholesterol, and glycemia were analyzed in blood samples drawn between 8 and 9 AM. Serum 25-OHD levels were determined by commercially available radioimmunoassay in the biochemistry department of our hospital. Patients were interviewed to determine their usual dietary intake of vitamin D. The amount of vitamin D intake per day was similar ($P > .05$) between the psoriasis (140 IU) and control (115 IU) groups. Intake of vitamin D supplements was an exclusion criterion. Dietary vitamin D intake was not significantly correlated with serum 25-OHD concentration ($P > .05$).

Statistical analysis

The Kolmogorov-Smirnov test was used to examine the distribution of variables and the Levene test to

Abbreviations used:

BMI:	body mass index
BP:	blood pressure
CI:	confidence interval
CRP:	C-reactive protein
IDDM:	insulin-dependent diabetes mellitus
MS:	multiple sclerosis
OHD:	hydroxyvitamin D
OR:	odds ratio
PASI:	Psoriasis Area and Severity Index
RA:	rheumatoid arthritis
UV:	ultraviolet
VDR:	vitamin D receptor

study the variance. When the distribution was normal, the Student *t* test was applied to compare mean values of quantitative variables, and when not normal, the Mann-Whitney U test was used. Qualitative variables were analyzed with χ^2 test or with Fisher exact test if at least one cell had an expected count less than 5. Binary logistic regression models (Wald method) were used to measure the association between psoriasis and vitamin D insufficiency (<30 ng/mL) in a multivariate analysis. Correlations among variables were studied by means of the Pearson coefficient, and multiple linear regression analysis was used to determine the independent predictors of vitamin D levels. The outcome variable was serum vitamin D concentration, and the model included the variables that proved significant in bivariate analyses (PASI, BMI, and CRP). The standardized coefficient of determination was calculated. *P* less than or equal to .05 was considered significant. Software was used for the data analyses (SPSS 17.0, SPSS Inc, Chicago, IL).

RESULTS

We studied 43 Caucasian patients (28 male and 15 female) with generalized psoriasis plaques. The mean time period with psoriasis was 19.91 years, the mean PASI value was 4.42, and the mean body surface area was 4.38. Of these 43 patients with psoriasis 14% had nail psoriatic arthritis and 7% had psoriatic arthritis. No gender differences were observed in any of the above parameters. A family history of psoriasis was reported by 46.8% of psoriatic patients versus 8.7% of the control subjects ($P < .0001$, odds ratio [OR] 10.59, 95% confidence interval [CI] 3.80-29.52). Onset of the disease was at an earlier age in the patients with a family history of psoriasis (20.70 ± 13.23 vs 29.20 ± 12.77 years; $P = .039$).

The control group comprised 43 outpatients (28 male and 15 female) without psoriasis who had other dermatologic diseases. The two groups did not significantly differ in age, Fitzpatrick skin phototype distribution (all psoriatic patients or control subjects had phototypes II, III, or IV), estimated time spent outdoors (in hours), smoking habit, or alcohol consumption.

Mean BMI values were borderline significantly higher in patients than in control subjects ($P = .052$) (Table I). A positive significant correlation was found between PASI and BMI ($r = 0.405$; $P = .007$). Triglyceride levels were significantly higher in psoriatic patients than in control subjects ($P = .01$), but no significant differences were found in systolic or diastolic BP, high-density lipoprotein cholesterol, or glucose levels (Table I).

The mean serum 25-OHD concentration was significantly lower in patients than in control subjects (24.41 ± 7.80 vs 29.53 ± 9.38; $P = .007$) (Fig 1). Vitamin D deficiency (<20 ng/mL)[16] was observed in 25.6% of patients with psoriasis versus 9.3% of control subjects ($P = .043$, OR 2.75, 95% CI 1.02-7.96); vitamin D insufficiency (<30 ng/mL) was found in 79.1% of patients with psoriasis versus 58.1% of control subjects ($P = .037$, OR 1.36, 95% CI 1.01-1.83) (Table II). Multivariate studies with binary logistic regression showed a strong association between the presence of psoriasis and vitamin D insufficiency (<30 ng/mL), even after adjustment for BMI, age, sex, dietary vitamin D intake, total sun exposure, and Fitzpatrick skin phototype as confounding factors (OR 2.89, 95% CI 1.02-7.64, $P < .03$) (Table III).

No significant correlation was found between 25-OHD levels and PASI, body surface area, mean time with psoriasis, systolic BP, diastolic BP, high-density lipoprotein cholesterol, triglycerides, or glucose levels ($P > .05$). No differences in mean 25-OHD levels were found as a function of the presence/absence of psoriatic arthritis, nail psoriasis, or family history of psoriasis (data not shown).

A significant negative correlation was found between BMI and serum 25-OHD level ($r = -0.30$, $P = .005$). A receiver operating characteristic curve was performed, and an optimal cut-off BMI value of 27 (area under the curve = 0.65, $P = .024$) was obtained; above this value, psoriatic patients had a higher risk of vitamin D insufficiency (sensitivity of 82.3% and specificity of 51.7%) (Fig 2).

No significant differences in mean CRP or erythrocyte sedimentation rate values were found between patients and control subjects (0.251 vs 0.381 mg/dL for CRP, $P = .520$; 9.30 vs 7.77 mm/h for erythrocyte sedimentation rate, $P = .42$; respectively). High-sensitivity CRP was greater than 0.3 mg/dL in 25.6% of the psoriatic patients. In the psoriasis group, the CRP value was inversely correlated with the serum 25-OHD concentration

Table I. Demographics and possible confounding factors about serum 25-hydroxyvitamin D concentration and cardiovascular risk factors in patients with psoriasis and control subjects

Variables	Psoriasis	Control	*P* values
Age, y, mean ± SD	44.33 ± 8.71	43.95 ± 11.37	.865
Fitzpatrick skin phototype, n (%)			
II	8 (18.6)	4 (9.3)	.458
III	22 (51.2)	25 (58.1)	
IV	13 (30.2)	14 (32.6)	
Estimated time spent outdoors, h/wk, mean ± SD	25.99 ± 18.78	28.22 ± 20.33	.598
Smoking, n (%)			
Yes (>5/d)	21 (48.8)	17 (39.5)	.385
No	22 (51.2)	26 (60.5)	
Usual alcohol intake, n (%)			
Yes (>40 g/d)	18 (41.9)	18 (41.9)	1.000
No	25 (58.1)	25 (58.1)	
BMI, mean ± SD	29.68 ± 7.07	27.17 ± 4.45	.052
Systolic BP, mm Hg, mean ± SD	127.18 ± 13.97	125.53 ± 13.48	.57
Diastolic BP, mm Hg, mean ± SD	80.79 ± 11.35	78.48 ± 9.50	.31
HDL-C, mg/dL, mean ± SD	50.88 ± 12.64	54.60 ± 13.69	.19
Triglycerides, mg/dL, mean ± SD	129.29 ± 67.45	94.48 ± 55.52	.01
Glycemia, mg/dL, mean ± SD	97.53 ± 24.92	94.13 ± 21.56	.51

BMI, Body mass index; *BP*, blood pressure; *HDL-C*, high-density lipoprotein cholesterol.

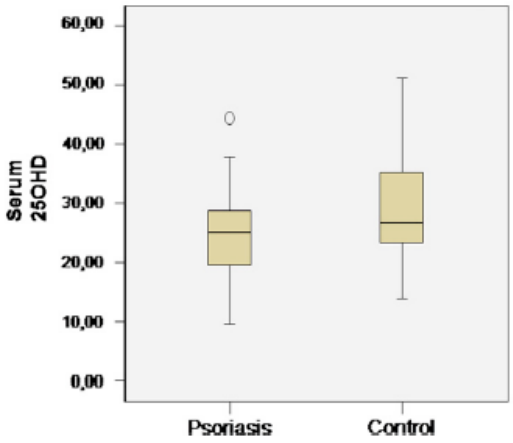

Fig 1. Comparison of mean serum 25-hydroxyvitamin D (*OHD*) concentration between psoriasis and control groups. Serum 25-OHD concentration was significantly lower in patients with psoriasis versus control subjects (24.41 ± 7.80 vs 29.53 ± 9.38; $P = .007$).

($r = -0.391$; $P = .009$) (Fig 3) and positively correlated with the BMI ($r = 0.528$; $P < .0001$).

The multivariate linear regression model showed that serum 25-OHD concentration was negatively associated with CRP level and BMI (R^2 of adjusted model = 0.26; $P = .009$) (Table IV).

DISCUSSION

In this study, multivariate analysis showed that serum 25-OHD levels were significantly lower in psoriatic patients than in control subjects after adjusting for confounding factors. The 25-OHD levels were negatively associated with CRP, a marker of inflammatory activation, and with BMI in multiple linear regression analysis. Psoriatic patients with BMI greater than or equal to 27 kg/m^2 were found to have a greater risk of 25-OHD insufficiency, with high sensitivity and specificity. A strength point of this study was that all patients were studied during the same 4-week period, thereby avoiding seasonal variations.

Vitamin D has long been regarded as essential for bone development, growth, mineralization, and the maintenance of skeletal integrity, and vitamin D status is increasingly considered important in various

Table II. Mean (SD), minimum, and maximum serum 25-hydroxyvitamin D concentration and percentages of deficiency (<20 ng/mL) and insufficiency (<30 ng/mL) 25-hydroxyvitamin D levels in patients and control subjects

25-OHD	Psoriasis	Control	*P* values
Mean ± SD, ng/mL	24.41 ± 7.80	29.53 ± 9.38	.007
Minimum	9.50	13.80	-
Maximum	44.30	51.10	-
<10 ng/mL	2.3%	0%	-
<20 ng/mL	25.6%	9.3%	.043
<30 ng/mL	79.1%	58.1%	.037
≥ 30 ng/mL	20.9%	41.9%	.037

OHD, Hydroxyvitamin D.

Table III. Binary logistic regression model for vitamin D insufficiency (<30 ng/mL)

Variable	OR	95% CI	*P* value
Psoriasis (vs control)	2.82	1.04-7.59	.04
Male sex (vs female)	0.68	0.22-2.06	.50
Age	0.99	0.95-1.04	.91
Food intake of vitamin D	1.29	0.72-2.32	.37
Total sun exposure	1.02	0.99-1.04	.13
Fitzpatrick skin phototype	0.89	0.41-1.92	.77

Presence of psoriasis was independent factor associated with vitamin D insufficiency after controlling for multiple confounding factors.
CI, Confidence interval; *OR*, odds ratio.

chronic diseases. In fact, the high prevalence of vitamin D insufficiency is defined as a global health problem, and most experts recommend a level greater than or equal to 30 ng/mL.[17] More than 90% of vitamin D synthesis is dependent on ultraviolet (UV) exposure (cutaneous synthesis),[18,19] and vitamin D deficiency was recently demonstrated in patients with lupus erythematous, a photosensitive disorder that requires strict sun avoidance.[20] However, vitamin D levels were not influenced by sun exposure in the current study, which found no significant differences in sun exposure (in hours/week) between patients and control subjects. Unlike patients with lupus erythematosus, patients with psoriasis know the clinical benefit of moderate doses of UV radiation and do not avoid sun exposure systematically.

We observed a significant negative correlation between BMI and serum 25-OHD concentration, as previously reported.[21,22] One reason proposed for this relationship has been the lesser physical activity and therefore reduced sun exposure of heavier individuals.[23] However, BMI proved to be an independent predictor of hypovitaminosis D in our multivariate linear regression analysis, even when the model included daily sun exposure. Moreover, we found no correlation between BMI and hours of daily sun exposure (data not shown). Other possible explanations include the reduced bioavailability of vitamin D as a result of its sequestration in fat[24,25] and the activity of this vitamin as a body mass regulator. From a teleological and phylogenetic standpoint, the reduction in UV radiation during the autumn induces the organism of mammals to gain weight and prepare for the winter.[26] In the current study, BMI proved to be an independent predictor of 25-OHD deficiency in patients with psoriasis, with a high sensitivity and specificity (receiver operating characteristic curve) for the optimal cutoff point of 27 kg/m^2.

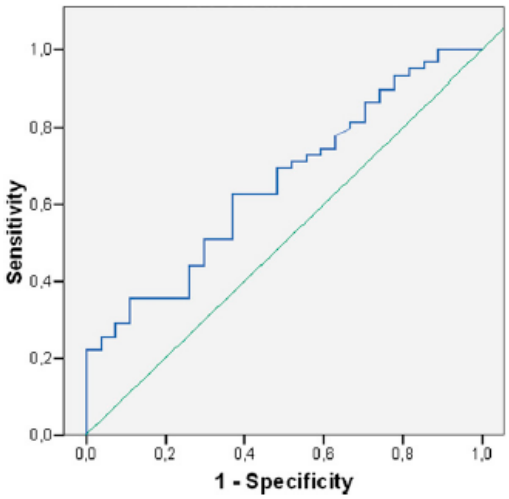

Fig 2. Receiver operating characteristic (*ROC*) curve was created to determine optimal cut-off value of body mass index (BMI) to predict vitamin D insufficiency in patients with psoriasis (area under curve = 0.65, $P = .024$). Patients with psoriasis and BMI greater than or equal to 27 had high risk of vitamin D insufficiency (sensitivity = 82.3%; specificity = 51.7%). *1—Specificity*, False-positive rate.

The relationship between age and vitamin D levels is controversial. Some authors have correlated age with vitamin D in a direct[27,28] or indirect[29,30] manner, whereas others have found no correlation, as in the current study[31] (Table III).

Our case-control study found significantly lower serum 25-OHD levels in psoriatic patients than in control subjects. Other autoimmune diseases have been associated with low vitamin D levels, such as RA, IDDM, and MS.[11,13] Visscher et al[32] reported fluctuations in MS consistent with seasonal changes in serum vitamin D levels, proposing that the development and behavior of this disease was influenced by latitude, an environmental factor.[33-35] In the case of psoriasis, the prevalence varies among regions, although the prevalence is higher further toward the poles than between the tropics.[36] Hence, there is some epidemiological-ecological evidence of a relationship between autoimmune disease and latitude in terms of radiation and vitamin D levels.

Evidence has gradually accumulated on the regulatory role of vitamin D in the immune system. The presence of VDRs has been reported in most immune cells, including activated $CD4^+$ and $CD8^+$ lymphocytes, and in antigen-presenting cells such as dendritic cells.[37] In addition, many immune system cells express 1α-hydroxylase,[37] which is regulated by immune signals and not by calcium.[38]

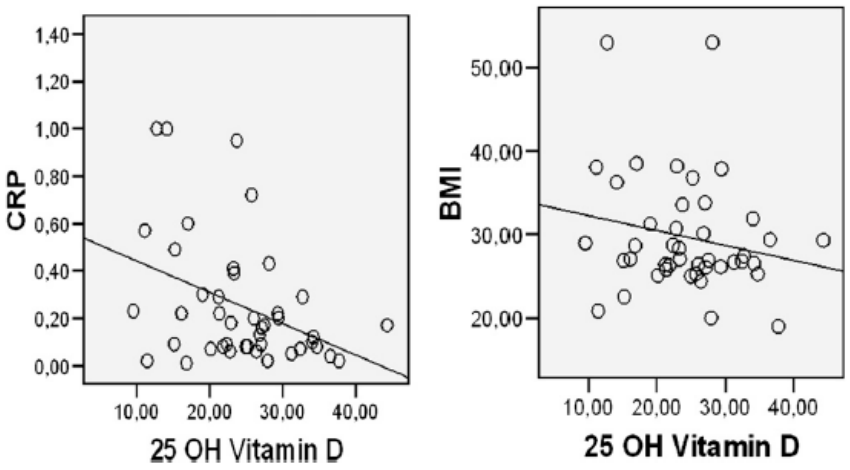

Fig 3. In psoriasis group, C-reactive protein (*CRP*) levels were significantly and negatively correlated with serum 25-hydroxy (*OH*) vitamin D concentrations ($r = -0.391$; $P = .009$) and with body mass index (*BMI*) values ($r = -0.30$, $P = .005$).

Table IV. Multiple linear regression analysis of independent predictors of serum 25-hydroxyvitamin D concentration in psoriatic patients

Predictors	Standardized β	*t* value	*P* value
PASI	0.35	2.31	.26
CRP	−0.34	−2.08	.024
BMI	−0.16	−0.89	.037
Constant	29.2	5.83	.0001

Model adjusted $R^2 = 0.26$; $P = .009$.
BMI, Body mass index; *CRP*, C-reactive protein; *PASI*, Psoriasis Area and Severity Index.

Compromised vitamin D status has been associated with an increased risk for Th1 cytokine-mediated autoimmune diseases, including IDDM, MS, inflammatory bowel disease, and RA.[9,39] Furthermore, animal studies demonstrated that 1,25-dihydroxyvitamin D prevents the development or ameliorates the symptoms of chronic inflammatory autoimmune reaction.[40-45] Conversely, vitamin D deficiency has been shown to accelerate the development and increase the incidence of experimental MS and IDDM.[46,47] Another instance of a relationship between vitamin D deficiency and autoimmunity was suggested by Silverberg et al,[48] who reported very low 25-OHD levels (<15 ng/mL) in patients with vitiligo who had another autoimmune disease.

Systemic vitamin D administration has shown clinical benefits in psoriatic patients. Werner de Castro et al[49] described the resolution of adalimumab-induced psoriasis after high doses of oral vitamin D, and Perez et al[50] found a significant improvement in clinical parameters after oral calcitriol. Gaál et al[51] reported that treatment with alfacalcidol significantly reduced the percentage of interferon-γ-producing $CD8^+$ T lymphocytes and serum interferon-γ levels in patients with psoriatic arthritis in comparison with control subjects. In a pilot study, Huckins et al[52] found a statistically significant improvement in tender joint count and physician global impression after treatment with 1,25-dihydroxivitamin D3 in patients with psoriatic arthritis. The effectiveness of vitamin D analogs for the topical treatment of psoriasis is very well documented.[10]

Deficient 25-OHD levels in patients with psoriasis may be associated with alterations in isoenzymes that affect the synthesis of vitamin D. Some studies have shown differences in VDR polymorphisms between patients with psoriasis and the general population.[53] However, few data are available on the isoenzyme polymorphisms that influence serum 25-OHD levels, such as 7-dehydrocholesterol reductase (responsible for the availability of 7-dehydrocholesterol in the skin), liver 25-hydroxylase, CYP2R1 (involved in the conversion of vitamin D into 25-OHD), and CYP24A1 (a key degradation enzyme). In addition, polymorphisms in *GC* gene, which encodes vitamin D–binding protein, have a major effect on serum 25-OHD concentration.[54]

Deficient 25-OHD levels in psoriatic patients may also be secondary to an inflammatory environment, and CRP was negatively correlated with 25-OHD in the current study. Chodorowska et al[55] reported that plasma acute-phase protein levels (CRP and

fibrinogen) were significantly elevated in patients with psoriasis versus in healthy control subjects, and a recent study showed low 25-OHD levels to be associated with endothelial dysfunction and inflammatory activation markers (CRP and asymmetric dimethylarginine concentrations).[56]

Study participants were asked to estimate the hours that they spent outdoors on weekdays and at weekends. Although not an optimal method to evaluate sun exposure, the same method was used in both groups and no significant differences were found. Other confounding factors associated with UV radiation, such as changes in latitude or climate, were minimized by recruiting all patients from the same geographic area and studying them all in the same 4-week period. Finally, new studies with larger numbers of patients are required to analyze the pathogenic mechanisms underlying the relationship between 25-OHD deficiency and psoriasis.

In conclusion, serum 25-OHD levels are significantly lower in psoriatic patients than in healthy control subjects, as found in other autoimmune or inflammatory conditions. These data support the idea of intervention studies with vitamin D in patients with psoriasis. In psoriatic patients, low 25-OHD levels are associated with markers of inflammatory activation (CRP), which may explain this deficiency. These findings also suggest that vitamin D levels are associated with obesity and that psoriatic patients with a BMI greater than or equal to 27 are likely to have vitamin D insufficiency (sensitivity of 82.3% and specificity of 51.7%).

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INVESTIGATIVE REPORT

Association of 25-hydroxyvitamin D with Metabolic Syndrome in Patients with Psoriasis: A Case-control Study

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Vitamin D deficiency has been related to higher cardiovascular risk and the metabolic syndrome (MeS) criteria in patients with psoriasis. The main objective of this study was to analyze the association of 25-hydroxyvitamin D (25-OHD) serum levels with MeS (NCEP-ATP III criteria) in 46 Spanish patients with psoriasis. without arthritis and systemic treatment and 46 control subjects, matched by sex and age. Psoriasis patients showed significant lower level of 25-OHD than controls (30.5 vs. 38.3 ng/ml; p=0.0001). Patients with MeS had significantly lower serum levels of 25-OHD than those without MeS (24.1±7.5 vs. 32.8±8.9, p=0.007) and, a negative correlation was found between 25-OHD and waist circumference, diastolic blood pressure, fasting glucose, and triglyceridemia. In the control group no significant correlation between 25-OHD and MeS was found. Although the sample was small, our results suggest a potential protective role for 25-OHD in the metabolic profile of patients with psoriasis without arthritis. Key words: psoriasis; vitamin D; metabolic syndrome; cardiovascular risk.

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Vitamin D has classically been associated with phosphorus-calcium metabolism and bone physiology. However, the finding of vitamin D receptors at different sites (1) suggests that vitamin D also has important extraskeletal functions. So, low vitamin D levels have been associated with adverse cardiovascular outcomes (2, 3) and metabolic syndrome (MeS). Individuals meeting ATP-III criteria for MeS have been found to have a greater likelihood of a cardiovascular event over the following 10 years (4).

Psoriasis has been associated with a higher prevalence of MeS and an increase in cardiovascular events (5–7) as also observed for other inflammatory dermatological diseases (8).

Several studies have reported vitamin D deficiency in patients with autoimmune diseases (9) as well as in psoriatic patients (10, 11).

Given the scarcity of published data relating vitamin D status and MeS in psoriasis, we conducted a case control study in order to evaluate the association of serum 25-hydroxyvitamin D (25-OHD) levels with the presence of MeS and metabolic parameters in psoriatic patients.

PATIENTS AND METHOD

Psoriatic patients

Patients with active psoriasis were systematically recruited from the outpatient clinic of the Dermatology department of San Cecilio University Hospital (Granada, Southern Spain). Inclusion criteria were: a clinical diagnosis of psoriasis, age ≥18 years, and residence in the metropolitan area of Granada. Exclusion criteria were: "sunny" holidays in the previous month, intake of calcium or vitamin D supplements in the previous 3 months, psoriatic arthritis (CASPAR criteria), psoriasis systemic treatment in the previous 6 months, antihypertensive, lipid-lowering, or antidiabetic therapy in the previous 3 months, or medical history of rheumatoid arthritis, type 1 diabetes mellitus, inflammatory bowel disease, multiple sclerosis, or renal function impairment.

Control individuals

Control individuals from the same geographic area were recruited from dermatology outpatient clinic (mainly nevi, seborrheic keratosis, or verruca)

matched with psoriasis patients by sex and age (± 2 years). Individuals were recruited with a time difference lower than 7 days since their matched psoriatic patient was evaluated. Exclusion criteria were the same established for psoriatic patients group. All patients or controls were recruited between July 18 and August 30 2011 to avoid bias due to seasonal variations in vitamin D.

The study was approved by the Ethics Committee of San Cecilio University Hospital and written informed consent was obtained from all patients in accordance with the Helsinki Declaration.

Clinical and laboratory parameters

Data were gathered on: age, sex, family history of psoriasis and age at diagnosis. We also recorded current tobacco habit (pack-years), alcohol intake (g/week), and an estimation of the time spent in the open air over the previous four weeks. Patients were asked about their consumption of vitamin D-rich and fortified foods in their usual diet, including: salmon, sardine, tuna, egg yolk, and vitamin-D fortified butter, margarine, milk, yogurt, cheese, and breakfast cereals (12). These data were used to calculate their daily vitamin D intake (in international units –IU-). Physical activity was assessed as the usual level of exercise over the previous year by means of the Tromsø physical activity questionnaire, which has proven to be a good predictor of the heart rate at rest and physical condition, comparable to the objective assessment of activity by accelerometry (13).

We recorded the participants' waist circumference, weight and height and calculated their body mass index (BMI; kg/m^2). Fitzpatrick phototype was also evaluated. Systolic (SBP) and diastolic (DBP)blood pressures were measured after a 5-minute rest and again after a 10-minute interval, and the mean values were recorded. Moreover, in psoriatic patients *psoriasis area and severity index* (PASI), and *body surface area* (BSA) were also registered.

Blood samples were drawn between 8 AM and 9 AM for laboratory analysis of biochemical parameters [triglycerides (TG), total cholesterol (TC), LDL, HDL, and fasting glucose], intact parathyroid hormone (iPTH), serum calcium, serum phosphorus, serum creatinine and determination of serum 25-(OH)D levels by

radioimmunoassay. Prevalence of the MeS was calculated according to NCEP-ATP-III criteria (14).

Statistical analysis

After descriptive statistical analysis of the general characteristics of the study participants, the Kolmogorov-Smirnov test was used to examine the distribution of variables and the Levene test to study the variance. The Student's *t* test was applied to compare mean values of quantitative variables when the distribution was normal and the Mann-Whitney *U* test when it was not. Qualitative variables were analyzed with the chi-square test or with Fisher's exact test if at least one cell had an expected count <5. For paired samples the Student's t test for paired samples and McNemar test were used. Pearson's coefficient was used to test the correlation between quantitative variables and serum 25-(OH)D level. Binary logistic regression models (Wald method) were used to measure the association between the presence of MeS and vitamin D levels in a multivariate analysis. P≤0.05 was considered significant. SPSS 17.0 was used for the data analyses (SPSS, Inc, Chicago, IL).

RESULTS

This study includes 92 individuals, 46 psoriatic patients without arthritis who were receiving no systemic treatment for psoriasis or any antidiabetic, antihypertensive, or lipid-lowering therapy and 46 healthy controls.

Table 1 summarizes data on the MeS parameters and the confounding factors associated with vitamin D status. Patients with psoriasis presented lower significant 25-OHD levels than controls (30.5±9.3 *vs.* 38.3±9.6 ng/ml; p=0.0001); 54.4% vs. 22.6% in the control group (p<0.0001) evidenced vitamin D insufficiency (<30 ng/ml). A higher proportion of individuals met MeS criteria in the psoriatic group (30.4% vs. 17.4% in control) (p=0.143), and the patients had increased fasting glucose (102.1 vs. 86.5 mg/dl p=0.026) and TG (140.7 vs. 103.6 mg/dl, p=0.017) levels.

In psoriatic patients, 25-OHD serum levels were negatively associated with age (r=-0.477, p=0.001), BMI (r=-0.410, p=0.005), waist circumference (r=-0.454, p=0.002), alcohol intake (r=-0.305, p=0.039), DBP (r=-0.320, p=0.030),

fasting glucose (r=-0.329, p=0.026), and serum TG (r=-0.368, p=0.012) [Fig. S1; available from http://www.medicaljournals.se/acta/content/?doi=10.2340/00015555-XXXX]. A trend to signification correlation was found between 25-OHD level and SBP (r=-0.287; p=0.053), sun exposure (r=0.266; p=0.074), and daily vitamin D intake (r=0.257; p=0.085). No significant correlation was found between psoriasis-related variables (PASI, BSA, family history of psoriasis and "time with psoriasis") and 25-OHD levels[1].

In control group, a positive correlation was found between 25-OHD levels and sun exposure (r=0.427, p=0.003) and between 25-OHD levels and HDL-c levels (r=0.286, p=0.054).

Both groups were divided regarding the presence of MeS (Table S1; available from http://www.medicaljournals.se/acta/content/?doi=10.2340/00015555-XXXX). In psoriasis group, the mean serum 25-OHD level was significantly lower in patients with MeS (24.1±7.5 vs. 32.8±8.9, p=0.007). In control group no significant differences were found in 25-OHD levels among individuals with and without MeS. Patients with psoriasis and MeS presented nearly significant higher values of PASI (3.61 vs. 6.18, p=0.08). Also patients and controls with MeS showed higher significant BMI than patients or controls without MeS. No significant differences were found in age, sex, smoking status, alcohol intake, physical activity, sun exposure, or daily vitamin D intake in patients or controls regarding the presence of metabolic syndrome.

The binary logistic regression model for MeS in psoriatic patients showed a positive significant association with 25-OHD insufficiency (p=0.038) after controlling for age, BMI, alcohol intake, sun exposure, vitamin D intake and

[1]In psoriasis group, serum 25-OHD levels were calculated according to the presence of NCEP-ATP III criteriaand were significantly lower in patients with higher waist circumference (≤102 cm vs.>102 cm: 34.30±8.71 vs. 26.39±8.22 ng/ml, p=0.004), higher fasting glucose (<100 mg/dl vs. ≥100 mg/dl: 32.55±9.10 vs. 24.05±6.80 ng/ml, p=0.007), and higher TG (<150 mg/dl vs. ≥150 mg/dl: 32.49±8.69 vs. 26.45±9.44 ng/ml, p=0.024), and a trend to signification was found for DBP (< 85 mmHg vs. ≥85 mmHg: 32.91±9.29 vs. 27.67±8.66, p=0.085). No significant differences in 25-OHD serum levels were found as a function of the presence of systolic hypertension or low HDL-C levels.

physical activity (Table SII; available from http://www.medicaljournals.se/acta/content/?doi=10.2340/00015555-XXXX).

DISCUSSION

In this study serum 25-OHD levels were significantly lower in patients with psoriasis than in controls. Moreover, in psoriatic group serum 25-OHD level was significant and inversely correlated with some MeS criteria, i.e., waist circumference, DBP, fasting glucose and TG levels. Accordingly, psoriatic patients with MeS showed a significantly lower level of 25-OHD than patients without MeS. Low level of 25-OHD found in psoriatic patients has been previously described (10, 11).

Waist circumference and BMI (proxies for adiposity)were previously reported to be negatively associated with vitamin D in general and psoriatic populations (10, 15). This relationship can be partially explained by the liposolubility of vitamin D and its reduced bioavailability in bodies with a high fat content (15), although a significant negative association between MeS and vitamin D independent of adiposity was observed in a study of morbidly obese patients (16). In our study the association between 25-OHD and MeS persisted after binary logistic regression that included the BMI. Regarding lower level of vitamin D in obese, a lesser exposure to the sun has been suggested due to poor mobility or cosmetic concerns[2]. Besides the possible reduction of vitamin D biodisponibility in obese, it has been suggested that vitamin D could regulate adipogenesis and that pre-adipocyte differentiation inhibition is mediated *via* the vitamin D receptor-dependent inhibition of C/EBPα and PPARY expression (17).

Regarding other MeS criteria, all have shown an inverse correlation with 25-OHD levels in epidemiological or experimental studies supporting these associations. Vitamin D receptors are present in human cells that can contribute

[2]However, we controlled this potential confounding factor in the present study by various means: exclusively enrolling residents of the same locality (Granada metropolitan area, Southern Spain); excluding patients who had been on a sunny holiday in the previous month; performing the study within a narrow time interval; and obtaining a self-estimate of sun exposure during the previous month. Moreover, no significant differences in sun exposure were found between obese and non-obese patients (data not shown).

to modifying blood pressure (e.g., cardiomyocytes, vascular smooth muscle cells, endothelial cells, and renin-producing juxtaglomerular cells) (18, 19). Experimental studies have reported a regulative role for vitamin D on renin system (19, 20). Moreover, vitamin D supplementation has been reported to have a beneficial effect on blood pressure in humans (21) and rats (22). A role for vitamin D in glucose metabolism is supported by the presence of vitamin D receptors (23) and the 1α-hydroxylase enzyme (24) in β pancreatic cells and by experimental findings of increased glucose-mediated insulin secretion in animals after vitamin D administration (25). The present finding of an inverse association between serum 25-OHD and TG values is also in agreement with cross-sectional or longitudinal studies (26, 27). Moreover, pro-inflammatory cytokines related with lipolysis (increase of free fatty acids) and insulin-resistance can be regulated by vitamin D (28, 29). Although in our sample significant correlation between vitamin D and HDL-c has not been found, a significant direct correlation has been found in other studies. It could be explained by the direct relationship found between vitamin D and apolipoprotein A-I, the main component of HDL-c. However, intrinsic mechanism is unknown (30). See Fig. S2 (available from http://www.medicaljournals.se/acta/content/?doi=10.2340/00015555-XXXX) for an integrated view of potential interrelations between different components of MeS and 25-OHD.

Currently, the intrinsic mechanisms that regulate the extraskeletal functions of vitamin D are not well known. In the study by Oh J et al. (31), macrophages from group of patients (obese, diabetic, hypertensive patients with vitamin D deficiency) showed a significant suppression of foam cell formation by reducing acetylated or oxidized low-density lipoprotein cholesterol uptake when were cultured in a media with 1,25-$(OH)_2$D *vs.* macrophages cultured in a vitamin D-deficient media. However this significant effect was not observed in a control group (obese, nondiabetic, hypertensive patients with vitamin D deficiency). In this sense, differences in correlation between MeS parameters and vitamin D have been found in our study in psoriasis group *vs* control group.

There are few studies evaluating the benefit of vitamin D supplementation on metabolic parameters. In the study of Al-Daghri et al (32) a mild benefit in cholesterol profile after one year of vitamin D supplementation in a general population was found. Moreover, different benefit on vitamin D supplementation has been reported depending on population features; a higher benefit seem to exist in patients receiving dialysis than in general population (33). So, based on difference found in 25-OHD-metabolic parameters correlation among psoriasis group and control group in the present study, it might be hypothesized that a higher benefit can result after vitamin D supplementation in a psoriasis population.

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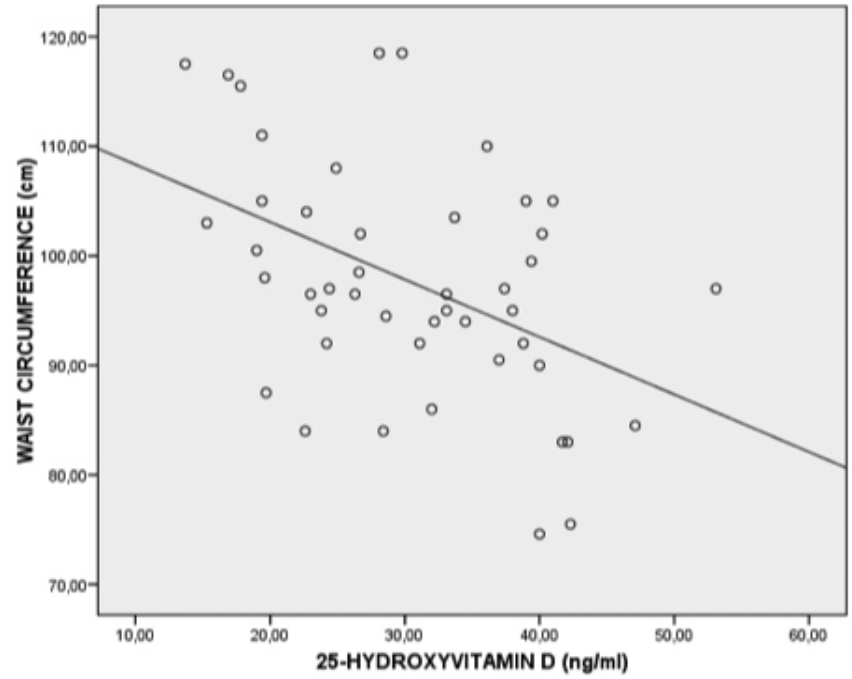
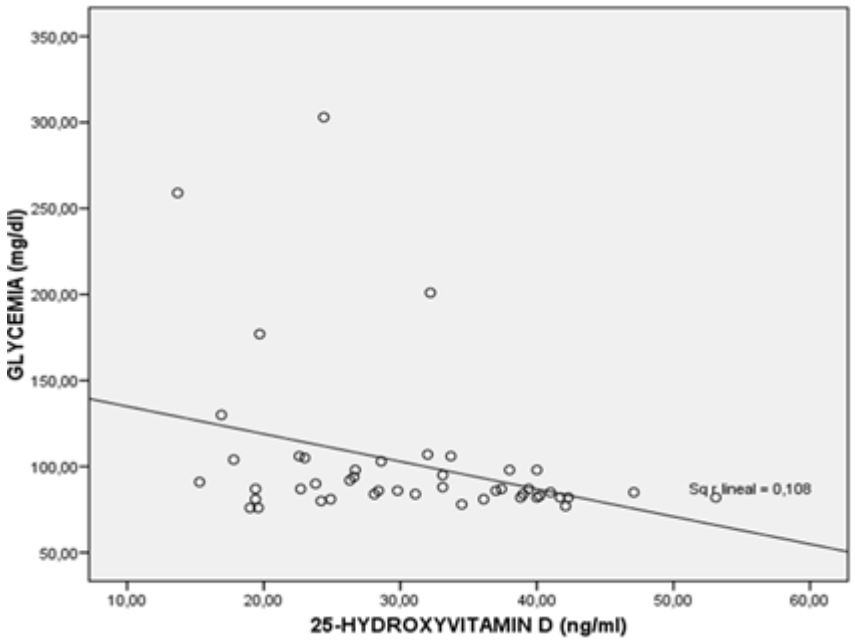
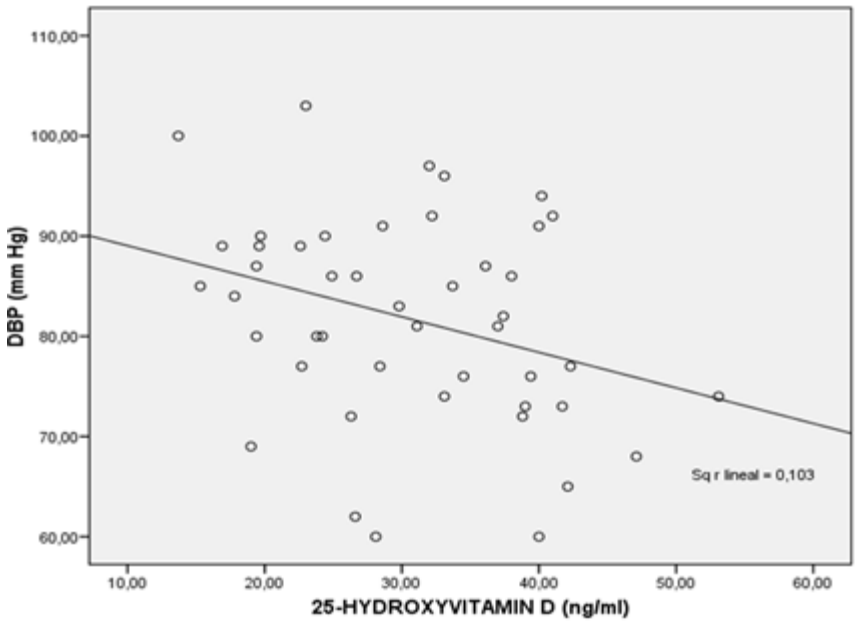
Table 1: General data of the study population.

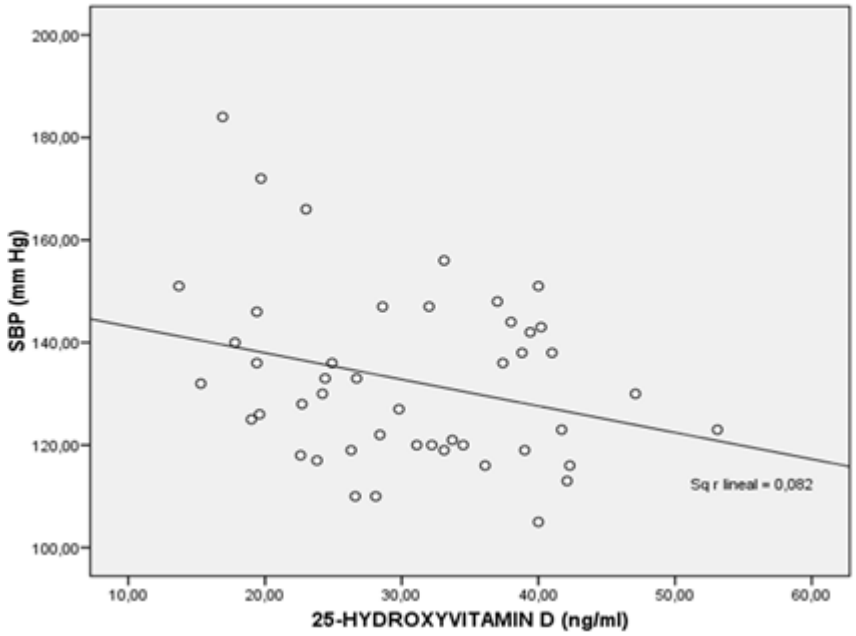
Variable	PSORIASIS	CONTROL	p value
	N=46	N=46	---
Age; yrs (mean±SD)	45.57±9.96	45.89±10.06	0.876
Sex; male (%)	26 (56.5)	26 (56.5)	1.000
PASI (mean±SD)	4.28±4.38	---	---
BSA; % (mean±SD)	5.10±7.08	---	---
Time with psoriasis; yr (mean±SD)	18.58±11.81	---	---
Family history of psoriasis: n (%)	20 (43.5)	---	---
Fitzpatrick skin phototype; I-III (%) IV-VI (%)	 22 (47.8) 24 (52.2)	 25 (54.4) 21 (45.6)	0.532
Waist circumference; cm (mean±SD)	97.57±10.74	94.58±11.75	0.207
BMI; kg/m^2 (mean±SD)	28.50±5.44	26.84±3.80	0.093
Smoking; pack-years (mean±SD)	11.97±12	9.85±12.28	0.405
Alcoholism; grams/week (mean±SD)	89.83±135.41	71.54±92.56	0.452
Physical activity; level 1 (%)	17 (37.0)	19 (41.3)	0.669
Vitamin D intake; IU/day (mean±SD)	188.72±136.83	172.92±102.18	0.532
Sun exposure; hours/week (mean±SD)	25.98±16.42	23.87±17.14	0.548
SBP; mm Hg (mean±SD)	132.52±16.76	126.07±25.95	0.288
DBP; mm Hg (mean±SD)	81.76±10.28	76.30±16.07	0.095
Fasting glucose; mg/dl (mean±SD)	102.09±45.21	86.46±9.36	0.026
Total-C; mg/dl (mean±SD)	207.57±37.05	201.54±38.85	0.452
LDL-C; mg/dl (mean±SD)	129.57±31.04	125.85±35.22	0.593
HDL-C; mg/dl (mean±SD)	52.52±14.38	54.54±13.36	0.487
TG; mg/dl (mean±SD)	140.74±91.64	103.61±47.46	0.017
MeS; n (%)	14 (30.4)	8 (17.4)	0.143
Calcium; mg/dl (mean±SD)	9.34±0.40	9.34±0.44	0.964
Phosphorus; mg/dl (mean±SD)	3.25±0.54	3.11±0.55	0.184
iPTH; pg/ml (mean±SD)	41.90±14.70	39.80±14.05	0.402
Creatinine; mg/dl (mean±SD)	0.75±0.13	0.76±0.13	0.783
25-OHD; ng/ml (mean±SD) <20 ng/ml (%) 20-<25 ng/ml (%) 25-<30 ng/ml (%) 30-<40 ng/ml (%) >40 ng/ml (%)	30.52±9.29 9 (19.6) 7 (15.2) 9 (19.6) 14 (30.4) 7 (15.2)	38.31±9.56 0 (0) 0 (0) 8 (17.4) 23 (50.0) 15 (32.6)	0.000

Fig. S1. Correlation analysis between 25-hydroxyvitamin D and components of the metabolic syndrome. 25-hydroxyvitamin D is inversely related to waist circumference, glycemia, DBP, SBP and triglyceridemia.






110,00
100,00
90,00
80,00
70,00
60,00
DBP (mm Hg)
Sq r lineal = 0,103
10,00
20,00
30,00
40,00
50,00
60,00
25-HYDROXYVITAMIN D (ng/ml)


200,00
180,00
160,00
140,00
120,00
100,00
SBP (mm Hg)
Sq r lineal = 0,082
10,00
20,00
30,00
40,00
50,00
60,00
25-HYDROXYVITAMIN D (ng/ml)

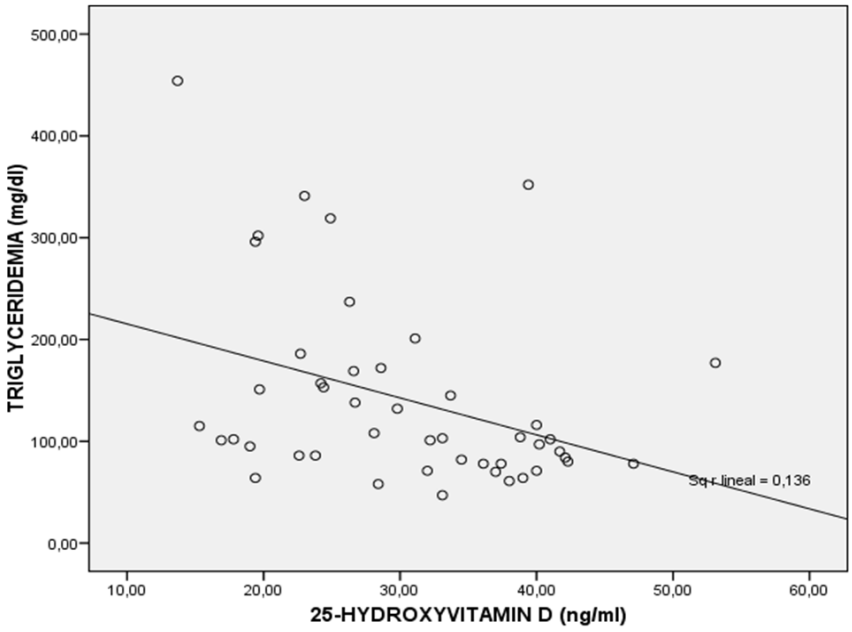
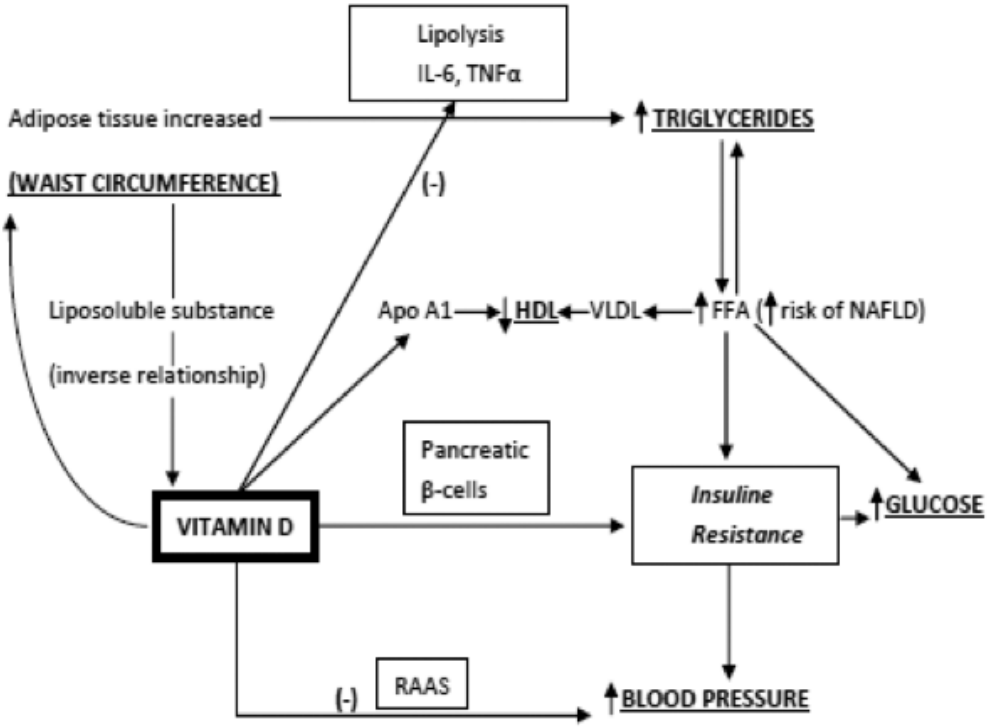

500,00
400,00
300,00
200,00
100,00
0,00
TRIGLYCERIDEMIA (mg/dl)
10,00
20,00
30,00
40,00
50,00
60,00
25-HYDROXYVITAMIN D (ng/ml)
Sq r lineal = 0,136

Fig. S2. Pathogenic mechanisms that may explain the association between MeS and vitamin D deficiency in psoriatic patients.



RAAS: "renin-angiotensin-aldosterone system".
Metabolic syndrome criteria in bold: waist circumference, high blood pressure, triglycerides, glucose, and HDL.
Inverse relationship between vitamin D and waist circumference (adipose tissue): vitamin D influences the inhibition of pre-adipocyte differentiation.Waist circumference is an essential component of the MeS and is related with a higher level of triglycerides, free fatty acids and insulin resistance. Vitamin D influences the lipolysis of triglycerides by inhibiting the secretion of pro-inflammatory cytokines (IL-6 and TNFα).Moreover, various authors have reported that vitamin D exerts an influence on pancreatic β-cells and the renin-angiotensin-aldosterone system. Finally, a positive relationship has been documented between vitamin D and HDL-C.

Table Table SI. Mean and standard deviation (SD) of different variables according to the presence of the metabolic syndrome in both psoriasis and control group.

VARIABLES	PSORIASIS		p value	CONTROL		p value
	No MeS	MeS		No MeS	MeS	
n (%)	32 (69.6)	14 (30.4)		38 (82.6)	8 (17.4)	
Age; yrs (mean±SD)	45.12±10.45	46.83±8.71	0.460	44.64±10.21	52.86±5.73	0.026
Sex; male (%)	58.82	50.00	0.738	53.85%	71.43%	0.446
Time with psoriasis	18.80±11.82	17.92±12.30	0.764	---	---	---
PASI; (mean±SD)	3.61±3.83	6.18±5.38	0.080	---	---	---
BSA; % (mean±SD)	4.11±5.95	7.91±9.34	0.121	---	---	---
Family history of psoriasis n (%)	15/34 (44.1)	5/12 (41.7)	0.883	---	---	---
BMI; yrs (mean±SD)	27.46±5.37	31.42±4.68	0.005	25.89±3.18	32.09±2.46	0.000
Smoking; pack-years (mean±SD)	11.42±11.37	13.50±14.04	0.723	9.12±12.56	10.32±11.79	0.835
Alcoholism; grams/week (mean±SD)	77.88±102.92	123.67±203.81	0.832	63.10±70.57	118.57±172.26	0.631
Physical activity; level 1 (%)	32.35	50.00	0.314	41.03	75.00	1.000
Vitamin D intake; IU (mean±SD)	194.63±140.99	171.99±128.64	0.679	175.56±90.62	158.23±161.26	0.202
Sun exposure; h/week (mean±SD)	35.75±21.41	28.17±21.02	0.271	25.53±15.71	28.52±21.24	0.842
25-OHD; ng/ml (mean±SD)	32.80±8.85	24.05±7.50	0.007	37.65±9.84	41.99±7.41	0.112

Table Table SII. Binary logistic regression model for the metabolic syndrome (NCEP-ATP III) in psoriatic patients. 25-hydroxyvitamin D shows an independent association with MeS after adjusting for potential confounding factors.

Variable	**OR**	**95% CI**	**p**
Age	0.948	0.853-1.053	0.317
BMI	1.080	0.926-1.259	0.328
Alcohol intake	0.999	0.993-1.005	0.825
Sun exposure	1.000	0.960-1.042	1.000
Vitamin D intake	1.003	0.996-1.010	0.429
Physical activity	1.260	0.243-6.534	0.783
25-OHD insufficiency	0.844	0.720-0.990	0.038

VITAMIN D INSUFFICIENCY IS ASSOCIATED WITH HIGHER CAROTID INTIMA-MEDIA THICKNESS IN PSORIATIC PATIENTS: A CASE-CONTROL STUDY.

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Running Head: "Vitamin D and Intima-media thickness in psoriatic patients"

Words: 3430 Table:6 Figures 3

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VITAMIN D INSUFFICIENCY IS ASSOCIATED WITH HIGHER CAROTID INTIMA-MEDIA THICKNESS IN PSORIATIC PATIENTS: A CASE-CONTROL STUDY.

Abstract

Background: Psoriasis has been recently associated with vitamin D insufficiency and cardiovascular risk factors regarding to healthy controls. Various studies have reported that serum 25-hydroxyvitamin D (25-OHD) levels are inversely associated with chronic inflammatory systemic diseases, cardiovascular risk factors, and cardiovascular outcomes.

Objective: The main objective was toanalyze the association between 25-hydroxyvitamin D serum level and subclinical carotid atherosclerosis (maximal intima-media thickness [MIMT]) in patients with psoriasis and controls. Also MIMT was compared in patients and controls and associated factors were analyzed.

Patients and Method: The above associations were investigated in a case-control study with 88 individuals: 44 psoriatic patients without arthritis from the Dermatology outpatient clinic of a reference hospital in Granada (Spain) and 44 controls. Confounding factors related to 25-OHD serum levels and cardiovascular risk factors were also analyzed.

Results: 25-OHD levels were significantly lower in psoriatic group regarding the control group (29.20 vs. 38.00 ng/ml $p<0.0001$) and a significant negative correlation was found between serum 25-OHD levels and the MIMT (r_s=-0.678,

p<0.0001) in psoriatic patients and no correlation was found in healthy controls. This association is remained after adjusting for confounders. Serum 25-OHD levels were significantly lower (p=0.003) in psoriatic patients with carotid atheromatous plaque (22.38±10.23 ng/ml) than in those without (31.74±8.62 ng/ml). A positive correlation was found between the time with psoriasis and the MIMT independently of other confounding factors including age. Patients with larger history of psoriasis presented higher significant MIMT than controls (638.70±76.21 vs 594.67±80.20**μ**m; p=0.026 for ≥6 yrs with psoriasis).

Conclusions: In patients with psoriasis, lower serum 25-OHD levels were associated with higher MIMT after adjusting for selected confounding factors. Moreover, the risk of MIMT increases with a longer history of psoriasis, regardless of the patient age.

Key words: vitamin D, 25-hydroxyvitamin D, carotid artery atherosclerosis, cardiovascular risk factors, psoriasis.

INTRODUCTION

Atheromatosis is currently understood in the setting of a chronic inflammatory process. Thus, a parallelism has been described between the pathogenesis of a psoriasis plaque and that of an atherosclerotic plaque, with considerable overlap at the cellular and cytokine level. Thus, it has been found that macrophages and Th1 cells play a key role in the development of both plaque types.[1]

Carotid plaque and intima media thickness, which can be measured in a non-invasive manner, are predictors of future vascular events.[2,3] Individuals with higher carotid intima media thickness levels have an increased risk of cardiovascular disease. Classical cardiovascular risk factors are associated with atherosclerosis,[4,5] and chronic inflammation has also been implicated in this disease.[6] With regard to psoriasis, an increased prevalence of cardiovascular risk factors and higher grade of atheromatosis are well documented in psoriatic patients.[7]

Vitamin D deficiency is observed in numerous chronic systemic inflammatory diseases, including psoriasis, for reasons that have yet to be clarified.[8-10] However, vitamin D is known to have an immunoregulatory function and appears to act on Th1 lymphocytes and macrophages.[11] Low vitamin D levels have also been associated with a higher risk of cardiovascular disease and mortality.[12-15]

With this background, we carried out a study to evaluate the relationship between serum 25-OHD and carotid intima media thickness in psoriatic patients without arthritis and controls to evaluate the association between the carotid intima media thickness and other psoriasis-related clinical parameters.

PATIENTS AND METHODS

Psoriatic patients

Psoriatic patients were consecutively recruited from among those attending the Dermatology outpatient clinic of San Cecilio University Hospital (Granada), between 14th June and 17th August 2011. Inclusion criteria were: age ≥18 yrs, clinical diagnosis of psoriasis, and signing of informed consent to study participation. Exclusion criteria were: psoriatic arthritis, diagnosed by a rheumatologist based on previous medical history or CASPAR criteria; systemic treatment for psoriasis in the previous 12 months; phototherapy treatment in the previous 3 months; intake of calcium or vitamin D supplements in the previous 3 months; a "sunny" holiday in the previous 4 weeks; receipt of antidiabetic drugs; antihypertensive or lipid-lowering treatment; previous arterial or venous thrombotic events and any chronic inflammatory disease or autoimmune disease, e.g., systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, type 1 diabetes mellitus or renal insufficiency.

Control individuals

Control individuals were recruited from Dermatology outpatient clinic (mainly nevi, seborrheic keratosis, or verruca) matched with psoriasis patients by sex, age (± 2 years). Other inclusion criterion was signing of informed consent. Exclusion criteria were: a "sunny" holiday in the previous 4 weeks; receipt of antidiabetic drugs; antihypertensive or lipid-lowering treatment; previous arterial or venous thrombotic events and any chronic inflammatory disease or

autoimmune disease, e.g., psoriasis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, type 1 diabetes mellitus or renal insufficiency. No control individuals refuse to participate in the study. Patients with full selected criteria were recruited with a time of difference lower than 7 days since psoriatic patients were evaluated.

The study was approved by the Ethics Committee of San Cecilio University Hospital, and written informed consent was obtained from all patients in accordance with the Helsinki Declaration.

Clinical and laboratory parameters

Data were gathered on the following patient or control characteristics: age, sex, Fitzpatrick skin type, daily vitamin D intake based on the consumption of vitamin D-rich foods,[16] self-reported time spent outdoors in the previous 4 weeks (h/week), smoking (pack-years), and alcohol intake (g/week). Exclusively in patients with psoriasis the following parameters were obtained: psoriasis area and severity index (PASI), body surface area (BSA), the number of years since psoriasis onset ("time with psoriasis") and any family history of the disease. Self-reported physical activity was recorded, based on the four response categories of Tromsø´squestionnaire:[17] level 1 (reading, watching television, or engaging in sedentary activities), level 2 (at least 4 h/week walking, bicycling, or engaging in other types of physical activity), level 3 (at least 4 h/week exercising to keep fit and/or participating in recreational athletics), and level 4 (regular, vigorous training or participating in competitive

sports several times a week). Only levels 1 and 2 of physical activity were considered, because of no patient or control reported a higher level.

The weight (with light clothing and no shoes) and height (no shoes) of patients and controls were measured and used to calculate the body mass index (BMI, kg/m^2). Systolic (SBP) and diastolic (DBP) blood pressures were measured after a 5-minute rest and again after a 10-minute interval, and the mean values were recorded. Total serum cholesterol (total-C), HDL-C, LDL-C, atherogenic index (total-C/HDL-C), triglycerides (TGs), fasting glucose, glycosylated hemoglobin (HbA1c), 25-OHD (determined by commercial radioimmunoassay), serum creatinine, intact parathyroid hormone (iPTH), serum calcium and phosporus were studied in samples drawn between 8 and 9 AM after a rest period of ≥ 30 min.

The carotid intima media thickness was measured by ultrasonography in both common carotid arteries, following the technique proposed by the American Society of Echocardiography[18] and using a high-resolution B-mode cardiovascular ultrasound machine (MyLab25Gold, Esaote Biomedica, Genova, Italy) with a 10 Mhz linear transducer. All measurements were carried out by a single experienced radiologist blinded to the clinical information. The reproducibility of MIMT and plaque detection results has been documented.[19] The carotid intima media thickness was measured in the distal common carotid artery at 1 cm proximal to the carotid bulb, using automated edge detection software (QIMT, Esaote Biomedica, Genova, Italy). We recorded the presence of atherosclerotic plaques, defined as a localized thickening > 1.2 mm that did

not uniformly involve the whole artery, and the maximum carotid intima media thickness (MIMT) value in either left or right carotid of each patient or control.

Statistical analysis

SPSS 17.0 (SPSS Inc, Chicago, IL) was used for the data analyses. After a descriptive analysis, the Spearman correlation test was used to determine the relationship of serum 25-OHD or MIMT with other quantitative variables. T student test (Mann-Whitney U test, if Student's t test was not possible) was used to compare values of quantitative variables distributed in two independent samples and Chi-square test (Fisher's exact, if Chi-square test was not possible) test to compare qualitative variable results. For paired samples the Student's t test for paired samples and McNeman test were used. A multiple linear regression analysis was performed to analyze the association between MIMT and 25-OHD after adjusting for confounding factors. The standardized coefficient of determination was calculated. $P \leq 0.05$ was considered statistically significant.

RESULTS

General data

This study included 88 individuals, 44 healthy control and 44 patients with psoriasis without arthritis and not undergoing systemic psoriasis therapy or any antidiabetic, antihypertensive, or lipid-lowering treatments. None of the patients who were eligible for the study refused to participate. Table 1 reports the clinical features of both study groups: a lower significant serum level of 25-OHD in patients with psoriasis regarding to controls was found (29.20±9.16 vs. 38.00±10.16; p=0.0001). Among the group of patients with psoriasis 54.5% (vs. 22.7% p<0.0001, in the control group) evidenced vitamin D insufficiency (<30 ng/ml), despite the evaluation was performed in summer months. No significant differences were found in others variables including iPTH, calcium and phosphorus except for a significant higher value of fasting serum glucose in psoriatic patients (101.34±46.58 vs. 88.23±9.36 mg/dl; p=0.040).

25-hydroxyvitamin D serum levels: correlation with Maximal Intima Media Thickness and with other parameters

Table 2 exhibits the results of Spearman correlation (r_s) analysis of the relationship between 25-OHD serum levels and other quantitative variables. In patients with psoriasis, serum 25-OHD was negatively and significantly correlated with the MIMT (r_s=-0.678, p=0.000) [Fig. 1]. Moreover, serum 25-OHD showed also an inverse correlation with age (r_s=-0.499, p=0.001), BMI (r_s=-0.300, p=0.048), serum total-C (r_s=-0.475, p=0.001), LDL-C (r_s=-0.465,

p=0.001), and TG (r_s=-0.396, p=0.008) levels. No significant correlation between PASI and 25-OHD levels was found (p>0.05). In the control group, 25-OHD did not show a significant correlation with MIMT. However a positive significant correlation was found between serum 25-OHD and SBP (r_s=-0.348, p=0.020), DBP (r_s=-0.353, p=0.019) and HDL-c (r_s=0.305, p=0.044) in the control group.

Factors associated with Maximal Intima Media Thickness and atheroma plaque

In psoriasis group, MIMT was positively and significantly correlated with classical cardiovascular risk factors (table 3) such as age (r_s=0.701, p=0.000), BMI (r_s=0.356, p=0.018), DBP (r_s=0.310, p=0.041), and serum total-C (r_s=0.363, p=0.015), and TG (r_s=0.355, p=0.026) levels. Regarding vitamin D status, negative correlations were found between the MIMT and daily vitamin D intake (r_s=-0.295, p=0.052). Regarding related-psoriasis features, the MIMT was not significantly associated with the BSA, PASI, or family history of psoriasis (data not shown) but was positive and significantly associated with the years since clinical onset of the disease ("time with psoriasis") [r_s=0.318, p=0.036]. No significant correlation between age and time with psoriasis was found (r=0.059; p=0.705), as patients with type 1 and 2 psoriasis were included.

In the control group a significant correlation between MIMT and age (r_s=0.49; p=0.001), BMI (r_s=0.38; p=0.01), fasting glucose (r_s=0.33; p=0.027) was found (table 3).

Patients with psoriasis were divided between those with values above and below the median MIMT value of the study sample (634.5**µ**m) [table 4]. In comparison to the lower-MIMT group, the age (39.68±7.82 vs. 52.77±6.89 yrs, p=0.000), percentage of sedentary patients ("level 1" of physical activity: 27.27 vs. 63.63%, p=0.033), DBP (75.36±10.63 vs. 84.32±9.69 mmHg, p=0.008), fasting glucose level (93.77±47.35 vs. 108.91±45.62 mg/dl, p=0.008), serum total-C (197.09±42.99 vs. 221.14±34.45 mg/dl, p=0.019) and LDL-C (123.41±35.02 vs. 140.64±29.78 mg/dl, p=0.043) levels were significantly elevated in the higher-MIMT group. The mean serum 25-OHD level was significantly higher in the lower-MIMT group (33.21±9.52 vs. 25.19±6.90 ng/ml, p=0.006). No significant differences were found in the other study variables.

In comparison to the psoriatic patients without atheromatous plaques, those with plaques (n=5, table 5) showed a significantly higher serum total-C (204.41±39.17 vs. 245.80±32.38 mg/dl, p=0.023) and a tendency to a significantly higher age (45.31±10.05 vs. 53.40±3.05 yrs, p=0.053) and LDL-C levels (128.79±32.69 vs. 157.20±29.40 mg/dl, p=0.058), and they had a significantly lower daily vitamin D intake (140.19±84.11 vs. 46.12±40.16 IU, p=0.003) and serum 25-OHD level (31.74±8.62 vs. 22.38±10.23 ng/ml, p=0.003).

Table 6 lists the confounding factors included in the multiple linear regression analysis for the relationship between 25-OHD and MIMT in psoriatic patients (R^2 of adjusted model=0.627; p=0.0001). Despite the inclusion of key potential

confounders in the model, the association between MIMT and serum 25-OHD remained statistically significant (standardized **β**=-0.485, p=0.003). Moreover, a significant association was found between the MIMT and the time since clinical onset of psoriasis ("time with psoriasis") after controlling for the same confounding factors (standardized **β**=0.227, p=0.045).

The sample was divided between patients with serum 25-OHD <30 ng/ml (vit D insufficiency) and those with serum 25-OHD ≥30 ng/ml. Figure 2 shows that the mean MIMT was higher in the group with vitamin D insufficiency (677.75±65.49 vs. 597.25±66.52 **μ**m, p=0.001). This association between vitamin D insufficiency (dependent variable) and MIMT remained statistically significant (p=0.006) in a multivariable binary logistic regression analysis after adjustment for age, BMI, physical activity, DBP, alcohol intake, sun exposure, daily vitamin D intake, fasting glucose, and serum total-C, LDL-C and TG levels (data not shown).

Comparison of Maximal Intima Media Thickness among patients with psoriasis and control group

No significant differences regarding MIMT in patients with psoriasis and controls for the whole study population were found (641.16±76.77 *vs.* 626.14±110.24; p=0.460). However when patients with a larger history of psoriasis were analyzed, they presented a higher significant MIMT than age-sex matched controls (638.70±76.21 *vs.* 594.67±80.20; p=0.026, for patients with a psoriasis (n=33) history> 6 years regarding controls (n=33) and 645.38±75.66 *vs.* 582.90±73.00; p=0.001, for patients with a psoriasis (n=29) history >8 years regarding controls (n=29)). [Figure 3]. There were no differences in values of BMI, total-c, LDL-c, or HDL-c between both groups of study (data not shown).

DISCUSSION

Patients with psoriasis presented lower significant serum levels of 25-OHD, with a higher significant percentage of vitamin D insufficiency than healthy controls. In patients with psoriasis, a significant negative association was found between serum 25-OHD levels and the MIMT, a marker of preclinical atherosclerosis[20] after controlling for confounding factors. We also observed a significant positive association between the years with psoriasis (since clinical onset) and the MIMT that was independent of the other confounders, including patient age.

Serum 25-hydroxyvitamin D levels

Data showed a lower level of vitamin D in patients with psoriasis than in control. Patients with psoriasis group showed very low levels of serum 25-OHD despite conducting the study during the summer, when vitamin D levels in the general population are at their highest (54.5% of them showed vitamin D insufficiency). This result has been reported by some authors[9,10] and vitamin D insufficiency as a predisposing factor for development of autoimmune diseases has been proposed as hypothesis.[10]

25-hydroxyvitamin D and Maximal intima-media thickness in patients with psoriasis

- *Data suggesting a direct influence of 25-hydroxyvitamin D on atherosclerosis*

In patients with psoriasis, serum 25-OHD level was significantly lower in the patients with higher MIMT values, and this association remained significant after a multiple linear regression analysis that included other variables associated with serum 25-OHD and/or MIMT levels (BMI, time with psoriasis, sun exposure, vitamin D intake, alcohol intake, physical activity, fasting glucose, and serum total-C, LDL-C, and TG). This association was recently reported in individuals with HIV-infection or type 2 diabetes and in the general population.[21-24]

Atherosclerosis is currently considered an inflammatory process in which an important role is played by immune system cells such as Th1 lymphocytes and macrophages. A review by Späh F[1] describes various pathogenic characteristics shared by chronic inflammatory systemic and cardiovascular diseases, including their inflammatory cytokine profile and the local and systemic presence of inflammatory markers. Both psoriasis and atherosclerosis are mediated immunologically by a Th1 cytokine pattern, and vitamin D shifts this pattern in favor of a Th2 response, playing an immunoregulatory role.[25]The precise relationship of cellular vitamin D with atherosclerosis is not clear. However, Oh J et al[26] cultivated macrophages from obese patients with diabetes and hypertension in a vitamin D-deficient medium and reported an increased

formation of modified LDL (acetylated and oxidized) and foam cells (which play a key role in atherosclerosis) in comparison to macrophages cultivated in a 1,25-dyhydroxyvitamin D-supplemented medium. This suggests that vitamin D may have a direct effect on the development of atherosclerosis, which could explain our finding of an association between lower serum 25-OHD levels and higher MIMT. In addition, *in vitro* studies have shown that vitamin D receptor (VDR) activation inhibits the production of atherogenic cytokines (interferon-**γ**, interleukin-1**β**, and interleukin-6) and upregulates antiatherogenic cytokines (interleukin-10).[27] Thus, VDR knockout mice possess increased levels of proatherogenic factors, including interleukin-6 and tumor necrosis factor-**α** (TNF-**α**).[28] Further evidence was provided by the report of substantial atherosclerosis in transgenic rats that constitutively express vitamin D-24-hydroxlyase.[29] These data suggest a probable direct effect of vitamin D on the development of atherosclerosis.

- *Data suggesting an indirect influence of 25-hydroxyvitamin D on atherosclerosis*

In the present study, a statistically significant inverse correlation was observed between serum 25-OHD and serum total-C, LDL-C, and TG levels, as previously reported.[30-32] We also found a tendency to significance for serum 25-OHD to be related to fasting glucose, HbA1c, insulin resistance, and the prevalence of type 2 diabetes, consistent with previous studies.[33-35] A role for vitamin D in glucose metabolism has been indicated by the presence of VDRs[36] and 1**α**-

hydroxylase[37]in pancreatic **β**-cells, and animal studies found vitamin D to be responsible for an increase in glucose-mediated insulin secretion.[38]

Blood pressure, another cardiovascular risk factor, was inversely associated with serum vitamin D levels in previous studies[39]. VDRs are localized in various cells related to blood pressure regulation, including cardiomyocytes, vascular smooth muscle cells, endothelial cells, and renin-producing juxtaglomerular cells.[40-42] It has also been reported that vitamin D may be related to smooth muscle cell proliferation,[43] inflammation,[44] and thrombosis.[45] In addition, a relationship has been proposed between vitamin D and the physiology of the renin-angiotensin system, based on experimental findings that the renin-angiotensin axis is regulated by 1,25-hydroxyvitamin D through the suppression of renin gene expression.[40,46] Thus, renin overexpression was produced in wild-type mice by the pharmacological inhibition of vitamin D synthesis.[40] In humans, vitamin D supplementation was reported to have beneficial effects on metabolic parameters.[32,47,48] The inverse associations observed between vitamin D and cardiovascular risk factors suggests that this vitamin may exert an indirect influence on the development of atherosclerosis.

No significant correlation between 25-OHD and MIMT in control group were found, although others studies have found such association[49]. In the above-mentioned experiment performed by Oh J et al,[26] the effect of vitamin D on macrophages differed according to the characteristics of the individuals from whom they derived (obese diabetic hypertensive patients *vs.* controls). So, with small sample Oh J study, benefit of vitamin D on reduction of modified LDL

particles and foam cells development was not found in control group. In that sense, it seems that the influence of vitamin D status on the physiology of psoriasis patients could differ from that in other populations. From this standpoint, it could be explained the differences in correlation found between 25-OHD and MIMT in both group evaluated. However and certainly, there is much to know about the physiopathogenic details of extraskeletal functions of vitamin D and elements that determine the influence of vitamin D in these extraskeletal functions can be an issue in the future.

Maximal Intima Media Thickness and time with psoriasis

An increased risk of cardiovascular disease and atherosclerosis has been reported in patients with psoriasis and attributed to their greater inflammatory state *versus* controls.[7] However, these case-control studies cannot confirm that the inflammatory status distinguishing the patients from the controls is responsible for their more advanced state of atheromatosis. Longitudinal studies are required to evaluate the correlation between inflammatory status and atheromatosis. Di Minno et al[50] found a lower IMT in patients with psoriatic arthritis under anti-TNF treatment (note the important role played by TNF-**α** in both systemic inflammatory disease and atheromatosis) than in those receiving methotrexate. In this way, the influence of the inflammatory status on the atheromatosis process is revealed. Hürlimann D et al[51] adopted a longitudinal approach to the relationship between inflammatory status and endothelial function. They examined rheumatoid arthritis patients refractory to methotrexate and prednisone before and after a 12-week course of infliximab

(anti-TNF drug) and observed an improvement in endothelial function as well as in analytical results.

We studied the relationship between atheromatosis (MIMT) and the time with psoriasis. In our limited sample, no significant differences regarding MIMT in the whole group were found. However, interestingly when patients with lower than 6 years of psoriasis history were excluded and psoriasis group is compared with the corresponding age-sex matched controls, significant difference are found in MIMT. This difference is higher when patients with or lower than 8 years of psoriasis history were excluded. So, when patients with several years of exposition to this inflammatory disease were evaluated, differences in atheromatosis process (MIMT) are easily manifested. This result is also confirmed in multiple linear regression analysis (table 5) in which the variable "time with psoriasis" is an independent factor associated to MIMT. Hence, it is important to highlight that patients with psoriasis of many years of evolution may be at higher risk of a cardiovascular event, regardless of their age.

The study limitations include its cross-sectional nature. With a higher study sample is likely to find significant differences in MIMT between psoriatic patients and controls as previous studies have shown[7]. An interventional study is required to establish whether the inverse association found between serum 25-OHD and MIMT represents a causal relationship. The study design (e.g., short study period to avoid seasonal variations in vitamin D levels and inclusion/exclusion criteria) also resulted in a small sample size, although high statistical significance values were obtained, even in the multivariate analysis.

In conclusion, this study shows an inverse association between serum 25-OHD and MIMT in psoriatic patients without arthritis after controlling for potential confounding factors. To our best knowledge, this is the first report of arelationship between 25-OHD and MIMT in patients with psoriasis. These data are supported by several studies that suggest a possible direct and indirect influence of vitamin D on the atherosclerosis process. Interventional studies to determine the effects of vitamin D supplementation on the atherosclerosis process in psoriatic patients without arthritis would be necessary. Moreover, a direct association has been found between time with psoriasis and MIMT after adjusting for potential factors, including age, suggesting that the chronic inflammation status generated by psoriasis over time may influence the atherosclerosis process. Finally, patients with psoriasis of many years of evolution may be at greater risk of a cardiovascular event, regardless of their age.

Table 1. General data of both groups of study, including classical cardiovascular risk factors and possible confounding factors for serum 25-hydroxyvitamin D.

Variable	Psoriasis	Control	p value
Age; yrs (mean±SD)	46.23±9.84	45.73±10.05	0.814
Sex; male (%)	59.1	59.1	1.000
PASI (mean±SD)	3.89±3.50	---	---
BSA; % (mean±SD)	3.87±4.54	---	---
Time with psoriasis; yr (mean±SD)	16.51±11.99	---	---
Fitzpatrick skin phototype; I-III (%) IV-VI (%)	 27 (61.4) 17 (38.6)	 30 (68.2) 14 (31.8)	0.503
BMI (kg/m^2)	27.99±4.61	26.88±3.71	0.224
Smoking (pack-years)	13.46±18.30	10.36±14.98	0.350
Alcoholism; grams/week (mean±SD)	72.16±124.56	70.80±94.99	0.954
Physical activity; level 1 (%)	20 (45.5)	20 (45.5)	1.000
Vitamin D intake; IU/day (mean±SD)	129.50±85.53	136.61±73.75	0.677
Sun exposure; hours/week (mean±SD)	31.98±19.99	32.84±19.17	0.837
SBP; mm Hg (mean±SD)	129.34±15.32	126.16±26.37	0.491
DBP; mm Hg (mean±SD)	79.84±11.02	76.75±16.11	0.296
Fasting glucose; mg/dl (mean±SD)	101.34±46.58	88.23±9.36	0.040
HbA1c; % (mean±SD)	5.75±1.35	5.39±0.30	0.083
Total-C; mg/dl (mean±SD)	209.11±40.38	202.05±39.29	0.408
LDL-C; mg/dl (mean±SD)	132.02±33.28	126.43±35.65	0.449
HDL-C; mg/dl (mean±SD)	53.32±13.50	54.52±13.73	0.679
TG; mg/dl (mean±SD)	127.86±79.17	105.09±48.62	0.108
Total-C/HDL-C; mg/dl (mean±SD)	4.08±1.00	3.90±1.28	0.457
Creatinine; mg/dl (mean±SD)	0.69±0.18	0.74±0.12	0.114
iPTH; pg/ml (mean±SD)	43.90±15.80	41.68±14.05	0.462
Phosphorus; mg/dl (mean±SD)	3.55±0.42	3.40±0.34	0.401
Calcium; mg/dl (mean±SD)	9.35±0.41	9.35±0.45	0.961
25-OHD; ng/ml (mean±SD) Minimum-Maximum <25 ng/ml (%) 25-35 ng/ml (%) >35 ng/ml (%)	29.20±9.16 13.70-56.00 19 (43.2) 13 (29.5) 12 (27.3)	38.00±10.16 21.10-64.80 2 (4.55) 20 (45.45) 22 (50)	0.000
MIMT; μm (mean±SD)	641.16±76.77	626.14±110.24	0.460

Table 2. Spearman correlation analysis between different variables and 25-hydroxyvitamin D in patients with psoriasis and controls.

Predictor variables	Standardized β	T value	p value
Age	0.377	2.818	0.008
BMI	0.148	1.351	0.187
Time with psoriasis	0.227	2.089	0.045
Sun exposure	0.014	0.113	0.911
Vitamin D intake	0.028	0.217	0.830
Alcohol intake	-0.129	-1.004	0.324
Physical activity	-0.112	-0.945	0.352
Fasting glucose	-0.012	-0.092	0.928
Total-C	0.431	1.315	0.199
LDL-C	-0.492	-1.508	0.142
TG	0.013	0.085	0.933
25-OHD	-0.485	-3.202	0.003
Constant		4.014	0.000

Table 3. Spearman correlation between different variables and the maximal intima-media thickness among patients with psoriasis and controls.

Predictor variables	Standardized β	T value	p value
Age	0.377	2.818	0.008
BMI	0.148	1.351	0.187
Time with psoriasis	0.227	2.089	0.045
Sun exposure	0.014	0.113	0.911
Vitamin D intake	0.028	0.217	0.830
Alcohol intake	-0.129	-1.004	0.324
Physical activity	-0.112	-0.945	0.352
Fasting glucose	-0.012	-0.092	0.928
Total-C	0.431	1.315	0.199
LDL-C	-0.492	-1.508	0.142
TG	0.013	0.085	0.933
25-OHD	-0.485	-3.202	0.003
Constant		4.014	0.000

Table 4. Distribution of variables according to the MIMT value (above or below median value of 634.5 **μ**m in the study population) in psoriatic patients.

Predictor variables	Standardized β	T value	p value
Age	0.377	2.818	0.008
BMI	0.148	1.351	0.187
Time with psoriasis	0.227	2.089	0.045
Sun exposure	0.014	0.113	0.911
Vitamin D intake	0.028	0.217	0.830
Alcohol intake	-0.129	-1.004	0.324
Physical activity	-0.112	-0.945	0.352
Fasting glucose	-0.012	-0.092	0.928
Total-C	0.431	1.315	0.199
LDL-C	-0.492	-1.508	0.142
TG	0.013	0.085	0.933
25-OHD	-0.485	-3.202	0.003
Constant		4.014	0.000

Table 5: Distribution of variables based on presence of atheromatous plaques in common carotid artery in patients with psoriasis.

Predictor variables	Standardized β	T value	p value
Age	0.377	2.818	0.008
BMI	0.148	1.351	0.187
Time with psoriasis	0.227	2.089	0.045
Sun exposure	0.014	0.113	0.911
Vitamin D intake	0.028	0.217	0.830
Alcohol intake	-0.129	-1.004	0.324
Physical activity	-0.112	-0.945	0.352
Fasting glucose	-0.012	-0.092	0.928
Total-C	0.431	1.315	0.199
LDL-C	-0.492	-1.508	0.142
TG	0.013	0.085	0.933
25-OHD	-0.485	-3.202	0.003
Constant		4.014	0.000

Table 6. Multiple linear regression analysis of independent predictors of maximal intima-media thickness in psoriatic patients.

Predictor variables	Standardized β	T value	p value
Age	0.377	2.818	0.008
BMI	0.148	1.351	0.187
Time with psoriasis	0.227	2.089	0.045
Sun exposure	0.014	0.113	0.911
Vitamin D intake	0.028	0.217	0.830
Alcohol intake	-0.129	-1.004	0.324
Physical activity	-0.112	-0.945	0.352
Fasting glucose	-0.012	-0.092	0.928
Total-C	0.431	1.315	0.199
LDL-C	-0.492	-1.508	0.142
TG	0.013	0.085	0.933
25-OHD	-0.485	-3.202	0.003
Constant		4.014	0.000

Figures

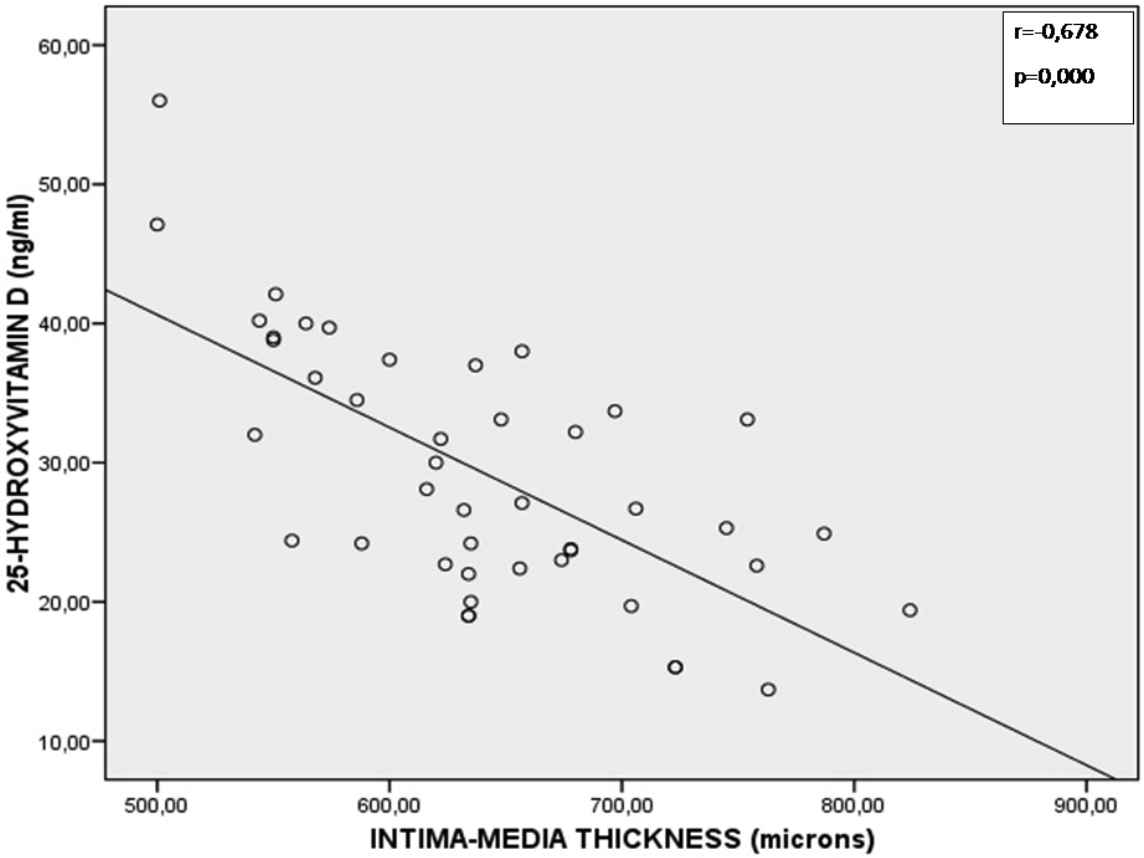

Figure 1. Negative correlation between serum 25-OHD level and the MIMT in psoriatic patients.

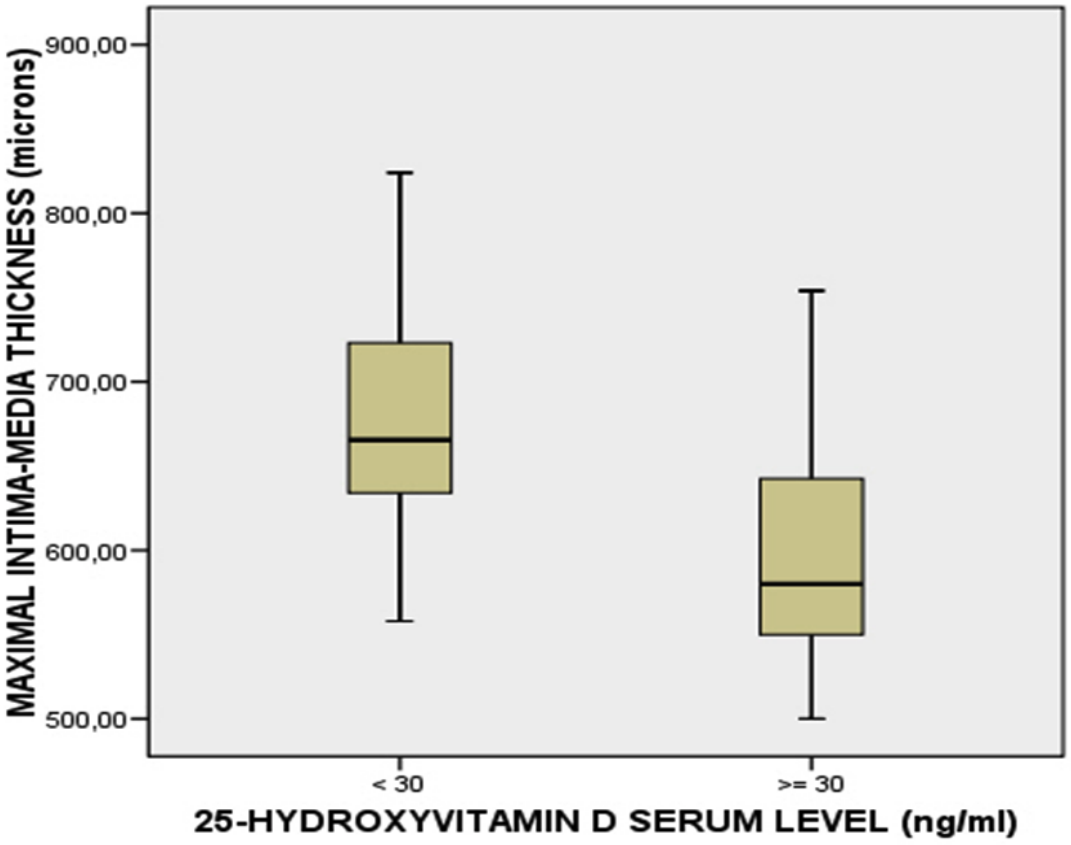

Figure 2. Mean MIMT value based on vitamin D status. The mean MIMT was higher in patients with serum 25-hydroxivitamin D <30 ng/ml (vitamin D insufficiency) than in those with serum 25-hydroxyvitamin D ≥30 ng/ml (677.75±65.49 vs. 597.25±66.52 ng/ml, p=0.001).

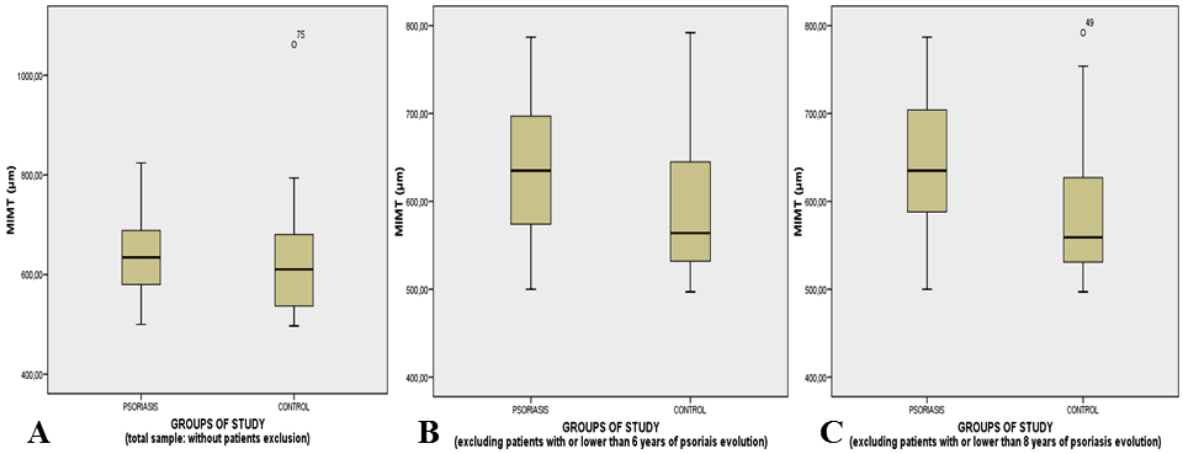

Figure 3. Comparison of MIMT among both groups of study with total sample (A), excluding patients with a history of psoriasis lower or equal than 6 years with their corresponding control matched by age and sex (B) and excluding patient with a history of psoriasis lower or equal than 8 years (C).

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ABBREVIATIONS

25-OHD: 25-hydroxyvitamin D

BMI: body mass index

BSA: body surface area

DBP: diastolic blood pressure

HbA1c: glycated hemoglobin A1c

HDL-C: high density lipoprotein cholesterol

IMT: intima-media thickness

iPTH: intact parathyroid hormone

IU: international units

LDL-C: low density lipoprotein cholesterol

MIMT: maximal intima-media thickness

SBP: systolic blood pressure

TG: triglycerides

Total-C: total cholesterol

PASI: psoriasis area and severity index

VDR: vitamin D receptor

ASSOCIATION OF 25-HYDROXYVITAMIN D WITH METABOLIC PARAMETERS IN PSORIATIC PATIENTS WITH AND WITHOUT ARTHRITIS

Abstract

Background: Psoriasis has been related to a higher prevalence of cardiovascular risk factors. Vitamin D deficiency has been associated with metabolic syndrome, cardiovascular disease and psoriasis. However a study of vitamin D status differentiating patients with psoriatic arthritis and without psoriatic arthritis has not yet been performed.

Objective: The objective was to assess the relationship of 25-hydroxyvitamin D [25-(OH)D] levels with lipid and glucose metabolism parameters in psoriatic patients with and without arthritis.

Patients and method: We studied 122 patients with psoriasis (61 without arthritis and 61 with arthritis) from the Psoriasis Unit (Dermatology Department) and Rheumatology Department of our hospital. We analyzed lipid and glucose metabolism variables and serum 25-(OH)D concentrations. Measurements were conducted within a two-month period to minimize seasonal bias in 25-(OH)D levels.

Results: In the psoriatic patients without arthritis, serum 25-(OH)D levels were inversely correlated with fasting glucose (r=-0.285; p=0.026), total cholesterol (r=-0.440; p=0.000), LDL (r=-0.415; p=0.001), total cholesterol/HDL (r=-0.303; p=0.018), and triglyceride (r=-0.280; p=0.029) values. This association

remained statistically significant for glucose, total cholesterol, and LDL after controlling for confounding factors in multivariate analysis. No association was found between serum 25-(OH)D levels and any study parameter in the patients with psoriatic arthritis.

Conclusions: Serum 25-(OH)D was inversely related to lipid and glucose metabolism parameters in psoriatic patients without arthritis, whereas no such association was observed in psoriatic patients with arthritis. Interventional studies are warranted to assess the effects of vitamin D supplements on the metabolic profile of psoriatic patients without arthritis.

Key words: psoriasis, psoriatic arthritis, vitamin D, lipids, glucose.

INTRODUCTION

Psoriasis and psoriatic arthritis has been associated with a higher prevalence of metabolic syndrome, obesity, hypertension, hyperlipidemia, diabetes mellitus, and atherosclerosis and with an increase in cardiovascular events secondary to these risk factors (acute myocardial infarction, stroke, and peripheral vascular events) [1-3] as other dermatological inflammatory diseases.[4,5] Chronic inflammation related with psoriasis could explain the higher risk of metabolic syndrome and subclinical atherosclerosis found.[2]

Vitamin D deficiency has also been associated with psoriasis, metabolic syndrome (higher glucose and lipids serum levels) [6] and cardiovascular disease.[7] Besides vitamin D is mainly implicated in calcium-phosphorus metabolism, recent reports suggest that vitamin D receptor and CYP271B enzyme (responsible for 25-hydroxyvitamin D [25-(OH)D] synthesis) are found in many different tissues.[8-11] It may be valuable to study the extraskeletal functions of vitamin D in psoriatic patients, given recent reports of their reduced levels of this vitamin associated with higher levels of chronic inflammation (CRP, C reactive protein).[12-13] Vitamin D supplementation may also play an important immunopathogenic role in this disease, and oral calcitriol supplementation was reported to produce a major clinical improvement in psoriasis lesions.[14] Furthermore, psoriatic patients receiving alfacalcidol showed a significant reduction in the percentage of activated CD3/CD69-positive and CD8-positive interferon-gamma-producing T cells and in serum interferon-

gamma levels over the first 3 months and in the clinical activity of the disease over the 6-month follow-up period.[15]

The relationship between serum 25-hydroxyvitamin D and different metabolic parameters associated with higher cardiovascular risk in patients with psoriasis has not been studied previously. Moreover, a deficiency of vitamin D has been previously reported in patients with psoriasis[12]; however, this vitamin D status has not been performed differentiating patients with psoriatic arthritis and without psoriatic arthritis. Vitamin D presents anti-inflammatory properties and oral supplementation of vitamin D could be of benefit for psoriasis lesions and metabolic profile.[14]

With this background, a cross-sectional study was conducted to assess the relationship of serum 25-hydroxyvitamin D [25-(OH)D] with lipid and glucose metabolism parameters in patients with psoriatic arthritis (PA) and psoriatic patients without arthritis.

PATIENTS AND METHODS

Patients with PA were systematically recruited from among outpatients of the Dermatology (Psoriasis Unit) and Rheumatology Departments of our hospital, and psoriatic patients without arthritis from the same sources with similar age and sex distribution than PA patients. Inclusion criteria were: a clinical diagnosis of psoriasis or PA (according to CASPAR criteria), age ≥18 years, and residence in the metropolitan area of Granada (Southern Spain). Exclusion criteria were: a medical history of rheumatoid arthritis, type 1 diabetes mellitus, or inflammatory bowel disease; intake of calcium or vitamin D supplements or receipt of phototherapy, lipid-lowering, antidiabetic, or oral corticoid therapy during the previous two months; or treatment with cylosporine during the previous 4 months. Patients who met these selection criteria and signed informed consent (in accordance with the Helsinki Declaration) were enrolled in the study; no selected patients refused to participate. The study was approved by the Ethics Committee of San Cecilio University Hospital.

Clinical and laboratory parameters

Data were gathered on: age, sex, family history of psoriasis, years with diagnosis of psoriasis or PA, and age at the diagnosis (in patients with PA, the age at the earliest diagnosis –cutaneous psoriasis or PA) and type of treatment. We also recorded current tobacco habit, alcohol intake (g/week), and an estimation of the time spent in the open air over the previous three weeks.

Physical activity was assessed according to the usual level of exercise over the previous year. The Tromsø physical activity questionnaire was selected because it has proven to be a good predictor of the heart rate at rest and of the physical condition, comparable to the objective assessment of activity by accelerometry[16]. This questionnaire has four response categories: level 1, reading, watching television or other sedentary activities; level 2, at least 4 h/week walking, cycling, or carrying out other types of physical activity; level 3, at least 4 h/week of keep fit exercise or participation in recreational athletic activities; and level 4, intense training or participation several times a week in competition sports. However, because our study sample included no individuals with activity level 3 or 4, only two levels (1 and 2) were considered in our analysis.

Participants underwent physical examination for determination of the Psoriasis Area and Severity Index (PASI) and the Fitzpatrick phototype. We also recorded their weight (light clothes, without shoes) and height (without shoes) and calculated their body mass index (BMI; kg/m^2). Blood samples were drawn between 8 a.m. and 9 a.m. for laboratory analysis of biochemical parameters [triglycerides (Tg), total cholesterol (TC), LDL, HDL, fasting glucose, and glycosylated hemoglobin–HbA1c-] and determination of serum 25-(OH)D levels by radioimmunoassay. At the same session, patients were interviewed by a single researcheron their weekly intake of vitamin D-rich foods (salmon, sardines, tuna, eggs, butter, margarine, yogurt, cheese, milk, and cereals)[17] over the previous four weeks, and these data were used to estimate their daily

dietary intake of vitamin D expressed in international units (IUs). All patients were recruited between August 1 and September 20 2011 in order to avoid bias due to seasonal variations in vitamin D.

Statistical analysis

Descriptive statistical analysis was conducted of the general characteristics of the study participants. The *Kolmogorov-Smirnov* test was used to examine the distribution of variables and the Levene test to study the variance. The sample was stratified by 25-(OH)D level and when the distribution was normal, the Student's t test was applied to compare mean values of quantitative variables, and when not normal, the Mann-Whitney U test was used. ANOVA test was used when 3 groups were included in the analysis. Qualitative variables were analysed with chi-square test or with Fisher's exact test if at least one cell had an expected count <5. Binary logistic regression models (Wald method) were used to measure the association between psoriasis and vitamin D insufficiency (<30 ng/ml) in a multivariate analysis. Pearson's coefficient was used to test the correlation between quantitative variables and serum 25-(OH)D level. SPSS 17.0 was used for the data analyses (SPSS, Inc, Chicago, IL).

RESULTS

Out of an initial sample of 149 patients, 18 PA patients were excluded (6 for consumption of vitamin D supplements, 7 for receipt of lipid-lowering and/or antidiabetic therapy, and 5 for oral corticosteroid treatment) and 9 psoriatic patients without arthritis were excluded for receipt of lipid-lowering and/or antidiabetic treatment (fig. 1). The final study sample of 122 patients comprised two groups that each contained 61 patients (33 males and 28 females). Treatment of the psoriatic patients without arthritis was topical (calcipotriol and corticoids) in 22 patients (36.1%), methotrexate (MTX) in 15 (24.6%), and anti-TNF in 24 (39.3%). Treatment of the PA patients was with topical treatment (calcipotriol and corticoids) for psoriasis in 19 patients (31.15%) and all of them were taken non-steroidal anti-inflammatory drugs (NSAIDs); with MTX in 22 patients (36.07%), being combined with NSAIDs in 16 of them, and with anti-TNF therapy in 20 patients (32.79%).

The two groups (table 1) did not differ in the proportion with family history of psoriasis (30/61 in each group), time elapsed since psoriasis diagnosis (17.49±12.25 in psoriasis without arthritis *vs.* 16.02±12.31 in PA), or BMI (28.34±5.63 in psoriasis without arthritis *vs.* 28.42±3.98 in PA). Alcohol consumption (in g/week) was higher in the psoriatic patients without arthritis (79.61±123.68 *vs.* 39.49±74.14; p=0.035), and the percentage of patients with physical activity level of 2 was also higher in the psoriatic patients without arthritis (54.10% *vs.* 36.07%; p=0.045). Patient with psoriasis without arthritis presented higher significant TC (203.31±37.91 *vs.*188.89±37.65; p=0.042) and

no significant differences were found in 25-(OH)D levels according to sex (28.7 vs. 31.9 p=0.20).

Patients were divided into two groups (table 2) as a function of their serum 25-(OH)D level (<30 ng/ml and ≥30 ng/ml), calculating the mean values of study variables in each group.

Among the patients without arthritis, significantly higher TC (218.48 +/- 39.85 *vs.* 189.56 +/- 30.60; p=0.002), LDL (136.76 +/- 31.61 *vs.* 115.63 +/- 27.50; p=0.007), TC/HDL (4.54 +/- 1.17 *vs.* 3.72 +/- 0.85; p=0.003), and Tg (164.10 +/- 97.13 *vs.* 108.81 +/- 61.20; p=0.003) levels were found in those with lower 25-(OH)D level (< 30 ng/ml). A nearly significant higher proportion of active smokers in those with lower 25-(OH)D level was found (60% *vs.* 40%; p=0.055). No significant differences were found in mean HDL, HbA1c, or fasting glycemia values as a function of serum 25-(OH)D level. No significant differences were found in serum 25-(OH)D level in patients with psoriasis without arthritis according to treatment (31.29 vs. 29.84 vs. 30.24 ng/ml p=0.89 for patients with topical treatments, MTX and anti-TNF respectively). Binary logistic regression model for vitamin D insufficiency (<30 ng/mL) showed a positive significant association with TC, TC/HDL, LDL and Tg after controlling for age, sex, sun exposure, food intake of vitamin D and treatment for psoriasis (p=0.004; p=0.002; p=0.006; and p=0.01; for TC, TC/HDL, LDL and Tg respectively).

Among the PA patients, there was a significantly higher proportion of active smokers in those with lower 25-(OH)D level (61.90% *vs.* 38.10%; p=0.016) but no significant differences were found in others parameters (table 2).

Among the psoriatic patients without arthritis, serum 25-(OH)D levels were inversely and significantly correlated with age (r= -0.308; p= 0.016), fasting glycemia (r= -0.285; p= 0.026), TC (r= -0.440; p= 0.000), LDL (r= -0.415; p= 0.001), atherogenic index (r= -0.303; p =0.018), and Tg (r= -0.280; p= 0.029); i.e., lower 25-(OH)D levels were associated with higher values of these variables (fig. 2). No correlation with HDL was found (r= -0.006; p= 0.962). No significant correlation was found between serum 25-(OH)D levels and PSI or BSA. Among the PA patients, no significant association was found between serum 25-(OH)D level and any study variable, as shown in table 3.

DISCUSSION

General data

This study shows an inverse correlation between serum 25-(OH)D levels and different components of the lipid metabolism (TC, LDL, TC/HDL, Tg) and fasting glycemia among psoriatic patients without arthritis after controlling for confounding factors. However, this association was not observed among the PA patients.

Although not a primary objective, some of the present results deserve comment. In common with our findings, Husted JA et al[18] also found a lower proportion of active smokers and a lower alcohol consumption among patients with PA than among psoriatic patients without arthritis. There is a lack of prospective studies on the relationship between PA and tobacco consumption. Eder L et al[19] studied patients with negative HLA-C*06 and observed an inverse association between tobacco habit and the presence of PA but not the presence of psoriasis without arthritis. There were a greater proportion of patients with a higher level of physical activity (level 2) in the psoriatic group without arthritis than in the PA group, which would be explained by the physical limitations imposed by the locomotor symptoms of arthritis. The mean BMI was very similar between the groups in our study, in contrast to a report by Husted JA et al[18] of a greater frequency of overweight condition in PA patients than in psoriatic patients without arthritis. However, although the sample size was larger, their groups were not so homogeneous, unlike in our investigation, and there were major differences in age and disease duration between them.

Psoriatic patients without arthritis: relationship between 25-(OH)D and metabolic parameters

Previous published results have been controversial, with some authors reporting a positive correlation[20] and others finding no correlation after controlling for confounding factors in general population.[21] However, TC, LDL and TC/HDL in a cross-sectional study with 909 men, values were inversely correlated with 25-(OH)D serum levels and these associations remained significant after controlling for different confounders.[22] The biological rationale for these associations is not clear, and numerous exogenous factors may influence serum 25-(OH)D levels, notably diet, BMI, and ultraviolet radiation, although it was reported that only one-quarter of the inter-individual variability in 25-(OH)D levels can be explained by the season of the year, geographic latitude, or daily intake of vitamin D.[23-24] By contrast, twin and family studies demonstrated that genetic factors can contribute up to 43-53% of the variability in serum 25-(OH)D levels.[23-24] Wang TJ et al[25] reported significant differences in 25-(OH)D levels among patients with different polymorphisms in allelic regions related to the metabolism of this vitamin. One of these regions determines the synthesis of 7-dehydrocholesterol (7-DHC) reductase, which is responsible for the conversion of 7-DHC (precursor of vitamin D synthesis) to cholesterol (inverse pathway to vitamin D synthesis). In this context, Smith-Lemli-Opitz syndrome is characterized by low 7-DHC reductase activity and low serum cholesterol

levels.[26] These observations suggest an influence of this allelic region in cholesterol levels. Also, the relationship between 25-(OH)D and cholesterol is also supported by interventional studies, such as Al-Daghri´s study,[27] which shows a reduction in cholesterol levels after 12 months of vitamin D supplementation.

Large population studies have also shown inverse correlation between 25-(OH)D and Tg levels, as observed in our psoriatic patients without arthritis.[22] Barchetta et al[28] found the serum 25-(OH)D level to be an independent predicting factor for non-alcoholic fatty liver after controlling for different confounders, finding significantly lower levels in normal-weight individuals with non-alcoholic fatty liver than in those without this disease.

In the present study, serum 25-(OH)D was inversely correlated with the level of baseline glycemia. Different observational studies in diabetic and non-diabetic patients found serum 25-(OH)D levels to be inversely related to glucose level,[29-30] insulin resistance,[29-30] and prevalence of type 2 diabetes.[31] A role for vitamin D in glucose metabolism is supported by the presence of the vitamin D receptor[32] and the 1α-hydroxylase enzyme[33] in β pancreatic cells, and by experimental findings of an increased glucose-mediated insulin secretion in animals after vitamin D administration.[34]

Lack of correlation between 25-(OH)D and metabolic parameters in PA patients

Patients with a lower level of 25-(OH)D showed a higher proportion of active smokers than patients with higher level of 25-(OH)D. Althoughthe reason is not

well known, an inverse association between smoking and vitamin D levels has repeatedly been reported in scientific literature, both in health individuals and in patients with autoimmune or respiratory diseases[35,36,37]. No relationship was found between serum 25-(OH)D and metabolic parameters in the patients with PA. Hence, there appear to be differences in the association of 25-(OH)D with the different metabolic parameters between psoriatic patients with and without arthritis. Furthermore, the present study shows a higher level of 25-(OH)D in PA patients than in psoriatic patients without arthritis, and the difference was close to significant. However, we should consider that 6 PA patients were excluded from the analysis for receiving vitamin D supplements and may therefore have had a major 25-(OH)D deficit, whereas none of the psoriatic patients without arthritis received vitamin D supplementation. Little knowledge is available on intrinsic determinants of serum vitamin D levels. It is not known whether genetic differences between psoriatic patients with and without arthritis can differentially affect 25-(OH)D levels. Factors that have not yet been identified must also play a role in determining individual 25-(OH)D levels. In an *in vitro* study, Jisu Oh et al[38] found a lower proportion of "foamy" macrophages, key cells in the atheromatous process, in cultures with media supplemented with vitamin D than in those without this supplementation. This observation was made for macrophages from obese-diabetic-hypertensive patients but not for macrophages from non-diabetic controls. Their findings indicate that the extraskeletal functions of vitamin D can vary among different types of individual; however, some elements that determine these differences between psoriatic patients with and without arthritis remain unclear.

Need for future studies and limitations

Vitamin D supplementation is well established in patients with bone metabolism disorders, but there is little clinical experience of its utilization in other diseases. Vitamin D supplementation was recently reported to improve lipid and glucose metabolism.[27,39] In future studies of psoriatic patients, vitamin D could be assessed as a function of its immunoregulatory role (which may be of interest in the pathogenesis of psoriasis) and its role in the metabolism of lipids and glucose and in insulin resistance. With regard to the immunoregulatory role of vitamin D in psoriasis, we highlight the study by Perez et al[14] on the clinical benefits of vitamin D in psoriasis and the study by Gaál et al[15] on it influence on immunological expression in PA patients, although the sample sizes of these studies have been small. Wider interventional studies are necessary to adequately assess the potential benefit of supplementation with vitamin D in patients with psoriasis at dermatological, immunological-inflammatory, metabolic and articulation levels.

We conducted a cross-sectional study that supports the hypothesis of an association between vitamin D and metabolic parameters but does not allow a causal relationship to be established. Our study design prioritized the avoidance of seasonal variations in 25-(OH)D levels by imposing a short study period, but this inevitably reduced our sample size, and patients under treatment for psoriasis were included. Nevertheless, significant results were obtained despite the modest sample size. Moreover, no significant differences were found in mean serum 25-(OH)D levels according to treatment and the receipt of

treatment was included as a potential confounder in the multivariate analysis, which showed no changes in the associations between 25-(OH)D and the metabolic parameters studied. Furthermore, previous studies found no difference in lipid profile between patients treated and not treated with MTX[40] or between the lipid profile before and after anti-TNF therapy.[41]In any case, even suggesting that there is an influence of systemic treatment, there is a similar proportion of patients with systemic treatment in both groups. Thus, the use of treatments does not explain why patients with psoriasis without PA showed a significant correlation between the levels of 25-hydroxyvitamin D and other metabolic parameters in contrast with patients with PA.

In conclusion the low levels of vitamin D in psoriatic patients without arthritis were inversely associated with high levels of TC, LDL, TC/HDL, Tg and glycemia. Inverse association was remained for TC, LDL, TC/HDL, and Tg levels after controlling for confounding factors. These associations were not observed in psoriatic patients with arthritis. Interventional studies with vitamin D supplements are required to verify these metabolic benefits in psoriatic patients without arthritis. Further studies with larger samples are also warranted to confirm our findings in patients with psoriatic arthritis.

Figure legends:

Figure 1: Flow diagram of patient´s selection

Figure 2. Graphic representation of correlation between 25-hydroxyvitamin D level and lipid metabolism parameters in psoriatic patients without arthritis.

VitD: serum 25-(OH)D; COL: total cholesterol; TG: triglycerides; CTHDL: atherogenic index. Inverse correlations between the level of 25-(OH)D and A) LDL, B) total cholesterol, C) triglycerides, and D) atherogenic index was found.

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IV. DISCUSIÓN

IV. DISCUSIÓN

En la presente tesis hemos encontrado un incremento del riesgo cardiovascular en los pacientes con psoriasis grave respecto a un grupo control, medido mediante la prevalencia de síndrome metabólico y el valor medio de sus componentes y la prevalencia y valor medio de la ateromatosis carotidea subclínica. De forma correspondiente los pacientes con psoriasis mostraron una concentración mayor de insulina, homocisteína y reactantes de fase aguda (PCR, dímero-D, fibrinógeno y VSG) que los controles. Entre los pacientes con psoriasis, aquéllos con SM presentaron un nivel mayor de fibrinógeno, dímero-D y VSG; aquéllos con placa de ateroma presentaron un nivel mayor de PCR, fibrinógeno y dímero-D.

Por otra parte, hemos encontrado un nivel significativamente menor de vitamina D en los pacientes con psoriasis respecto a un grupo control agrupado por edad, sexo, época del año y latitud. Además, aquellos pacientes con psoriasis con un IMC> 27 kg/m^2 presentaban un mayor riesgo de insuficiencia de vitamina D. Los estudios realizados sugieren que un bajo nivel de vitamina D podría ser un FRCV no clásico. Así, el nivel plasmático de 25-OHD ha mostrado una correlación inversa y significativa con la prevalencia de SM y el grado de ateromatosis carotidea (medido como grosor máximo de íntima-media) en los pacientes con psoriasis vulgar. En los pacientes con artritis psoriásica no se ha mostrado la relación inversa y significativa encontrada en los pacientes con psoriasis sin artritis entre 25-OHD y parámetros metabólicos.

IV.1PSORIASIS Y ENFERMEDAD CARDIOVASCULAR

Los pacientes con psoriasis muestran una prevalencia de SM incrementada respecto a la población general (Langan SM y cols, 2012), condición que conduce a un incremento de RCV (Gisondi P y cols, 2007). Esta asociación ha sido cuestionada en base a que esta diferencia de prevalencia fuera debido a un incremento de malos hábitos de vida, como menor nivel de actividad física, incremento del consumo alcohólico o de tabaco. No obstante, como se observa en la Publicación I, el incremento en la prevalencia de SM y ateromatosis es controlado por estos factores de confusión. No obstante, la presencia de estos factores evidentemente puede incrementar adicionalmente el RCV (Altobelli E y cols, 2009; Schmitt J y cols, 2009). Últimamente se ha señalado la psoriasis como un factor de riesgo independiente para el desarrollo de infarto de miocardio, especialmente en pacientes jóvenes con psoriasis severa, en los que sería más fácil evidenciar ese incremento de riesgo respecto a la población general (Mallbris L y cols, 2004; Gelfand JM y cols, 2006). Esto puede ser explicado por la existencia de factores patogénicos comunes entre psoriasis y ECV, que justificarían "una potenciación" mutua.

Síndrome metabólico y psoriasis

En la publicación I se ha hallado una mayor prevalencia de SM en pacientes con psoriasis respecto al grupo control, como ya ha sido publicado en otros estudios con una muestra muy importante, como los 4065 pacientes con psoriasis y 40650 controles incluidos en el estudio de Langan y cols (Langan SM y cols,

2012). Como se acaba de comentar, la relación entre SM y psoriasis ha sido puesta en duda. En la publicación I cabe destacar que la diferencia de prevalencia fue altamente significativa pese a que no hubo diferencia en otros factores de confusión, como la edad, consumo de tabaco (excepto en la comparación de mujeres con psoriasis respecto a las mujeres control), alcohol, porcentaje de sedentarismo o consumo de medicación antihipertensiva, reductores de colesterol o antidiabéticos. Si hubo diferencias en el IMC entre pacientes con psoriasis y controles; no obstante, este parámetro fue incluido como posible factor de confusión en el análisis de regresión logístico binario que mostró la presencia de psoriasis como un factor asociado de manera independiente al SM.

Analizado desde otro punto de vista, hay que resaltar el hecho de que existan diferencias significativas en el IMC entre pacientes con psoriasis y su grupo control. La obesidad se ha planteado como un posible factor de confusión en la asociación entre psoriasis y ECV. La importancia de la obesidad como elemento patogénico del SM es ampliamente conocido y constituye un criterio de diagnóstico clínico del SM. Sin embargo, en los últimos años se ha planteado como un factor de riesgo independiente para el desarrollo de la psoriasis (Azfar RS &Gelfand JM, 2008; Naldi L y cols, 2005). Además, algunos autores consideran que el incremento de IMC podría estar asociado con un curso más grave de la psoriasis (Neimann NL y cols, 2006; Murray ML y cols, 2009). No hay que olvidar que el panículo adiposo es fuente de importantes citoquinas inflamatorias con implicación patogénica tanto en el SM como en la psoriasis, como el TNF-α o IL-6 (Wakke M y cols, 2007; Gisondi P y cols, 2007).

Por otra parte, es interesante señalar que independientemente de otros factores de RCV se ha encontrado un nivel mayor de leptina sérica en pacientes con psoriasis (Chen YJ y cols, 2008). Además de esta hiperleptinemia, se han encontrado mayores niveles de leptina y de expresión del receptor de leptina en piel en pacientes con psoriasis grave respecto a pacientes con psoriasis leve y controles (Cerman AA y cols, 2008). Como se ha comentado previamente, la leptina se postula como una sustancia que parece estar en relación con la obesidad, la resistencia a la insulina y el SM (Seufert J y cols 2004; Boehncke WH y cols, 2011; Cerman AA y cols, 2008; Chen YJ y cols, 2008). Esta asociación constituiría un elemento patogénico "más primitivo" que la propia obesidad y justificaría la discutida asociación entre psoriasis y SM más allá de la obesidad.

Abundando en la idea de asociación entre SM y psoriasis hay que destacar que en la publicación I encontramos una correlación positiva entre distintas características de psoriasis (PASI, BSA, tiempo con psoriasis) y los parámetros constituyentes del SM (perímetro abdominal, TAS, TAD, trigliceridemia y glucemia). Con el tamaño de muestra con el que se trabajó (no excesivamente grande) existió falta de significación tan solo entre PASI y glucemia por un lado y entre tiempo con psoriasis y trigliceridemia. Además se encontró una relación inversa entre HDL-c y PASI y BSA.

Aterosclerosis y psoriasis

En la publicación I encontramos que los pacientes con psoriasis presentan un mayor porcentaje de placas de ateroma y un mayor GIM que el grupo control.

Aunque los pacientes con psoriasis presentan, como hemos comentado, una mayor prevalencia de SM, las diferencias se mantienen con el grupo control en un análisis multivariante que incluye el SM. De manera que el propio SM, la edad y el presentar psoriasis se muestran como factores de riesgo independientes en relación con el proceso de ateromatosis. En este sentido hay que señalar que se encontró una correlación positiva y estadísticamente significativa entre el GIM y el PASI y el tiempo con psoriasis, lo cual apoya la idea de dicha asociación (Antonucci VA y cols, 2012; Flammer AJ & Ruschitzka F, 2012).

Esta asociación independiente entre psoriasis y ateromatosis puede ser justificada por la existencia de un gran paralelismo en la vía patogénica de ambas condiciones. Como ha sido comentado en la introducción, ambas patologías pueden ser consideradas desde el punto de vista patogénico enfermedades inflamatorias crónicas. Ambas condiciones se caracterizan desde el punto de vista inmunopatogénico por un patrón de respuesta tipo Th1 y son desde el punto de vista citopatogénico y por las citoquinas inflamatorias liberadas patologías altamente similares (Späh F, 2008; Flammer AJ & Ruschitzka F, 2012).

En relación con el carácter inflamatorio de la ateromatosis y su relación con la psoriasis, en la publicación I encontramos que los pacientes con psoriasis presentaban un mayor valor en todos los parámetros inflamatorios medidos (PCR, fibrinógeno, D-D y VSG –excepto VSG en varones con psoriasis y controles-) [Sander D y cols, 2012]. Hay que decir además que se encontró una correlación positiva y significativa entre los parámetros de extensión y actividad

usados en psoriasis (PASI, BSA) y los parámetros inflamatorios comentados, lo cual sugiere un fenómeno de conexión entre lo ocurrido a nivel cutáneo y a nivel sistémico (Antonucci VA y cols, 2012). Por otra parte, los pacientes con placas de ateroma presentaron un mayor valor en todos estos parámetros, excepto en la VSG.

Por tanto, la relación entre psoriasis-inflamación-ateroclerosis parece evidente. En este sentido, hay que mencionar que tanto en la Publicación I como en el estudio IV de esta tesis doctoral se halla una relación directa entre grado de ateromatosis y tiempo de evolución de la psoriasis (manteniendo significación estadística en el análisis multivariante en el estudioIV,a pesar de ser incluida la edad del paciente en el modelo). Estos resultados sugieren igualmente que la exposición de los pacientes con psoriasis a un ambiente inflamatorio a lo largo del tiempoinfluye en el proceso de ateromatosis. En los últimos años se han aportado nuevas evidencias a este tema en relación con la evaluación cardiovascular realizada en pacientes con psoriasis tratados con las nuevas terapias biológicas. Así, la existencia de una vía patogénica inflamatoria común podía lógicamente conducir a la hipótesis de que un tratamiento antiinflamatorio frente a la psoriasis podía aportar al mismo tiempo un beneficio cardiovascular. Sin embargo, tratamientos sistémicos clásicos de la psoriasis como el metotrexate o la ciclosporina, aunque podían presentar un efecto antiinflamatorio beneficioso, presentaban también otros efectos adversos como hipertensión, toxicidad renal, hipercolesterolemia o hiperhomocisteinemia que podían contrarrestar su efecto beneficioso a nivel cardiovascular (Wakee M y cols, 2007). Sin embargo, la incorporación de las nuevas terapias biológicas,

con un perfil de efectos adversos menor ha permitido demostrar grandes beneficios a nivel cardiovascular en distintas enfermedades inflamatorias crónicas, como la artritis reumatoide. Así, en el estudio de Hürlimann D y cols (Hürlimann D y cols, 2002) pacientes con artritis reumatoide, tras ser tratados con terapia anti-TNF-α (infliximab) mostraron una mejoría en la función endotelial (mejoría de la vasodilatación mediada por flujo), con reducción significativa de la PCR y de la actividad de la enfermedad.De manera análoga, Mäki-Petäjä y cols (Mäki-Petäjä y cols, 2006) mostraron un mayor valor en la velocidad de la onda de pulso en pacientes con artritis reumatoide que en sujetos controles y una reducción significativa de la misma tras tratamiento anti-TNF, junto con mejoría de la función endotelial, obteniendo valores comparables a los sujetos control.

Por tanto, parece evidente la relación e influencia mutua entre aterosclerosis y psoriasis mediada por la existencia de un medio inflamatorio común. Así, pocos son los autores que dudan de la importancia dela psoriasis como enfermedad sistémica, más allá de la piel, con importante repercusión sobre el estado cardiovascular. De esta manera, el médico debe de ser consciente de este hecho. El tratamiento de la psoriasis moderada grave está justificado más allá de la morbilidad que pueda generar desde el punto de vista dermatológico. Así, como se ha mostrado, el riesgo de ateromatosis en pacientes con psoriasis viene influenciado por factores relacionados con la propia enfermedad como son su gravedad (evaluada mediante PASI) y el tiempo de evolución de la enfermedad, mientras que el control de la enfermedad mediante medicación sistémica podría aportar un beneficio cardiovascular, especialmente con las

nuevas terapias biológicas. No obstante, estudios similares a los comentados serían necesarios para confirmar dicha hipótesis en pacientes con psoriasis.

IV.2PSORIASIS Y DÉFICIT DE VITAMINA D

En distintas enfermedades de carácter autoinmune se ha observado un déficit de vitamina D. La esclerosis múltiple (EM) fue la enfermedad autoinmune clásicamente relacionada con déficit de vitamina D, señalándose pronto una correlación inversa, de tipo ecológico, entre EM y nivel de 25-OHD. El estudio de Kampman MT y cols (Kampman MT y cols, 2008) hace referencia a este fenómeno y señala la vitamina D como un posible factor protector en esta enfermedad, al ser Noruega una excepción entre los países nórdicos al presentar una menor prevalencia de EM. Ello lo explican por la dieta rica en vitamina D procedente de una alta ingesta de ácidos grasos omega-3 de origen marino. Otras enfermedades autoinmunes que han sido asociadas a déficit de vitamina D son el lupus (Kamen DL y cols, 2006) o la artritis reumatoide (Furuya T y cols, 2013; Song GG y cols, 2012).

Sin embargo, muchos de esos trabajospresentan limitaciones metodológicas, relacionadas con las dificultades relacionadas con el estudio del estado de la vitamina D. De este modo por ejemplo, el de Kamen DL y cols (Kamen DL y cols, 2006) consiste en un estudio caso-control en el que se muestra un nivel de vitamina D significativamente menor en pacientes con lupus respecto a controles. En este estudio los pacientes son comparados con controles agrupados por edad y sexo. No obstante, no se controlan otros potenciales factores de confusión como el fototipo cutáneo, la ingesta diaria de vitamina D, tiempo promedio de exposición solar o si los pacientes presentaban hábitos de fotoprotección solar debido a la condición de médica de base, de gran

relevancia en el curso clínico del lupus. Un aspecto a resaltar de la publicación II realizada por nuestro grupo de trabajo, es el control de los principales factores de confusión asociados con el nivel de vitamina D (fototipo cutáneo, cálculo de tiempo promedio de exposición solar, ingesta de vitamina D, edad, índice de masa corporal). En el momento de iniciar nuestro estudio no existía en la literatura científica ningún estudio tipo caso-control comparando el nivel de 25-OHD en pacientes con psoriasis. De forma simultánea, unos meses antes de la publicación de nuestro trabajo y apoyando los resultados publicados por nosotros, Gisondi P y cols publicaron un caso-control con el mismo objetivo (Gisondi P y cols, 2012).

¿Cuál es el motivo de este déficit de vitamina D en enfermedades inflamatorias crónicas? Hipótesis patogénica

Las enfermedades inflamatorias crónicas de carácter autoinmune son un grupo de enfermedades diferentes entre sí pero que tienen en común el presentar un patrón de respuesta inmunitaria desequilibrado (muchas de ellas, como la psoriasis o la artritis reumatoide, a favor de una respuesta tipo Th1, con una reducción de los linfocitos Treg).

Como ha sido comentado, en los últimos años se está señalando un déficit de vitamina D en estas enfermedades respecto a grupos control. En este punto se plantea si el déficit de vitamina D es un fenómeno secundario planteado en el ambiente inflamatorio continuo o primario. Es decir, los pacientes con enfermedades inflamatorias crónicas tienden a presentar un cierto grado de déficit de vitamina D una vez manifestada la enfermedad o el déficit de vitamina D predispone a la manifestación de enfermedades inflamatorias

crónicas. En el primer caso, aunque seguiría manteniendo interés puesto que se pueden plantear la evaluación del status de vitamina D y la posible repercusión en la clínica relacionada con el metabolismo óseo y fosforo-cálcico, el recorrido sería mucho menor. En cambio, si se tratara del segundo supuesto el interés de la vitamina D en las enfermedades inflamatorias crónicas se vería incrementado exponencialmente. Esto sería así porque, además de que incluiría al primer supuesto, abriría la puerta a toda una evaluación sobre el papel patogénico íntimo de la vitamina D en estas enfermedades y sobre el beneficio de la intervención con vitamina D en las enfermedades inflamatorias crónicas.

Por lo comentado hasta este momento (localización extrarrenal de RVD, 1α-hidroxilasa, experimentos mostrando influencia de vitamina D sobre células del sistema inmune…), los indicios a favor de un papel patogénico de la vitamina D en las enfermedades inflamatorias crónicas es amplio. Siguiendo esta vía podríamos plantear la hipótesis de que, en virtud de las funciones inmunorreguladoras de la vitamina D, ésta podría actuar como factor favorecedor entre el conjunto de múltiples elementos patogénicos que puedan participar en el desarrollo de la enfermedad.

Como hemos comentado, se conocen clásicamente una serie de elementos extrínsecos relacionados con el ambiente y hábitos del individuo y relacionados con el propio fenotipo del individuo que influyen en la concentración sérica de 25-OHD. No obstante, planteando el nivel de vitamina D como un rasgo fenotípico cualquiera, se sabe que el fenotipo es el resultado del ambiente y la genética. El nivel sérico de 25-OHD no podía ser una excepción. Como fue previamente comentado, el estudio de Wang TJ y cols (Wang TJ y cols,

2010),puso de manifiesto la existencia de una correlación entre diferentes SNP ligados a *loci* relacionados con el metabolismo de la vitamina D y un menor nivel de vitamina D pese a ajustar por factores de confusión, como la ingesta o la estación del año. Por tanto, se vio que los niveles de vitamina D de los individuos viene determinado además de por los clásicos factores, por factores genéticos, hereditarios o íntrínsecos. Además, la importancia cuantitativa de la influencia genética sobre la concentración plasmática ha sido puesta de manifiesto, señalando que la genética puede determinar hasta un 53% de las variaciones en la concentración de vitamina D (Hunter D y cols, 2001; Shea MK y cols, 2009).

Por tanto, si nos establecemos en la idea del déficit de vitamina D como fenómeno primario o previo al desencadenamiento de las EICs nos podemos plantear a su vez dos cuestiones: el déficit de vitamina D actúa como factor precipitante pero ¿este elemento precipitante se da de manera casual? Es decir, el déficit de vitamina D por características intrínsecas o constitución del paciente se presenta de manera casual en un paciente con toda una constelación de elementos patogénicos que en suma precipitan finalmente la clínica de una determinada EIC; o en cambio, ¿el déficit de vitamina D provocado por esta característica constitucional está asociado o ligado desde el punto de vista genético a otros elementos patogénicos determinantes de las EICs? Es decir, este déficit constitucional de vitamina D ¿se presenta de manera significativamente mayor en pacientes con EICs?. Esta pregunta podría ser en cierto grado aclarada realizando un estudio caso-control en el que se

compararala presencia de SNP asociados con un mayor o menor grado de déficit de 25-OHD.

En cualquier caso, *a priori*, en virtud de los datos en relación con el papel inmunorregulador de la vitamina D se puede establecer que el déficit de vitamina D podría tener influencia como elemento patogénico al favorecer la respuesta Th1 en detrimento de la respuesta Th2 y Treg. Así, Jefferey y cols muestran que el equilibrio en la respuesta linfocitos T inflamatorios/linfocitos T reguladores está influenciada por la disponibilidad de vitamina D en el ambiente de la sinpasis inmunológica (Jeffery LE y cols, 2012).

IV.3VITAMINA D Y ENFERMEDAD CARDIOVASCULAR

A finales del siglo XX, con la generalización del tratamiento frente a la hipercolesterolemia y la hipertensión hizo pensar que la incidencia de la enfermedad coronaria y resto de enfermedades cardiovasculares se vería drásticamente reducida. Sin embargo, en una revisión posterior del estado de la cuestión se ha estimado que la enfermedad cardiovascular continúa siendo la principal causa de mortalidad general en los países Occidentales, por encima de todas las causas de cáncer (Murray CJ & López AD, 1997). Esto sugiere que más allá de los factores de riesgo cardiovascular clásicos, otros elementos patogénicos, probablemente relacionados con el aspecto inflamatorio de la enfermedad cardiovascular, deban de ser atendidos más precisamente en los próximos años.

En 1974 a partir de un estudio caso-control con una pequeña muestra se llegó a la conclusión de que consumo mantenido de altas cantidades de vitamina D podía estar en relación con un incremento de infarto de miocardio (Linden V, 1974). En relación con estos resultados se realizaron posteriores estudios casos-control abordando la relación entre vitamina D y riesgo cardiovascular. Así, en 1978 fue publicado un estudio que, en contra de los resultados del primer trabajo, hallaron que los pacientes ingresados por enfermedad cardíaca isquémica presentaban niveles significativamente menores que un grupo control (Lund B y cols, 1978). Resultados que fueron concordantes con otros estudios realizados posteriormente (Vik B y cols, 1979; Scragg R y cols, 1990).

Recientemente se han incrementado el número de estudios de tipo observacional, destacando el realizado por Wang TJ y cols (Wang TJ y cols, 2008), en el que evalúan la relación entre el nivel de 25-OHD y la incidencia de un evento cardiovascular provenientes de la cohorte de Framingham incluyendo 1739 pacientes. El riesgo estaba incrementado entre aquellos individuos con un nivel de 25-OHD <15 ng/ml respecto a aquellos que tenían un nivel igual o mayor a 15 ng/ml, siendo el riesgo mayor para aquellos pacientes con hipertensión.

No obstante, la controversia en relación con la significación clínica de la vitamina D en la enfermedad cardiovascular se ha mantenido hasta nuestros días. Los estudios realizados a nivel clínico entre vitamina D y riesgo cardiovascular (RCV) han ofrecido resultados dispares. Así, Wang L y cols (Wang L y cols, 2010) muestran en un meta-análisis de 17 estudios de cohorte prospectivos y ensayos aleatorizados. Señalan que 5 estudios prospectivos realizados en pacientes en diálisis y otro realizado en población general mostraban una reducción significativa de la mortalidad por enfermedad cardiovascular entre aquellos individuos que tomaban suplemento de vitamina d. En cambio, otros 8 estudios también con suplemento de vitamina D mostraban una reducción del riesgo cardiovascular pero sin alcanzar significación estadística. Finalmente, evaluaron 4 estudios prospectivos, en los que no vieron diferencias de incidencia de enfermedad cardiovascular entre aquellos que tomaban suplementos de calcio respecto a los que no lo tomaban, lo cual sugiere que el posible beneficio de la vitamina D en el estado

cardiovascular podría ser, al menos en parte, independiente del efecto sobre el metabolismo del calcio.

IV.3.A VITAMINA D Y SÍNDROME METABÓLICO

Se ha planteado que los bajos niveles de vitamina D encontrados en individuos obesos pueda estar en relación con una menor exposición solar debido a reducción en su movilidad o al tipo de ropa utilizada (8; 12, 21 Looker AC, 2005; Snijder MB y cols, 2005). En este sentido, hay que decir que en nuestro estudio (publicación III) no se incluían grandes obesos con limitaciones de la movilidad y además el factor de exposición solar fue específicamente controlado como potencial factor de confusión.

La vitamina D es una hormona liposoluble, de manera que en personas con un mayor panículo adiposo queda retenida, reduciendo su disponibilidad en circulación (Wortsman J y cols, 2000). Por tanto, surge una lógica pregunta: puesto que la obesidad es un elemento central en el SM, ¿es espuria la relación inversa encontrada entre vitamina D y SM?. En este sentido es interesante señalar el estudio de Botella-Carretero y cols (Botella-Carretero y cols, 2007), en el que un grupo de pacientes, todos ellos con obesidad mórbida, fueron divididos según la presencia o no de SM. Según este diseño, los pacientes fueron distribuidos en ambos grupos sin diferencias en el valor del IMC y comprobaron que el grupo que cumplía criterios de SM presentaban valores de vitamina D significativamente menores que el grupo sin SM. En concordancia con este estudio, en la publicación III encontramos que los pacientes con SM presentaban un nivel significativamente menor de vitamina D en el análisis multivariante pese a incluir el IMC como factor de confusión.

En cuanto al resto de componentes relacionados con el SM, existen distintos indicios que señalan la probable influencia de la vitamina D sobre los distintos componentes del SM (verapartado I.3.C-*Influencia a nivel metabólico*).Además, hay distintos estudios de tipo observacional que sugieren un papel protector de la vitamina D sobre el SM o alguno de sus elementos. Entre ellos hay que destacar el estudio de Maki y cols (Maki KC y cols, 2012), en el que entre más de 3500 individuos analizados, el nivel sérico de 25-OHD y la ingesta de vitamina D se asociaron de manera inversa con la prevalencia de SM. De manera análoga, entre 10.066 mujeres analizadas de 45 o más años se encontró un nivel inverso entre la ingesta de vitamina D y la prevalencia de SM (Liu S y cols, 2005).

Entre los estudios más recientes hay que destacar el estudio de Kayniyil S y cols (Kayinil S y cols, 2013), consistente en un estudio de cohortes con seguimiento a 3 años, evaluando la aparición de SM. Encontraron una relación inversa entre el nivel sérico de 25-OHD y la incidencia de SM. Por lo tanto, es un resultado que está de acuerdo con todo lo comentado previamente, con la diferencia de tratarse de un estudio observacional tipo cohorte, diseño que presenta un riesgo mucho menor de sesgos.

No obstante, queda mucho por saber en relación con las funciones extraesqueléticas de la vitamina D. Así, en la publicación III de la presente tesis la correlación altamente significativa encontrada entre nivel sérico de 25-OHD y SM no se da en absoluto en el grupo control.Estos datos sugieren que la influencia de la vitamina D sobre los parámetros de SM pueda ser mayor en los pacientes con psoriasis que en individuos de la población general. Este hecho

ha sido sugerido también por Al-Daghri y cols (Al-Daghri NM y cols, 2013), en un estudio en el que encontraron correlación inversa y estadísticamente significativa entre el nivel de 25-OHD e IMC, colesterol, LDL e insulina, mientras que en el grupo control solo se halló una asociación débil y no estadísticamente significativa.

Por tanto, los pacientes con psoriasis pueden plantearse como un grupo concreto en el que evaluar el beneficio del suplemento con vitamina D para evaluar su beneficio sobre el SM y la influencia sobre sus componentes o criterios diagnósticos de una manera individualizada.

Por otra parte hay que decir que en el estudio V encontramos que mientras en el grupo de pacientes con psoriasis vulgar se da dicha correlación significativa entre nivel de vitamina D y los parámetros metabólicos, ello no ocurre el grupo de pacientes con artritis psoriásica. Es sabido que existen diferencias clinico-epidemiológicas entre los pacientes con psoriasis vulgar y los pacientes con artritis psoriásica y que incluso estas diferencias se dan entre los propios pacientes con psoriasis vulgar dependiendo de si son HLA-Cw6 positivos o negativos. Así, los pacientes con HLA Cw6 positivos presentan con mayor frecuencia clínica de psoriasis guttata, mayor extensión de placas, mayor correlación con infección de vías respiratorias superiores, mayor gravedad de psoriasis, más frecuente respuesta favorable a luz solar y menor frecuencia de distrofia ungueal y artritis psoriásica. Todo ello refleja que el psoriasis es una enfermedad multifactorial, con un amplio espectro de manifestaciones y diferencias y que no puede verse como "un todo homogéneo". Quizá el nivel de vitamina D y su grado de correlación con los parámetros metabólicos sea otro

rasgo fenotípico diferenciador. No obstante, nuestro estudio es un trabajo transversal de tipo epidemiológico y son necesarios estudios futuros profundizando en la biología de las funciones extraesqueléticas de la vitamina D y en su genética.

A modo de resumen gráfico, la figura I muestra las potenciales relaciones entre vitamina D y los distintos elementos componentes del SM.

IV.3.B VITAMINA D Y ATEROMATOSIS

Diferentes estudios han mostrado una relación inversa entre el nivel de 25-OHD y el grado de ateromatosis carotidea en población general, pacientes con diabetes mellitus tipo 2 y pacientes con lupus (Carrelli AL y cols, 2011; Targher G y cols, 2006; Ravenell RL y cols, 2012).Como ha sido comentado en el apartado anterior, la vitamina D parece tener una relación inversa respecto a los componentes del síndrome metabólico. Simplemente por este hecho se podría justificar la asociación entre vitamina D y ateromatosis. No obstante, en base al carácter inflamatorio de la atermatosis, la vitamina D podría estar relacionada con el proceso de ateromatosis también por medio de su influencia sobre la función de las células del sistema inmune. En este sentido hay que decir que en la publicación V de la presente tesis, la asociación inversa entre nivel de25-OHD y grosor máximo de íntima-media se mantiene estadísticamente significativa pese a incluir en el análisis multivariante los distintos parámetros metabólicos que se asociaron de manera significativa con el nivel sérico de 25-OHD. Así, los datos sugieren una asociación independiente entre el nivel de 25-OHD y el grado de ateromatosis. En relación con este resultado hay que señalar el estudio de J Oh et al (Oh J y cols, 2009). En este estudio se comparan macrófagos cultivados en un medio rico en 1,25-(OH)2D y un medio sin suplementación de vitamina D. Se comprobó que aquellos macrófagos cultivados en un medio enriquecido en vitamina D presentaban una menor modificación de partículas LDL (por oxidación y acetilación) y daban lugar a un porcentaje significativamente menor de "células espumosas"

(macrófagos con citoplasma rico en lípidos), que conocemos como células claves en el proceso patogénico de la ateromatosis. Actualmente, la relación entre vitamina D y el proceso de ateromatosis está siendo uno de los temas más intensamente estudiados. Así, muy recientemente ha sido publicado un estudio en cerdos que continua apoyando la influencia y beneficio que la vitamina D puede presentar en el proceso de ateromatosis (Gupta GK y cols, 2013). En dicho estudio se ha encontrado una expresión menor de RVD en las células de músculo liso en lesiones con proliferación neointimal de arterias coronarias respecto a zonas de íntima normal. Además, el porcentaje de reestenosis postangioplastia fue mayor de una manera significativa entre aquellos cerdos con déficit de vitamina D comparados con el grupo control. In vitro, han mostrado que el calcitriol inhibe la proliferación inducida por PDGF (factor de crecimiento de plaquetas) en células de músculo liso de arteria coronaria de cerdo y que el TNFα reduce de manera significativa la expresión y actividad de RVD en las células de músculo liso de arteria coronaria de cerdo.

Por tanto, los datos sugieren que la vitamina D podría ser una sustancia influente en el proceso de ateromatosis. Y esto podría ser así de una manera indirecta, mediante su asociación con el SM, y de una manera directa, mediante su influencia sobre distintas células involucradas en el proceso de ateromatosis, como las células musculares lisas y los macrófagos. Además, como se ha venido discutiendo a lo largo de esta tesis, parece que existiría una relación inversa entre vitamina D y distintos mecanismos inflamatorios; y ello no solo en el sentido de que la vitamina D por su influencia inmunorreguladora sea capaz de reducir la expresión de distintas citoquinas pro-inflamatorias, sino que algunas

citoquinas pro-inflamatorias también pueden influir negativamente en la función extracelular de la vitamina D, como ha sido comentado para el TNFα en el estudio de Gupta GK.

En relación con el estudioIVhay que comentar que fue realizado con un número de pacientes reducido (44 pacientes con psoriasis y 44 controles) debido a que fue diseñado con la idea de obtener los mínimos sesgos estacionales a la hora de evaluar el nivel sérico de 25-OHD. Aún así, se obtuvo una correlación altamente significativa entre los pacientes con psoriasis, mientras que no se obtuvo significación entre los controles. Esto no quiere decir que no pueda existir esta asociación también entre los controles; de hecho, esta asociación se ha establecido en individuos procedentes de la población general (Carrelli AL y cols, 2011), eso sí con una muestra de 203 individuos. No obstante, en base a nuestros resultados, podemos sugerir que la relación entre vitamina D y ateromatosis podría ser superior en la población concreta de psoriasis que en la población general. En este sentido, nos remitimos al estudio de Al-Daghri et al (Al-Daghri NM y cols, 2013), en el que se señala una disparidad en la correlación entre vitamina D y la expresión de sus potenciales efectos sobre el metabolismo. De esta manera, la asociación es distinta en función del grupo de estudio analizado (diabetes vs control). Así, encontraron una correlación significativa entre vitamina D y parámetros metabólicos relacionados con el síndrome metabólico en el grupo de pacientes con diabetes, correlación que fue débil y no significativa en el grupo control. La realidad es que los mecanismos intrínsecos que modulan o influyen sobre las funciones extraesqueléticas de la vitamina D son desconocidos. Así, podrían existir distintos elementos no

identificados en este momento que determinen el resultado final de la acción de la vitamina D. Recurriendo nuevamente al estudio de J Oh et al (Oh J y cols, 2009), hay que decir que la diferencia encontrada en la transformación de macrófagos en "células espumosas"en función de la presencia o no de suplemento de vitamina D en el medio de cultivo fue significativa solo en el grupo A. Es decir en el grupo de macrófagos procedentes de pacientes obesos, hipertensos, diabéticos con déficit de vitamina D. Sin embargo, no se obtuvieron diferencias significativas en el comportamiento de los macrófagos cultivados en distintos medios en el grupo control. Por tanto, las diferencias vistas a nivel clínico en nuestro estudio parecen reflejarse a nivel citológico en el estudio de J Oh et al, de manera que los detalles fisiopatogénicos entorno a las funciones extraesqueléticas de la vitamina D son todo un mundo por explorar.

Por tanto, existe una relación entre psoriasis y SM-ateromatosis y a su vez entre nivel de 25-OHD y psoriasis, entre nivel de 25-OHD y SM y ateromatosis. Aunque múltiples son los elementos patogénicos que influyen en cada uno de estos procesos, parece que la vitamina D podría ser un elemento patogénico común en todos ellos (figura II), y cuya importancia clínica está por evaluar.

Limitaciones

El número de individuos utilizados en cada estudio es pequeño, especialmente en los trabajos en los que se estudia la vitamina D. Esto es así porque se perseguía reducir los sesgos relacionados con las oscilaciones estacionales de vitamina D en plasma.

Además, se trata de estudios transversales sin intervención. Los resultados obtenidos deben ser confirmados en estudios que incluyan intervención.

V. CONCLUSIONES Y PERSPECTIVAS

V.1 CONCLUSIONS

1. Patients with severe psoriasis show a higher prevalence of metabolic syndrome, higher prevalence of atheromatous plaque and higher intima-media thickness at carotid level than controls.

2. Patients with psoriasis show a lower 25-hydroxyvitamin D concentration than controls, being inversely correlated with CRP and BMI.

3. In patients with psoriasis, level of 25-hydroxyvitamin D shows a significant and inverse association with metabolic syndrome, different components of metabolic syndrome and carotid subclinical atheromatosis.

4. Acute phase parameters (CRP, ESR, fibrinogen, D-dimer) are significantly higher in psoriasis than controls, being higher among individuals with MS or higher PASI and BSA.

5. Psoriasis clinical parameters, such as PASI and time with psoriasis, are directly correlated with intima-media thickness.

6. Based on the present data, psoriasis must be considered as a systemic inflammatory disease with an increased cardiovascular risk. So, at practical level, management of psoriasis must be addressed in an integral manner.

7. Based on the present data, it should be advisable to perform interventional studies evaluating the benefit of vitamin D at dermatological, metabolic and cardiovascular level.

V.2 PERSPECTIVAS

En el presente estudio se ha observado un déficit de vitamina D en pacientes con psoriasis y su correlación inversa con el síndrome metabólico y la ateromatosis carotidea. Serían necesarios estudios de tipo intervención para evaluar el beneficio desuplementos orales de vitamina D tanto sobre el aspecto dermatológico, metabólico y cardiovascular, evaluando la posología más apropiada, el perfil de seguridad del suplemento de vitamina D y el grado de significación clínica. La investigación de la fisiopatología de las funciones extraesqueléticas de la vitamina D abre un amplio horizonte para los próximos años.

VI. REFERENCIAS

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VII. ANEXOS

VII ANEXOS

VII.1 FIGURAS

Figura I. Visión integral del papel patogénico de la vitamina D en el SM.

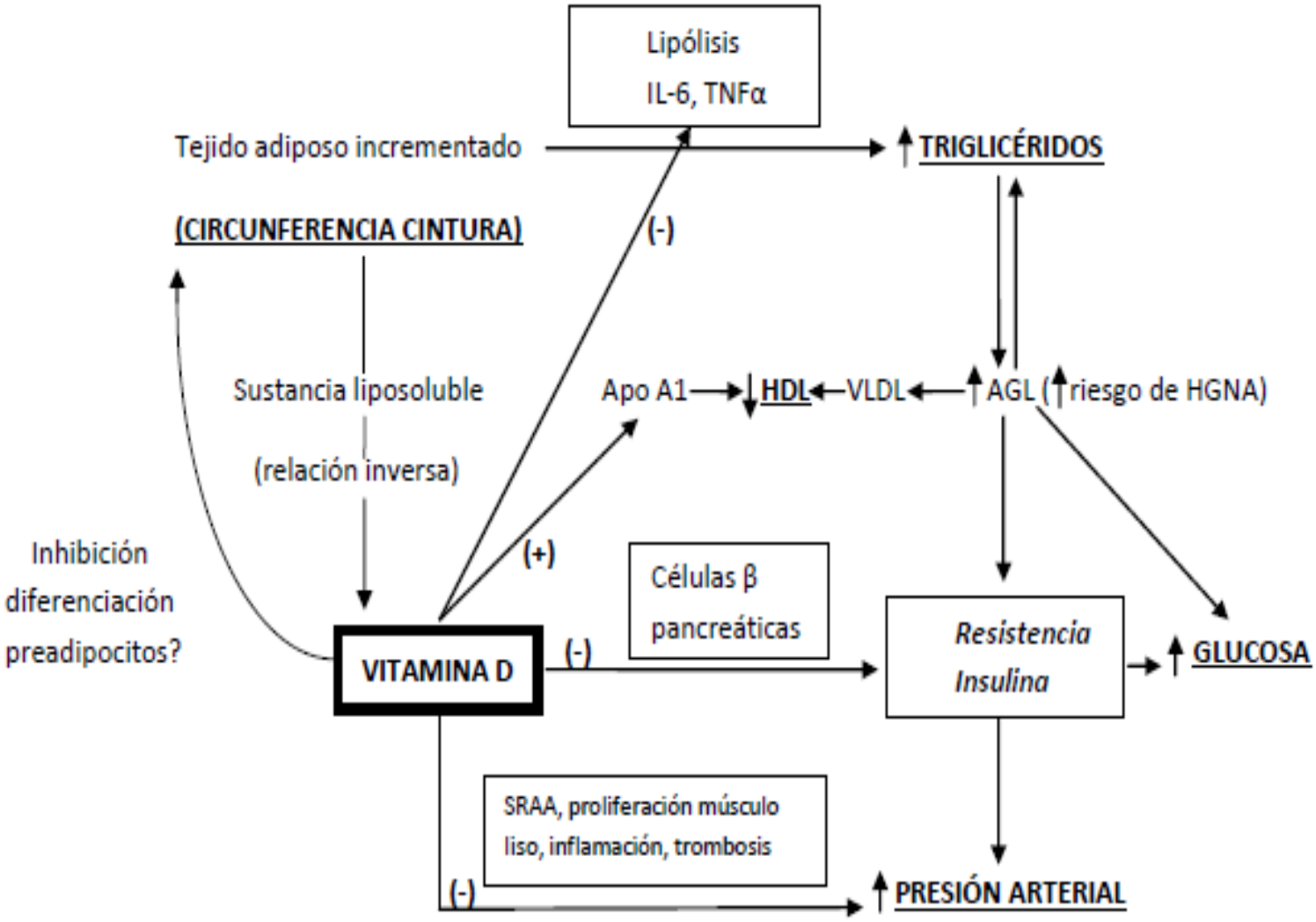
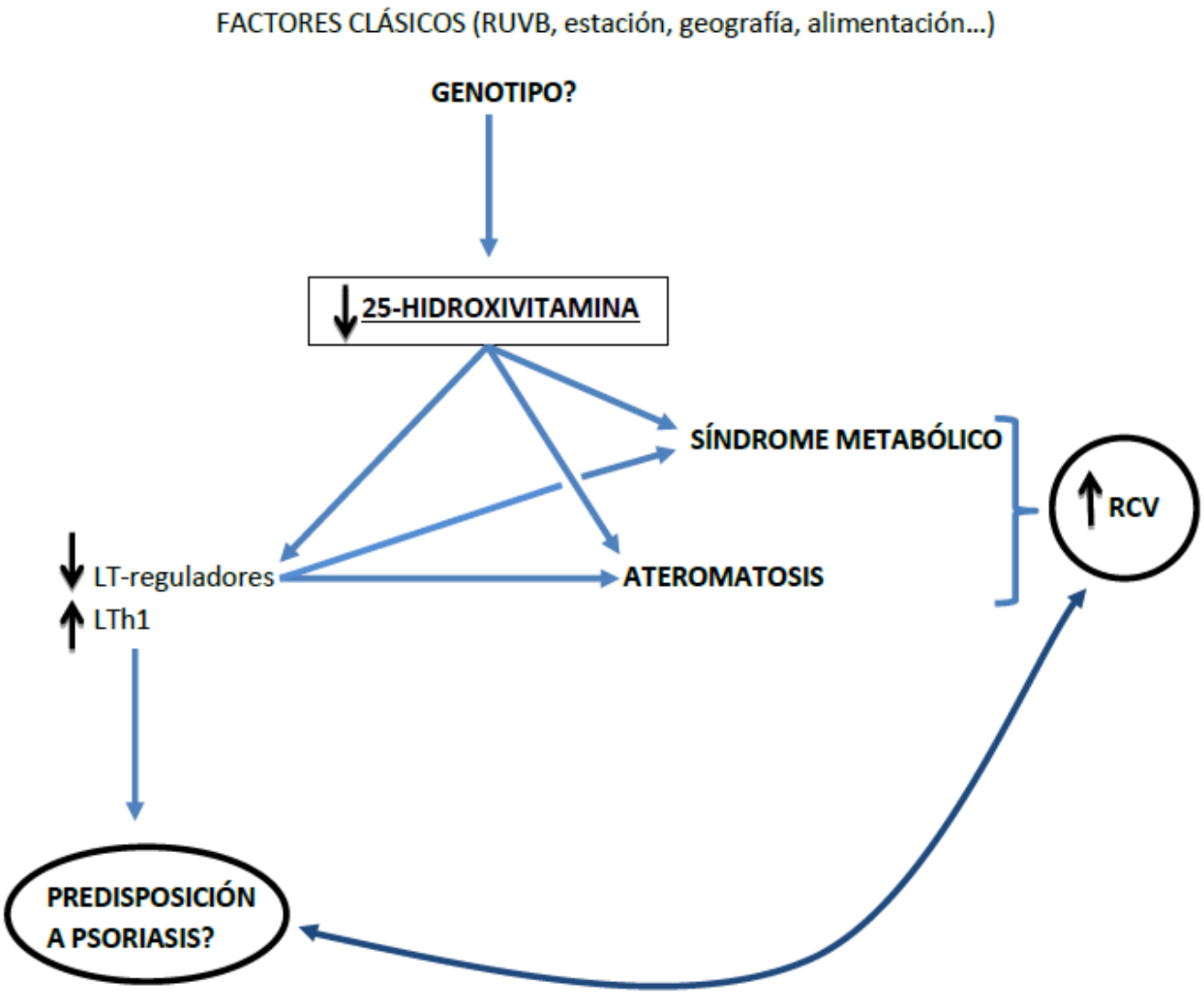


Figura II. Hipótesis de la interrelación psoriasis-riesgo cardiovascular-déficit de vitamina D



VII.2 ABREVIATURAS

1,25-(OH)2D3: 1,25-dihidroxivitamina D

25-OHD: 25-hidroxivitamina D

BSA: basal surface area

CDs: células dendríticas

CLA: "cutaneous lymphocite antigen" (antígeno linfocitario cutáneo)

CRP: C reactive protein

D-D: dímero D

EM: esclerosis múltiple

ESR: erythrocyte sedimentation rate

FRCV: factor/es de riesgo cardiovascular

ICAM-1: "intercellular adhession molecule 1" (mólecula de adhesión intercelular 1)

IL: interleuquina

INF: interferón

LDL:"low density lipoprotein" (lipoproteínas de baja densidad)

LFA-1: "leukocyte function associated antigen-1" (antigen asociado a la función leucocitaria)

LT: linfocitos T

PASI: psoriasis area and severity index

PCR: proteína C reactiva

PDGF: "platelet-derived growth factor" (factor de crecimiento derivado de plaquetas)

SM: síndrome metabólico

SNP: "single nucleotide polymorphisms" (polimorfismos de nucleótido único)

Th: "T helper" (linfocitos T colaboradores)

Tc: "T citotóxicos (linfocitos T citotóxicos)

TFG-β: "transforming growth factor beta" (factor de crecimiento transformador beta)

TNF: "tumoral necrosis factor" (factor de necrosis tumoral)

VSG: velocidad de sedimentación globular

VII.3CONSENTIMIENTO INFORMADO

VII.3.A CONSENTIMIENTO INFORMADO: ESTUDIO DE PSORIASIS Y RIESGO CARDIOVASCULAR

La psoriasis es una enfermedad inflamatoria crónica. Otras enfermedades inflamatorias crónicas con un proceso patogénico comparable a la psoriasis han mostrado un incremento del riesgo cardiovascular. Con el presente estudio queremos evaluar el riesgo cardiovascular en pacientes con psoriasis en relación a individuos de la población general no afectos de psoriasis. Usted como paciente con psoriasis o individuo "control" sin esta afectación dermatológica si acepta ser incluido en el estudio será evaluado mediante una analítica de sangre y una ecografía carotidea. Son técnicas de carácter rutinario que no implican grandes riesgos; la ecografía es prácticamente inocua, mientras que la extracción sanguínea tiene como principal riesgo el sangrado y la infección.

Yo_____, de_____ años de edad

He sido informado adecuadamente sobre las técnicas exploratorias y el objetivo de las mismas

Comprendo que la participación es voluntaria, siendo posible la retirada del mismo sin tener que dar explicaciones y sin que repercuta en mis cuidados médicos posteriores.

Conforme con la participación,

Fdo:

VII.3.BCONSENTIMIENTO INFORMADO: EVALUACIÓN DE VITAMINA D EN PACIENTES CON PSORIASIS Y PERSONAS SIN PSORIASIS

La psoriasis es una enfermedad inflamatoria crónica. Otras enfermedades inflamatorias crónicas han mostrado un menor nivel de vitamina D respecto a sujetos que no padecen dicho tipo de patología. Con el presente estudio queremos evaluar el nivel de vitamina D en pacientes con psoriasis en relación a individuos de la población general no afectos de psoriasis. Usted como paciente con psoriasis o persona sin esta afectación dermatológica si acepta ser incluido en el estudio será evaluado mediante un cuestionario, exploración física básica, analítica de sangre y ecografía carotidea.La extracción sanguínea es una técnica rutinaria que tiene como principal riesgo el sangrado y la infección en la zona de punción, mientras que la ecografía carotidea es una técnica de imagen no invasiva.

Yo_____, de_____ años de edad

He sido informado adecuadamente sobre las técnicas exploratorias y el objetivo de las mismas.

Comprendo que la participación es voluntaria, siendo posible la retirada del mismo sin tener que dar explicaciones y sin que repercuta en mis cuidados médicos posteriores.

Conforme con la participación,

Fdo: