Tesis doctoral

Modificación de marcadores de riesgo cardiovascular en psoriasis tras terapia anti-TNF

Autor:

Trinitario Pina Murcia

Directores:

Miguel Ángel González-Gay

Javier Llorca

Universidad de Cantabria

Facultad de Medicina, Departamento de Ciencias Médicas y Quirúrgicas

Santander, 2015

Miguel Ángel González-Gay Mantecón, Jefe de Sección del Servicio de Reumatología del Hospital Universitario Marqués de Valdecilla y Profesor Asociado de Ciencias de la Salud de la Universidad de Cantabria, y Javier Llorca, Catedrático de Medicina Preventiva y Salud Pública de la Universidad de Cantabria,

CERTIFICAN:

Que el trabajo titulado "**Modificación de marcadores de riesgo cardiovascular en psoriasis tras terapia antiTNF**" que presenta D. Trinitario Pina Murcia para optar al grado de Doctor ha sido realizado bajo nuestra dirección y reúne las características de originalidad y rigor científico requeridas.

Y para que conste y surta los efectos oportunos, expiden el presente certificado en Santander, a 15 de septiembre de dos mil quince.

A mi amigo Miguel Ángel González-Gay Mantecón.
Mi carrera profesional tiene un antes y un después gracias a él.

Al profesor Llorca.

Al resto de los autores de los artículos.

Este proyecto de investigación ha sido financiado con la ayuda de Abbie Inc.

CONTENIDO

ABREVIATURAS

ACV: accidente cerebrovascular

ADMA: dimetilarginina asimétrica

AR: artritis reumatoide

BSA: Body Surface Area

DM: diabetes mellitus

DMF: dilatación mediada por flujo

FRCV: factores de riesgo cardiovascular

GIMc: grosor íntima-media de la arteria carótida

GPRD: General Practitioners Research Database

HbA1c: hemoglobina glicosilada

HR: Hazard Ratio

HTA: hipertensión arterial

IAM: infarto agudo de miocardio

IC: intervalo de confianza

IFN: interferón

IL: interleucina

Rango IQ: rango intercuartílico

IMC: índice de masa corporal

Lp(a): lipoproteína a

NAPSI: Nail Psoriasis Severity Index

OPG: osteoprotegerina

OR: odds ratio

PASI: Psoriasis Area and Severity Index

PCR: proteína C reactiva

PCRus: proteína C reactiva ultra sensible

PGA: Physician's Global Assessment of disease severity

RBP-4: Proteína transportadora de retinol tipo 4

RI: resistencia insulínica

TC: tomografía computarizada

TNF-α: factor de necrosis tumoral alfa

UK: Reino Unido

VOP: velocidad de onda de pulso

VSG: velocidad de sedimentación globular

VTAE: volumen de tejido adiposo epicárdico

INTRODUCCIÓN

La psoriasis es una enfermedad inflamatoria crónica que viene definida por la presencia de unas lesiones cutáneas características. Tiene una distribución global con una prevalencia que varía geográficamente en función de factores genéticos y ambientales. La prevalencia más alta se da en Noruega y el Ártico (5-12%) y la más baja en indios norteamericanos y africanos occidentales (0-0.3%). En España es del 1.4%. Es una enfermedad que puede debutar a cualquier edad identificándose dos picos de incidencia, uno entre los 20-30 años y otro entre los 50-60. Cabe destacar que el 75% de los pacientes desarrollan la enfermedad antes de la 5ª década de la vida.

La etiología de la enfermedad es desconocida, pero se considera resultado de la interacción de factores genéticos, del sistema inmune y ambientales. Los factores genéticos condicionarían en el sujeto una predisposición a la enfermedad. Esta predisposición genética es compleja y condiciona una respuesta inmune innata y adquirida aberrante. Sobre esta base actuarían otros factores desencadenantes que determinarían la activación de linfocitos T y la alteración de la proliferación y diferenciación de queratinocitos, dando lugar a las lesiones cutáneas características. Este proceso está mediado entre otros por la liberación de citocinas entre las que destacan el factor de necrosis tumoral (TNF)-α, los interferones (IFN) gamma y alfa, interleucina (IL)-1, IL-2, IL-6, IL-17 e IL-22. Estas citocinas implicadas en la patogenia de la psoriasis también están implicadas en otros procesos inflamatorios crónicos, como la formación de la placa de ateroma en la aterosclerosis.

En las últimas 2 décadas se ha demostrado que los pacientes con enfermedades inflamatorias crónicas de base autoinmune (artritis reumatoide (AR), lupus,…etc.) pueden presentar una mortalidad cardiovascular mayor que la población general de la misma edad y sexo. Este incremento de mortalidad es debido en parte a un proceso de aterogénesis acelerada y es independiente de la presencia de factores de riesgo cardiovascular (FRCV) clásicos. La inflamación crónica parece contribuir de forma decisiva en el proceso de aterogénesis acelerada observado en estas enfermedades.

RIESGO CARDIOVASCULAR EN PSORIASIS

ENFERMEDAD CARDIOVASCULAR SUBCLÍNICA

ATEROSCLEROSIS SUBCLÍNICA

Diferentes técnicas de imagen permiten detectar aterosclerosis subclínica en nuestros pacientes. Estas técnicas son útiles para estimar el riesgo cardiovascular. Entre ellas son de especial utilidad la ecografía y la tomografía computarizada (TC). El grosor íntima-media de la arteria carótida (GIMc) medido mediante ecografía es un marcador validado de aterosclerosis subclínica. En población general el GIMc se correlaciona con los FRCV clásicos y es predictor de futuros eventos cardiovasculares, tanto coronarios como cerebrales. La rigidez aórtica medida por ecografía y expresada como velocidad de onda de pulso (VOP) es un predictor de futuros eventos cardiovasculares y de mortalidad global. El depósito de calcio en arterias coronarias medido por TC es un marcador indirecto de aterosclerosis coronaria y es predictor del desarrollo de morbimortalidad cardiovascular. El volumen de tejido adiposo epicárdico (VTAE) medido por TC se ha asociado al desarrollo de enfermedad coronaria. Diferentes estudios han puesto de manifiesto que los pacientes con psoriasis sin evidencia de enfermedad cardiovascular, en comparación con controles sanos, presentan un mayor GIMc, una mayor VOP aórtica, un mayor depósito de calcio coronario y un mayor VTAE.[1-9] Estos datos sugieren que los pacientes con psorasis podrían tener un mayor riesgo de eventos coronarios y cerebrovasculares en comparación con población general.

DISFUNCIÓN ENDOTELIAL

La disfunción endotelial es un marcador temprano de aterosclerosis. La disfunción endotelial implica una menor disponibilidad local de óxido nítrico que además de su acción vasodilatadora, inhibe la agregación plaquetaria, la proliferación de células musculares lisas y la interacción de los leucocitos con el endotelio. La dilatación mediada por flujo (DMF) es una técnica que permite valorar la dilatación dependiente del endotelio y establecer la existencia de disfunción endotelial. En arterias periféricas, como la arteria humeral, la ecografía de alta resolución ha permitido medir la DMF de forma sencilla y reproducible. La función endotelial en la arteria humeral se ha relacionado con la función endotelial coronaria y con la gravedad de las lesiones.

La DMF se correlaciona con el riesgo cardiovascular de tal forma que una mayor DMF ejerce un efecto protector frente a futuros eventos cardiovasculares. Diferentes estudios han puesto de manifiesto que los pacientes con psoriasis sin evidencia de enfermedad cardiovascular, en comparación con controles sanos, presentan una menor DMF.[9-13]

La dimetilarginina asimétrica (ADMA) es un potente inhibidor endógeno de la síntesis del óxido nítrico. El óxido nítrico ejerce una función anti-aterosclerótica y los niveles elevados de ADMA se han asociado con la presencia de disfunción endotelial, síndrome metabólico y riesgo cardiovascular aumentado. En pacientes con psoriasis los niveles plasmáticos de ADMA están elevados.[14]

FACTORES DE RIESGO CARDIOVASCULAR

TABAQUISMO

Un estudio poblacional llevado a cabo en Reino Unido (UK) por Neimann et al y que incluyó a más de 130 000 pacientes con psoriasis puso de manifiesto que los pacientes con psoriasis en comparación con población general presentan un mayor índice de tabaquismo (OR 1.31; IC 95%, 1.29-1.34).[15]

OBESIDAD

En un metaanálisis de estudios observacionales, Armstrong et al objetivaron una asociación entre psoriasis y obesidad.[16] En comparación con la población general, los pacientes con psoriasis tienen una mayor prevalencia e incidencia de obesidad. Según este estudio la psoriasis confiere a quien la padece un aumento del riesgo de obesidad de 1.66 veces (IC 95%, 1.46-1.89). Los pacientes con psoriasis grave tienen mas riesgo de obesidad que los pacientes con psoriasis moderada (OR psoriasis moderada 1.46; IC 95%, 1.17-1.82. OR psoriasis grave 2.23; IC 95%, 1.63-3.05).

HIPERTENSIÓN ARTERIAL

En otro metaanálisis de estudios observacionales, Armstrong et al también objetivaron una asociación entre psoriasis e hipertensión arterial (HTA).[17] En comparación con la población general, los pacientes con psoriasis tienen una mayor prevalencia e incidencia de HTA. Según este estudio la psoriasis confiere a quien la padece un aumento del riesgo de HTA de 1.58 veces (IC 95%, 1.42-1.76). Al igual que sucede con la obesidad,

los pacientes con psoriasis grave tienen mayor riesgo de HTA que los pacientes con psoriasis moderada (OR psoriasis moderada 1.30; IC 95%, 1.15-1.47. OR psoriasis grave 1.49; IC 95%, 1.20-1.86).

DIABETES MELLITUS

En un estudio poblacional llevado a cabo en Dinamarca por Khalid et al en el que se estudiaron los casos incidentes de diabetes mellitus (DM) durante un período de 13 años, se obtuvo en comparación con población general una razón de tasas de incidencia de 1.49 (IC 95%, 1.43-1.56) para psoriasis moderada y de 2.13 (IC 95%, 1.91-2.37) para psoriasis grave.[18]

DISLIPEMIA

Una revisión sistemática de la literatura llevada a cabo por Ma et al puso de manifiesto que los pacientes con psoriasis moderada o grave, en comparación con controles sanos, presentan unos niveles elevados de colesterol total, LDL-colesterol y triglicéridos, así como unos niveles bajos de HDL-colesterol.[19] Al igual que sucede con la obesidad, la HTA y la diabetes, los pacientes con psoriasis grave tienen mayor riesgo de dislipemia que los pacientes con psoriasis moderada.[19-21]

INSUFICIENCIA RENAL

También recientemente se ha puesto de manifiesto que los pacientes con psoriasis tienen un riesgo aumentado de enfermedad renal en comparación con población general.[22, 23] En un estudio poblacional llevado a cabo en UK por Wan et al, la OR de enfermedad renal crónica fue de 1.36 (IC 95%, 1.06-1.74) y 1.58 (IC 95%, 1.07-2.34) para psoriasis moderada y grave, respectivamente.[23]

RESISTENCIA INSULÍNICA

La resistencia insulínica (RI) es un trastorno metabólico caracterizado por una respuesta biológica atenuada a la acción de esta hormona, que tiene como consecuencia una disminución en la captación de la glucosa por las células del músculo y del tejido adiposo, una disminución en la producción hepática de glucógeno y un aumento en la producción hepática de glucosa. Este hecho conduce a un incremento en la secreción de insulina para compensar la elevación progresiva de los niveles de glucosa circulante.[24]

Se sabe desde hace décadas que la inflamación sistémica puede aumentar la RI a través de las acciones del TNF-α, mientras que el tratamiento con terapia antiTNF-α en pacientes con enfermedades reumáticas aumenta la insulinosensibilidad.[25, 26] Es más, la RI es un componente del síndrome metabólico que es un factor asociado a enfermedad cardiovascular.[27] Desde 1977, diversos autores han puesto de manifiesto que los pacientes con psoriasis presentan RI.[28-30]

SÍNDROME METABÓLICO

El síndrome metabólico se define como una interconexión de factores fisiológicos, bioquímicos, clínicos y metabólicos que confieren un riesgo aumentado de enfermedad cardiovascular aterosclerótica, DM tipo 2 y mortalidad global. Se caracteriza, entre otros rasgos, por la presencia de RI, HTA, dislipemia y obesidad.[31]

En un estudio retrospectivo llevado a cabo en Alemania por Sommer et al se valoró la prevalencia del síndrome metabólico en pacientes hospitalizados por psoriasis. En comparación con controles hospitalizados, la OR del síndrome metabólico en pacientes con psoriasis fue de 5.29 (IC 95%, 2.78-12.8).[32] En un estudio poblacional posterior llevado a cabo en UK se evidenció que los pacientes con psoriasis, en comparación con población general, presentan un riesgo elevado de síndrome metabólico (OR 1.41; IC 95%, 1.31-1.51). Además, al igual que sucede con la obesidad, la HTA, la DM y la dislipemia, los pacientes con psoriasis grave tienen mayor riesgo de síndrome metabólico que los pacientes con psoriasis moderada (OR psoriasis moderada 1.22; IC 95%, 1.11-1.35. OR psoriasis grave 1.98; IC 95%, 1.62-2.43).[33]

FACTORES EMERGENTES

ADIPOCINAS

El tejido adiposo blanco es un órgano endocrino que secreta una amplia variedad de sustancias llamadas adipocinas, éstas desempeñan un papel relevante en la fisiopatología de las enfermedades cardiovasculares. La acumulación de grasa visceral asociada con la disregulación de las adipocinas, afecta tanto al desarrollo de la placa aterosclerótica como a la ruptura de la misma. La inflamación sistémica a su vez también puede favorecer la producción de adipocinas tales como la leptina o la

resistina, y suprimir otras como la adiponectina, con un efecto favorable en el metabolismo y el riesgo cardiovascular.[34-37]

LEPTINA

La leptina es una hormona perteneciente a la superfamilia de citocinas de clase I. Es una de las principales adipocinas producida por los adipocitos del tejido adiposo blanco. Interviene en la regulación del apetito disminuyendo la ingesta y aumentando el consumo de energía al actuar sobre núcleos hipotalámicos específicos. La deficiencia genética en el gen que codifica la leptina o sus receptores provoca obesidad grave y diabetes mellitus.[34] La leptina también juega un papel importante en la inmunidad celular. En humanos, la deficiencia congénita de leptina resulta en un descenso del número de linfocitos TCD4 circulantes y en una alteración de la proliferación de linfocitos T así como de la producción de citocinas como el IFN-γ. Estas alteraciones se recuperan tras la administración exógena de leptina. Los niveles elevados de leptina potencian la respuesta inmune Th1 y suprimen la respuesta Th2. La leptina también incrementa la actividad de los macrófagos estimulando la producción de IL-1β, IL-6, TNF-α e IL-12. A nivel de células dendríticas, incrementa la producción de IL-1β, IL-6, TNF-α e IL-12p70, de tal forma que la interacción de células T naive con células dendríticas previamente expuestas a leptina provoca una fuerte polarización Th1.[38]

La expresión del gen de la leptina está regulada principalmente por la ingesta de alimentos, el estado energético, las hormonas, y los mediadores inflamatorios.

La leptina está asociada con las enfermedades cardiovasculares. Sus concentraciones elevadas en suero se relacionan con el infarto agudo de miocardio (IAM) y los accidentes cerebrovasculares (ACV), independientemente de los FRCV tradicionales.[39]

Por otra parte, se ha propuesto que la leptina desempeña un papel patogénico en las placas de ateroma debido a su asociación positiva con la PCR y el receptor soluble de la IL-6, dos mediadores inflamatorios implicados en la patogénesis de la aterosclerosis.[40]

Las acciones proaterogénicas de la leptina están sustentadas por varias observaciones experimentales que demuestran que esta adipocina induce la hipertrofia de células musculares lisas de los vasos y la producción de metaloproteinasa de matriz 2, que desarrolla acciones importantes en la ruptura de la placa. Además, la leptina podría

estimular la remodelación vascular mediante el aumento de la producción de citocinas profibróticas y se sabe también que aumenta la secreción de lipoproteín lipasas proaterogénicas, y la agregación plaquetaria e induce la expresión de la proteína C reactiva (PCR) en las células endoteliales de las arterias coronarias.[34,41]

Un metaanálisis puso de manifiesto que los pacientes con psoriasis presentan niveles séricos de leptina más elevados que los controles.[42] A nivel de parámetros clínicos se ha descrito una asociación positiva entre los niveles séricos de leptina y la gravedad y duración de la psoriasis, independientemente de la presencia de FRCV clásicos.[43-46]

A nivel de parámetros analíticos se ha comunicado una asociación entre las concentraciones séricas de leptina y los niveles séricos de IL-6, proteína C reactiva ultra sensible (PCRus), triglicéridos y LDLoxidado en pacientes con psoriasis.[47,48] No obstante, otros estudios no fueron capaces de confirmar estos hallazgos.[49,50] En estudios in vitro se ha demostrado que la leptina incrementa marcadamente la proliferación y secreción de citocinas proinflamatorias de los keratinocitos de pacientes con psoriasis.[51] Finalmente, en pacientes con psoriasis, los niveles séricos de leptina se han correlacionado con el GIMc.[4]

RESISTINA

La resistina fue inicialmente descubierta como una adipocina en modelos murinos y se sospechó que podía jugar un papel como nexo de unión entre obesidad y diabetes ya que era producida principalmente en los adipocitos.[52] Sin embargo, en humanos la resistina no es producida por los adipocitos sino por las células del compartimento estromal del tejido adiposo, principalmente los macrófagos.[53,54] Acorde con ello, se ha demostrado una débil correlación de los niveles séricos de resistina con el índice de masa corporal (IMC), mientras sí existe una buena correlación del IMC con la cantidad de leucocitos mononucleares en tejido adiposo.[38] La resistina también es producida por los monocitos en sangre periférica y aumenta su expresión durante la diferenciación de éstos a macrófagos. El lipopolisacárido y la citocinas IL-1β, IL-6 y TNF-α inducen la producción de resistina por los monocitos. Además, los niveles de resistina estimulan su propia producción por un mecanismo autocrino y estimulan a la vez la producción de IL-1β, IL-6 y TNF-α por los monocitos y de IL-12 por los macrófagos.[38]

Algunos autores han comunicado que los niveles séricos de resistina están elevados en sujetos obesos, sin embargo otros estudios no lo han confirmado.[55-58] Estudios poblacionales han puesto de manifiesto que los niveles elevados de resistina se asocian con trastornos metabólicos y RI, sin embargo la relación entre niveles de resistina y RI no ha sido consistente en otros estudios en humanos.[55,57,59-61] Los niveles de resistina también se han relacionado con la cardiopatía isquémica y la presencia de un mayor depósito de calcio coronario, pero de igual manera estos hallazgos no han sido consistentes con los resultados de otros autores.[58, 62-64] Por tanto, la asociación de la resistina con la RI y el riesgo cardiovascular no está todavía aclarada.

No obstante merece la pena destacar que la resistina aumenta la producción de TNF-α, IL-6, y otras moléculas de adhesión celular.[65] Además, los estudios in vitro han demostrado que la resistina aumenta la proliferación y migración del músculo liso vascular y de las células endoteliales.[66]

En resumen, es posible que la resistina participe en la fisiopatología cardiovascular en humanos por medio de la acción de los macrófagos implicados en la respuesta inflamatoria relacionada con la obesidad.

Se ha demostrado que los pacientes con psoriasis presentan unos niveles séricos elevados de resistina en comparación con controles, y que los niveles de resistina se correlacionan con la actividad de la enfermedad y los niveles de TNF-α.[38,48]

PROTEÍNA TRANSPORTADORA DE RETINOL TIPO 4

La proteína transportadora de retinol tipo 4 (RBP-4) es una adipocina que pertenece a la familia proteica de las lipocalinas que actúan transportando pequeñas moléculas hidrófobas. RBP-4 es concretamente la proteína transportadora del retinol (vitamina A).[67] Se produce en el hígado y en el tejido adiposo, y sus niveles están estrechamente relacionados con la obesidad, especialmente con la adiposidad visceral.[68, 69] Los niveles elevados de RBP-4 se han asociado con los componentes del síndrome metabólico en sujetos con RI.[69] En estudios poblacionales, RBP-4 se asoció con la presencia de obesidad, HTA y dislipemia.[70] RBP-4 también se ha correlacionado con el GIMc, sugiriendo la participación de esta adipocina en el proceso aterosclerótico y la enfermedad cadiovascular.[71,72] No obstante, y aunque parece existir una evidencia robusta del papel de RBP-4 en el metabolismo anormal de la glucosa y el desarrollo de

aterosclerosis en modelos murinos, en modelos humanos los resultados son contradictorios. Así, algunos autores han comunicado la ausencia de asociación de RBP-4 con obesidad y RI.[73,74] Existe cierta discrepancia en torno a los resultados de RBP-4 en pacientes con psoriasis. Algunos autores han comunicado que los pacientes con psoriasis presentan unos niveles elevados de RBP-4 en comparación con controles, y que dichos niveles se correlacionan con la gravedad de la psoriasis.[75] Sin embargo otros autores han encontrado resultados opuestos, con una reducción en los niveles de RBP-4 en pacientes con psoriasis.[49]

OSTEOPROTEGERINA

La osteoprotegerina (OPG) es una citocina perteneciente a la superfamilia de receptores del TNF. Es una glicoproteína que se expresa in vivo en células endoteliales, células musculares lisas de los vasos, osteoblastos y células estromales de la médula ósea.

Se describió inicialmente como una citocina antiresortiva a través de su unión a RANKL, y posteriormente se ha descrito su implicación en otros muchos procesos como la calcificación vascular, enfermedad ósea tumoral,…etc.[76]

En modelos murinos, la deleción selectiva de OPG provoca osteoporosis grave y calcificación de la aorta y arterias renales. La administración exógena de OPG a los ratones con deleción de OPG previene estas alteraciones. Estos datos sugieren que OPG podría tener un papel protector frente a la calcificación aterosclerótica.[77,78]

Sin embargo, en contra de lo que sugieren los estudios animales, en humanos los niveles elevados de OPG se han asociado de forma independiente con la presencia de calcificación coronaria, disfunción ventricular izquierda, eventos coronarios y mortalidad cardiovascular.[79-82]

En un estudio muy reciente se ha documentado que los pacientes con psoriasis, en comparación con sujetos sanos, presentan unos niveles séricos elevados de OPG.[8]

EVIDENCIAS CLÍNICAS DE ENFERMEDAD CARDIOVASCULAR

En 1978, McDonald y Calabresi llevaron a cabo el primer estudio que puso de manifiesto que los pacientes con psoriasis presentaban una mayor tasa de eventos

vasculares oclusivos que los pacientes sin psoriasis.[84] Desde entonces distintos autores han contribuido con sus trabajos a confirmar esta sospecha.

En UK, Gelfand et al publicaron en 2006 un estudio de cohortes prospectivo en el que analizaron la incidencia de IAM en 130 976 pacientes con psoriasis y 556.995 controles. La incidencia de IAM por 1000 personas año en controles y pacientes con psoriasis moderada y grave fue de 3.58 (IC 95%, 3.52-3.65), 4.04 (IC 95%, 3.88-4.21) y 5.13 (IC 95%, 4.22-6.17), respectivamente.[85] Posteriormente, en 2007 el mismo grupo analizó una cohorte retrospectiva procedente de la General Practitioners Research Database (GPRD), una base de datos médica iniciada en 1987 en UK con fines epidemiológicos. Compararon 137 519 pacientes con psoriasis frente a 575 433 controles y confirmaron que los pacientes con psoriasis grave en comparación con población general presentan un mayor riesgo de mortalidad.[86] En 2009 y 2010, analizaron dos cohortes retrospectivas de la misma base de datos concluyendo que los pacientes con psoriasis grave asocian una mortalidad cardiovascular aumentada en comparación con población general, y que este aumento de mortalidad es independiente de la presencia de FRCV (Hazard Ratio [HR] 1.57; IC 95%, 1.26-1.96).[87] También evidenciaron que los pacientes con psoriasis, especialmente si es grave, asocian un riesgo aumentado de ACV que es independiente de la presencia de factores de riesgo para ictus, y que la psoriasis moderada y grave son un factor de riesgo independiente para ACV.[88] El mismo grupo de investigación y basándose en la GPRD hicieron una estimación del riesgo cardiovascular atribuible a la presencia de psoriasis. Concluyeron que la presencia de psoriasis grave confiere un incremento del 6.2% en el riesgo absoluto a 10 años de padecer un evento cardiovascular.[89]

Estos hallazgos han sido confirmados por otros autores. En 2009 Prodanovich et al llevaron a cabo un estudio retrospectivo que incluyó a 3236 pacientes con psoriasis y 2 500 controles. Tras corregir el efecto de los FRCV clásicos encontraron una OR de 1.78 (IC 95%, 1.51-2.11) para enfermedad cardiovascular, de 1.70 (IC 95%, 1.33-2.17) para enfermedad cerebrovascular y de 1.98 (IC 95%, 1.32-2.82) para enfermedad vascular periférica. Además la psoriasis fue un factor de riesgo independiente para mortalidad.[90] En 2010, basándose en los datos procedentes de 3 ensayos clínicos y con un total de 1 591 pacientes con psoriasis, Kimball et al llevaron a cabo una estimación del riesgo a 10 años de enfermedad coronaria e ictus. Hallaron que, en comparación con población general, los pacientes con psoriasis moderada-grave tienen un riesgo un 28%

mayor, y para ictus un 11.8% mayor.[91] En 2011 Ahlehoff et al analizaron una cohorte retrospectiva basada en los registros nacionales daneses en el período comprendido entre 1997 y 2006.[92, 93] Compararon los datos de morbimortalidad cardiovascular de 36992 pacientes con psoriasis moderada-grave con 4 003 265 controles. La psoriasis moderada-grave se comportó como un factor de riesgo cardiovascular independiente de edad, sexo, comorbilidades, tratamientos y estatus socioeconómico. También asoció un riesgo aumentado de fibrilación auricular e ictus isquémico. En 2012 Armstrong et al analizaron a todos los pacientes que precisaron la realización de una coronariografía en la universidad de California entre 2004 y 2009. En comparación con la población general y tras ajustar por FRCV, los pacientes con psoriasis tuvieron mayor riesgo de enfermedad coronaria confirmada por coronariografía (OR 1.8; IC 95%, 1.2-2.8). Encontraron además una asociación del riesgo con la duración de la psoriasis. Así, los pacientes con duración de la psoriasis > 8 años tuvieron más riesgo de coronariografía patológica (OR 2.7; IC 95%, 1.2-5.9).[94]

Posteriormente, en 2013 un metaanálisis de la asociación entre psorasis y mortalidad cardiovascular, IAM e ictus concluyó que tanto la psoriasis moderada como grave se asocian a un incremento del riesgo de IAM e ictus, y la psoriasis grave además con una mortalidad cardiovascular aumentada.[95]

EFECTO DEL TRATAMIENTO SOBRE EL RIESGO CARDIOVASCULAR

En un estudio retrospectivo que incluyó a 7 615 pacientes con psoriasis se evidenció que los pacientes tratados con metotrexato presentaban una menor incidencia de eventos cardiovasculares (RR 0.73; IC 95%, 0.55-0.98).[96] Ahlehoff et al publicaron un efecto similar de metotrexato en una serie danesa de 6902 pacientes con psorasis (HR 0.53; IC 95%, 0.34-0.83).[97]

Los niveles elevados de PCR se han asociado con un riesgo elevado de IAM, ictus y otros eventos cardiovasculares.[98] Strober et al analizaron el efecto del fármaco anti-TNF etanercept sobre los niveles de PCRus en pacientes con psoriasis. Los pacientes con psoriasis presentaban niveles basales de PCRus elevados. Tras 12 semanas de tratamiento con etanercept los niveles de PCRus se redujeron.[99]

En un estudio prospectivo que incluyó a 16 pacientes con psoriasis grave, el tratamiento con terapia biológica mejoró la función ventricular izquierda.[100]

En un estudio retrospectivo, Ahlehoff et al demostraron que en los pacientes con psoriasis grave en tratamiento con terapias sistémicas, el uso de metotrexato y terapias biológicas se asocia a menores tasas de mortalidad, IAM e ictus en comparación con otras opciones de tratamiento.[101]

LA INFLAMACIÓN COMO FACTOR DE RIESGO CARDIOVASCULAR

La aterosclerosis ha sido considerada durante años una enfermedad degenerativa y una consecuencia inevitable del envejecimiento. Sin embargo, la investigación en las tres últimas décadas ha puesto de manifiesto que la aterosclerosis no es una enfermedad degenerativa ni tampoco inevitable, sino una enfermedad inflamatoria con una notable implicación del sistema inmune.[102]

En la población general, se ha observado que pequeños aumentos en la PCR, medidos por PCRus se asocian a un aumento del riesgo cardiovascular.[103] Acorde con ello, en las últimas dos décadas se ha demostrado que los pacientes con enfermedades inflamatorias crónicas de base autoinmune (AR, lupus,…etc.) pueden presentar una mortalidad cardiovascular mayor que la población general de la misma edad y sexo.[104,105] Este incremento de mortalidad es debido en parte a un proceso de aterogénesis acelerada y es independiente de la presencia de FRCV clásicos.

Los potenciales mecanismos por los que la inflamación contribuye a una aterosclerosis acelerada incluyen el desarrollo de disfunción endotelial, la activación de la cascada de la coagulación, la inducción de dislipemia secundaria, el aumento de la vulnerabilidad de la placa y el incremento de la calcificación de las arterias coronarias.[106,107]

Las complejas interacciones que existen entre los FRCV clásicos y nuevos marcadores, hacen que sea difícil establecer la contribución relativa de cada uno de ellos. A pesar de todo, existen estimaciones de lo que contribuiría cada factor clásico al riesgo total; así, se ha calculado que los factores clásicos explicarían un 80% del riesgo cardiovascular en los pacientes sin AR, pero sólo un 40% en pacientes con ella, sugiriendo que otros factores no clásicos o nuevos, realizan una importante contribución a este exceso de riesgo.[108]

JUSTIFICACIÓN Y OBJETIVOS

Hemos visto que en los últimos años ha surgido evidencia sobre el aumento de morbimortalidad cardiovascular en pacientes con psoriasis. De hecho, las enfermedades cardiovasculares son la causa más común de muerte en pacientes con psoriasis.[109] Ello es debido a un proceso de aterogénesis acelerada que condiciona una mayor prevalencia de enfermedad vascular coronaria, cerebrovascular y enfermedad vascular periférica.[90]

Los pacientes con AR, el prototipo de enfermedad inflamatoria crónica con aterogénesis acelerada, en particular aquellos con enfermedad grave, tienen resistencia a la insulina y niveles elevados de biomarcadores de disfunción endotelial.[110] También de gran importancia desde el punto de vista cardiovascular es la implicación de adipocinas como la leptina y la resistina que están estrechamente relacionados con el proceso inflamatorio en los pacientes con esta enfermedad crónica.[111]

Estudios recientes realizados en pacientes con AR han evidenciado una disminución de la incidencia de eventos cardiovasculares en pacientes tratados con anti-TNF.[112] Curiosamente y de acuerdo con estas observaciones, se ha informado de que el uso de anti-TNF mejora la resistencia a la insulina y los biomarcadores de disfunción endotelial en pacientes con AR.[113,114] En estudios adicionales, no se confirmó cambio en los niveles de leptina en pacientes con AR en tratamiento con anti-TNF.[115-17] Sin embargo, se ha comunicado una reducción significativa de los niveles de resistina, que se correlacionó positivamente con la disminución de algunos marcadores de laboratorio de la inflamación, como la proteína C-reactiva.[118]

Los fármacos antiTNF-α han demostrado ser útiles en el tratamiento de la psoriasis. En este sentido, adalimumab (anticuerpo monoclonal humano IgG1 anti-TNF-α) reduce los síntomas de la psoriasis moderada a grave.[119] Es más, el uso de estos agentes biológicos también parece disminuir la tasa de eventos cardiovasculares en pacientes con psoriasis.[101]

Teniendo en cuenta estas consideraciones, el objetivo del presente estudio consiste en determinar si en pacientes con psoriasis la terapia con el agente antiTNF-α adalimumab puede modificar la resistencia a la insulina, la disfunción endotelial (ADMA), y los niveles de adipocinas (leptina, resistina y RBP-4) y de OPG.

Estos factores podrían jugar un papel en el desarrollo de aterosclerosis acelerada en estos pacientes, y su mejora con tratamiento anti-TNF podría ser un indicador indirecto de la mejora del riesgo cardiovascular.

Estos objetivos se han plasmado en la publicación de cuatro artículos en dos revistas de dermatología.

MATERIAL Y MÉTODOS

PACIENTES Y TRATAMIENTO

Se reclutó de modo prospectivo una serie de 33 pacientes con diagnóstico de psoriasis en placa moderada a grave candidatos a ser tratados con terapia anti-TNF de acuerdo a las guías de práctica clínica españolas.[120] Los pacientes se reclutaron entre aquellos que cumplían los criterios de inclusión y que acudieron consecutivamente a las consultas externas de Dermatología del Hospital Universitario Marqués de Valdecilla, Santander, España. El diagnóstico fue establecido por un dermatólogo cualificado en base a la exploración física y biopsia por punch. El período de reclutamiento fue de 18 meses. Los pacientes recibieron una inyección subcutánea de 80 mg de adalimumab (Humira, Laboratorios Abbott S.A., Madrid, España) en la semana 0, seguida de una dosis de 40 mg cada dos semanas comenzando una semana tras la dosis inicial de 80 mg. Se llevó a cabo una valoración clínica y de parámetros analíticos en la visita basal (antes de inicio de tratamiento) y tras 6 meses de tratamiento. El protocolo del estudio pasó la evaluación del Comité Ético local, y todos los participantes firmaron el documento de consentimiento informado.

CRITERIOS DE INCLUSIÓN:

Pacientes mayores de 18 años.

Pacientes con diagnóstico de psoriasis crónica en placas moderada a grave que vayan a recibir tratamiento con inhibidores del TNF-α de acuerdo a las guías de práctica clínica españolas.[120]

Pacientes que hayan otorgado el consentimiento informado por escrito para participar en este estudio.

CRITERIOS DE EXCLUSIÓN:

Para evitar confusión con otros conocidos factores de riesgo para ateroesclerosis, los criterios de exclusión fueron;

IMC $\geq$35 Kg/m^2.

HTA, definida como una tensión sistólica/diastólica $\geq$140/90 mmHg o el uso de medicación antihipertensiva.

DM (diagnostico basado en los criterios 2006 de la Organización Mundial para la Salud) o el uso de medicación para el tratamiento de la diabetes.[121]

Antecedentes de enfermedad cardíaca isquémica o eventos cerebrovasculares (angor, IAM, insuficiencia cardíaca, enfermedad arterial periférica, accidente isquémico transitorio o ACV).

Insuficiencia renal crónica, definida por la presencia de creatinina sérica ≥ 1.3 mg/dl o filtrado glomerular < 60 ml/min.

Para evitar confusión con posibles factores de riesgo farmacológicos para la aterosclerosis, se excluyó a aquellos pacientes en tratamiento con esteroides, PUVA, retinoides o agentes biológicos desde los 6 meses previos a la visita basal, o tratamiento con fármacos tópicos desde las dos semanas previas a la visita basal. Se llevó a cabo un período de lavado de 4 semanas para el resto de fármacos sistémicos no incluidos en las consideraciones anteriores.

RECOGIDA DE VARIABLES CLÍNICAS

En la visita basal se recogieron las siguientes variables demográficas y clínicas: edad, sexo, edad de inicio de la psoriasis, edad en el momento del diagnóstico de la psoriasis, duración de la psoriasis, historial del consumo de alcohol y tabaco, tipo y dosis de medicación en uso, antecedentes familiares de enfermedad cardiovascular prematura en edades menores a 55 años en hombres o menores a 65 años en mujeres.

En la visita basal y tras 6 meses de tratamiento se llevó a cabo:

a. Una valoración de la actividad de la enfermedad que incluyó el porcentaje de la superficie corporal afecta (BSA-body surface area), el índice PASI (Psoriasis Area and Severity Index), el índice NAPSI (Nail Psoriasis Severity Index), y la valoración global de la enfermedad por el médico (PGA-physician's global assessment of disease severity).[122,123]
b. Cálculo del IMC (Kg/m^2).
c. Medición del perímetro abdominal (medido en centímetros en un nivel medio entre el margen costal inferior y la cresta ilíaca después de la exhalación, con una cinta métrica flexible alrededor de todo el cuerpo, en posición erguida con los pies juntos).

d. Toma de tensión arterial, registrada de acuerdo a las recomendaciones de las guías ESH/ESC. Resumiendo, dos determinaciones realizadas en la posición sentada después de un periodo de 5-min de descanso con un esfigmomanómetro de mercurio calibrado o un dispositivo oscilométrico automático validado. El valor de referencia es el promedio de las dos mediciones.[124]
e. Toma de muestras de sangre con determinación de PCRus, velocidad de sedimentación globular (VSG), glucemia, creatinina, tasa de filtrado glomerular MDRD (ecuación de cuatro variables), hemoglobina glicosilada (HbA1c), insulinemia, homocisteínemia, colesterol total, HDL-colesterol, LDL-colesterol, triglicéridos, apolipoproteína (apo)-A1, apo-B, lipoproteína (a) [Lp(a)], adipocinas séricas (leptina, resistina, RBP-4), y OPG sérica.
f. Cálculo de RI (índice HOMA), sensibilidad a la insulina (índice QUICKI) e índices aterogénicos (Colesterol total/HDL-colesterol, Apo-B/Apo-A1).

Se definió dislipemia como colesterol total > 250 mg/dl, o LDL-colesterol > 155 mg/dl, o HDL colesterol < 40 mg/dl en hombres o < 50 mg/dl en mujeres, o estar en tratamiento con agentes hipolipemiantes.

MÉTODOS DE LABORATORIO

Las muestras de sangre se tomaron entre las 08:00 y las 10:00 horas, tras 12 horas de ayuno nocturno. La glucosa, creatinina, colesterol total, HDL-col y triglicéridos se midieron con métodos estándar automatizados en un ADVIA 2400 Chemistry System de Siemens (Siemens Medical Solutions Diagnostics, Los Angeles, CA USA). Los niveles de LDL-colesterol se calcularon con la ecuación de Friedewald. La apolipoproteina A1, apolipoproteina B, Lipoproteína a (Lpa), homocisteína y PCRus se analizaron por inmunonefelometría (Behring Nephelometer Analyzer II, Behring Diagnostics, Marburg, Germany). La HbA1c se midió por cromatografía de alta resolución en fase líquida (HPLC-DiamatTM, Bio-Rad, München, Germany). Los niveles de insulina se determinaron mediante inmunoensayo específico automatizado (Liaison, DiaSorin, Stillwater, Minnesota). La VSG se determinó por el método Westergren.

La RI se calculó mediante la valoración del modelo de homeostasis de resistencia a la insulina (HOMA).[125] El índice HOMA (Homeostasis Model Assessment) propuesto por

Mathews et al en 1985, es el método más utilizado para diagnosticar RI. Deriva de la interacción entre la función celular β y la sensibilidad a la insulina en un modelo matemático donde se utilizan las concentraciones de glucosa e insulina en ayuno. El modelo se calibra con una función celular β del 100% y una resistencia a la insulina igual a la unidad, de acuerdo con la siguiente fórmula: HOMA-IR = [insulina plasmática en ayuno (μU/ml) x glucosa plasmática en ayuno (mmol/L)] / 22.5.* La sensibilidad a la insulina se calculó mediante el índice QUICKI (Quantitative Insulin Check Index) que se basa en un modelo logarítmico.[126] QUICKI = 1/[(log insulina plasmática en ayuno (μU/ml) + log glucosa plasmática en ayuno (mg/dl)].

Los niveles séricos de leptina, resistina, RBP4 y ADMA se determinaron con un kit comercial ELISA de acuerdo a las instrucciones del fabricante (para leptina: Linco Research, St. Charles, MO, USA; EZHL-80SK. Para resistina: Linco Research, St. Charles, MO, USA; EZHR-95K. Para RBP4: Phoenix Pharmaceuticals, Burlingame, CA, USA, EK-028-28. Para ADMA: Immunodiagnostik AG, Bensheim, Germany, K7860).

Los niveles séricos de OPG se determinaron también por ELISA. Se utilizaron microplacas de 96 pocillos impregnados con anticuerpo anti-OPG humana (Peprotech). Brevemente, se utilizó OPG humana recombinante (Peprotech, Cat. Nº 450-14) para la preparación de la curva estándar. Se realizaron diluciones seriadas desde 0.313 a 20 ng/ml. Se añadieron 50 μl de cada dilución en los pocillos correspondientes y se incubó durante 3 horas a temperatura ambiente. A continuación se lavó 4 veces con buffer y se añadieron 50 μl del preparado de anticuerpo anti-OPG humana en cada pocillo y se incubó durante una hora. Tras lavar el anticuerpo no fijado se añadieron en cada pocillo 50 μl de peroxidasa de rábano ligada a avidina (eBioscience) y se incubó durante 30 minutos. Finalmente, las microplacas se revelaron con el cromógeno líquido ABTS (Peprotech) y fueron leídas a 405 y 600 nm.

ANÁLISIS ESTADÍSTICO

Para el análisis estadístico se utilizó el paquete informático STATA 12/SE (StataCorp, College Station, TX, USA). Para la descripción de las variables se usan frecuencias y porcentajes para las variables categóricas, y media ± desviación estándar (SD) (o mediana y rangos intercuartiles) para las variables continuas.

Para la comparación de variables entre grupos se utilizó la prueba t-Student o U de Mann-Whitney.

Las correlaciones entre QUICKI, adipocinas, OPG y ADMA (antes de tratamiento y tras 6 meses de terapia con adalimumab) con variables continuas seleccionadas, se realizaron ajustando por edad, sexo y duración de la enfermedad utilizando el coeficiente de correlación parcial de Pearson (r).

Se estableció el nivel de significación estadística en $p<0.05$.

ARTÍCULOS PUBLICADOS

DOI: 10.1111/jdv.12814 JEADV

ORIGINAL ARTICLE

Anti-TNF-α therapy improves insulin sensitivity in non-diabetic patients with psoriasis: a 6-month prospective study

T. Pina,[1] S. Armesto,[2] R. Lopez-Mejias,[1] F. Genre,[1] B. Ubilla,[1] M.A. Gonzalez-Lopez,[2] M.C. Gonzalez-Vela,[3] A. Corrales,[1] R. Blanco,[1] M.T. Garcia-Unzueta,[4] J.L. Hernandez,[5] J. Llorca,[6,7], M.A. Gonzalez-Gay[1,*]

[1]Epidemiology, Genetics and Atherosclerosis Research Group on Systemic Inflammatory Diseases, Rheumatology Division, Hospital Universitario Marques de Valdecilla, IDIVAL, Santander, Spain
[2]Dermatology Division, Hospital Universitario Marques de Valdecilla, IDIVAL, Santander, Spain
[3]Pathology Division, Hospital Universitario Marques de Valdecilla, University of Cantabria, Santander, Spain
[4]Endocrinology Research Unit, Medical Laboratory Department, Hospital Universitario Marques de Valdecilla, IDIVAL, Santander, Spain
[5]Department of Internal Medicine, Hospital Universitario Marques de Valdecilla, University of Cantabria, Santander, Spain
[6]Department of Epidemiology and Computational Biology, School of Medicine, University of Cantabria, Santander, Spain
[7]CIBER Epidemiología y Salud Pública (CIBERESP), IDIVAL, Santander, Spain
*Correspondence: M.A. González-Gay. E-mail: miguelaggay@hotmail.com

Abstract

Objective Psoriasis is a chronic inflammatory disease associated with increased risk of cardiovascular death. Several studies have shown a beneficial effect of anti-TNF-α therapy on the mechanisms associated with accelerated atherogenesis in patients with inflammatory arthritis, including an improvement of insulin sensitivity. In this study, we aimed to determine for the first time whether the anti-TNF-α monoclonal antibody adalimumab may improve insulin sensitivity in non-diabetic patients with psoriasis.

Methods Prospective study on a series of consecutive non-diabetic patients with moderate to severe psoriasis seen at the Dermatology Division of Hospital Universitario Marques de Valdecilla (Northern Spain) who completed 6 months of therapy with adalimumab (80 mg at week 0 followed by 40 mg every other week, starting 1 week after the initial dose). Patients with chronic kidney disease, hypertension or body mass index $\geq$ 35 kg/m^2 were excluded. Metabolic and clinical evaluation including assessment of insulin sensitivity using the Quantitative Insulin Sensitivity Check Index (QUICKI) was performed at the onset of the treatment (time 0) and at month 6.

Results Twenty-nine patients (52% women; 38.6 $\pm$ 10.7 years) with moderate to severe psoriasis [body surface area (BSA) 37.9 $\pm$ 16.3%], Psoriasis Area and Severity Index [(PASI) 18.9 $\pm$ 7.8] were assessed. Statistically significant improvement (P=0.008) of insulin sensitivity was observed after 6 months of adalimumab therapy (QUICKI at time 0: 0.35 $\pm$ 0.04 vs. 0.37 $\pm$ 0.04 at month 6). Significant improvement of ERYTHROCYTE sedimentation rate, ultrasensitive C-reactive protein, BSA, PASI, Nail Psoriasis Severity Index, physician global assessment and psoriatic arthritis screening and evaluation questionnaire was also observed at month 6 ($P < 0.05$ for each variable).

Conclusion Our results support a beneficial effect of the anti-TNF-α blockade on the mechanisms associated with accelerated atherogenesis in patients with psoriasis.

Received: 26 August 2014; Accepted: 29 September 2014

Conflicts of interest

The authors had sole responsibility for data analysis and manuscript preparation. The opinions expressed in this study are those of the authors and do not necessarily represent those of Abbvie Inc. MAG-G has received the grant funding from Abbvie Inc, as outlined above.

Funding sources

The study was supported by a research grant from Abbvie Inc.

Introduction

Psoriasis is a chronic, non-infectious, inflammatory disease, characterized by an accelerated turnover of epidermal cells resulting in plaques of the skin. Contrary to what was formerly thought, it is now known that psoriasis is a systemic inflammatory condition extended beyond the skin with similarities to other inflammatory immune disorders.[1,2] In this context, patients with psoriasis often present impaired insulin resistance and are at an increased risk of cardiovascular death, as it has also been reported in patients with inflammatory arthritis such as rheumatoid arthritis (RA), psoriatic arthritis and ankylosing spondylitis (AS).[3–6]

In comparison with the general population, patients with moderate to severe psoriasis are at a two-fold risk of myocardial infarction, stroke and death, being the excess mortality predominantly due to coronary artery disease.[6–9] Even more, patients with psoriasis have greater prevalence of cardiovascular risk factors including hypertension, diabetes mellitus, dyslipidaemia, obesity and smoking.[10–15] Interestingly, even after adjusting for these risk factors, psoriasis keeps being an independent risk factor for cardiovascular death.[16,17]

Accelerated atherosclerosis seems to play the major role in the increased mortality observed in psoriasis. In keeping with previous reports on inflammatory arthritis, increased values of the common carotid artery intima-media wall thickness and impaired endothelial function have been reported in patients with psoriasis compared to controls, indicating early subclinical atherosclerosis associated with psoriasis.[18–21] In RA, the prototype of chronic inflammatory disease associated with accelerated atherosclerosis, endothelial dysfunction, an early step in the atherogenesis process, occurs as the result of a complex effect mediated by classic cardiovascular risk factors, genetic predisposition, chronic inflammation, pro-oxidative stress, a prothrombotic status and metabolic abnormalities such as insulin resistance and dyslipidaemia.[22] Insulin resistance is closely related to the presence of a chronic proinflammatory state and it is related to a cluster of specific cardiovascular disease risk factors such as central obesity, hypertension, high triglycerides and low HDL-cholesterol. This cluster is termed metabolic syndrome.[23] Interestingly, insulin resistance and metabolic syndrome have also been linked to psoriasis.[24–27]

Several studies have disclosed a beneficial effect of the tumour necrosis factor (TNF)-α antagonist therapy on the mechanism associated with accelerated atherogenesis in RA, including specifically the effect of these biological agents on insulin resistance.[28] In line with this, in a prospective study of RA patients with active disease, Gonzalez-Juanatey *et al.*[29] observed a persistent improvement of endothelial function after treatment with adalimumab, a fully human monoclonal antibody targeted against TNFα.

Adalimumab is indicated for the treatment of psoriasis. Since insulin resistance can promote endothelial dysfunction, and adalimumab treatment has been found to improve endothelial function in RA patients, in this study we have sought to assess if adalimumab may improve insulin sensitivity in patients with psoriasis who require this therapy because of moderate to severe disease. To this end, we set out a 6-month prospective study of patients with psoriasis, who received adalimumab due to active disease. To our knowledge, this is the first study assessing the effect of adalimumab therapy on surrogate markers of atherosclerosis in psoriasis.

Materials and methods

Patients and treatment

A series of 33 consecutive patients, with moderate to severe psoriasis who were due to start anti-TNF-α therapy on clinical indication (Spanish guidelines)[30] were recruited from the Dermatology outpatient clinics of the University Hospital Marques de Valdecilla (Santander, Northern Spain). Patients were 18 years of age or older. A trained dermatologist made the diagnosis of psoriasis by clinical examination and skin punch biopsy. To avoid confusion with other known risk factors for atherosclerosis, we excluded the following patients from the study: those with history of cardiovascular or cerebrovascular disease (angor pectoris, myocardial infarction, congestive heart failure, peripheral arterial disease, transient ischaemic attack or stroke), chronic kidney disease (serum creatinine ≥1.3 mg/dL or glomerular filtration rate < 60 mL/min), hypertension (blood pressure ≥140/90 mmHg) or current antihypertensive medication, diabetes mellitus (defined according to the 2006 World Health Organization criteria)[31] or current antidiabetic drugs, body mass index (BMI) ≥35 kg/m^2, having been treated with oral corticosteroids, PUVA, retinoids or biological drugs for the previous 6 months, or topical medications for the previous 2 weeks. A 4-week washout period for other non-biological systemic therapies was performed.

Following this protocol, 33 patients were included over the 18-month recruitment period. Four of the 33 patients discontinued intervention and, because of that, they did not complete the 6 months of therapy with adalimumab. The reasons were as follows: two lost to follow-up, one withdrawal (persistent failure to attend appointments) and one pregnancy.

Patients received subcutaneous injections of adalimumab (Humira, Abbot Laboratories S.A., Madrid, Spain) 80 mg at week 0 followed by 40 mg every other week, starting 1 week after the initial dose. The study protocol was approved by the local institutional ethics committee, and it was in accordance with the ethical standards outlined in the Declaration of Helsinki. Patients gave informed consent to participate in this study.

Evaluation of disease severity

At the time of enrolment, all patients underwent evaluation of their demographic and clinical characteristics. At baseline (before adalimumab) and after 6 months of therapy, all patients

were assessed for disease activity, including the per cent of body surface area affected (BSA), Psoriasis Area and Severity Index (PASI), Psoriatic Arthritis Screening and Evaluation questionnaire (PASE), Nail Psoriasis Severity Index (NAPSI) and physician's global assessment of disease severity (PGA).[32–35]

Metabolic and serological assessments

Blood samples, for routine biochemical parameters and specific determinations, were taken after a 12-hour overnight fast between 08:00 am and 10:00 am for two separate visits: prior to starting adalimumab (at time 0) and 6 months after initiation of treatment. Glucose, creatinine, total cholesterol, HDL-cholesterol and triglycerides were measured by standard automated methods on an ADVIA 2400 Chemistry System from Siemens (Siemens Medical Solutions Diagnostics, Los Angeles, CA USA), using the reagents supplied by Siemens. LDL-cholesterol was calculated by the Friedewald equation. Apolipoprotein (Apo)-A1, Apo-B, lipoprotein a (Lpa), homocysteine and ultrasensitive C-reactive protein (usCRP) were analysed by immunonephelometry (Behring Nephelometer Analyser II; Behring Diagnostics, Marburg, Germany). Glycated haemoglobin (HbA1c) was measured by high-performance liquid chromatography (DiamatTM, Bio-Rad, München, Germany). Insulin was quantified by specific automated immunoassay (Liaison, DiaSorin, Stillwater, MN, USA). Erythrocyte sedimentation rate (ESR) was determined using the Westergren method.

Assessment of insulin resistance/sensitivity

While the hyperinsulinaemic-euglycaemic clamp technique is the gold standard for evaluating insulin sensitivity, the Homeostasis Model Assessment (HOMA) for insulin resistance and the Quantitative Insulin Sensitivity Check Index (QUICKI) are widely used as non-invasive surrogate markers of insulin resistance and insulin sensitivity respectively.[36,37] Although results on HOMA and QUICKI are shown in this report, the use of the QUICKI is superior to the HOMA index since the variables are logarithmically transformed.[36]

Statistical analysis

Statistical analysis was performed using STATA 12/SE (StataCorp, College Station, TX, USA). Results were reported as mean ± standard deviation (SD). For the comparison of normally distributed variables between groups, Student's *t*-test was used. Correlation of insulin sensitivity (QUICKI) prior to adalimumab (at time 0) and after 6 months on treatment with selected continuous variables was performed adjusting for age, sex and disease duration via estimation of the Pearson partial correlation coefficient (*r*). Differences were considered statistically significant at $P < 0.05$.

Results

This study included 29 patients (52% women; mean ± SD 38.6 ± 10.7 years) with moderate to severe psoriasis (BSA 37.9 ± 16.3%, PASI 18.9 ± 7.8) who completed 6 months of therapy with adalimumab and were suitable for the comparative analyses. The mean disease duration was 18.2 ± 12.1 years. Table 1 summarizes the epidemiological features of these 29 patients at the onset of adalimumab therapy.

Table 1 Epidemiological features in 29 patients with psoriasis who completed 6 months of therapy with adalimumab

Variable	
Men/Women, *n* (%)	14 (48)/15 (52)
Age at the time of the study (years); mean ± SD	38.6 ± 10.7
Disease duration (years); mean ± SD	18.2 ± 12.1
Classic cardiovascular risk factors, *n* (%)	
Current smokers	10 (34)
Ever smoked	14 (48)
Obese (BMI > 30 kg/m^2)	7 (24)
Dyslipidaemia	13 (44)
BMI (kg/m^2); mean ± SD	27.5 ± 3.7
Waist circumference (cm); mean ± SD	96.1 ± 10.8

Effect of adalimumab therapy

Table 2 shows the differences observed in the clinical and serological parameters between time 0 (immediately before the onset of adalimumab therapy) and after 6 months of treatment with this biological agent.

Anti-TNF-alpha therapy yielded an improvement of insulin resistance as the mean ± SD HOMA values at month 6 (1.7 ± 1.3) were lower than those obtained before the onset of the therapy (2.2 ± 1.5). However, the difference did not achieve statistical significance ($P = 0.13$). Nevertheless, a significant improvement of insulin sensitivity in this cohort of non-diabetic patients was observed as QUICKI values increased from 0.35 ± 0.04 before adalimumab onset to 0.37 ± 0.04 at month 6 ($P = 0.008$). In keeping with that, a marginal decrease in the insulin/glucose ratio from 0.12 ± 0.07 to 0.10 ± 0.06 ($P = 0.07$) was also disclosed.

With respect to the effect of adalimumab therapy on lipids, we observed a non-significant increase of total cholesterol, and LDL-cholesterol after 6 months of adalimumab therapy. Since no variations in HDL-cholesterol were seen, the atherogenic index (total cholesterol/HDL-cholesterol) showed a non-significant increase. In contrast to these findings that may be due to the anti-inflammatory effect of adalimumab, a potential beneficial effect mediated by this drug was seen as the mean levels of Lpa fell from 20.0 mg/dL to 15.4 mg/dL. However, the difference was not statistically significant ($P = 0.21$). In addition, a non-significant reduction of homocysteine levels was also disclosed (15.9 ± 7.5 μmol/L before adalimumab therapy vs. 14.4 ± 9.8 after 6 months of therapy with this drug; $P = 0.11$).

Adalimumab therapy led to a significant reduction ($P < 0.05$ for each comparison) in all of the markers of disease activity including ESR, usCRP, BSA, PASI, NAPSI, PGA and PASE. (Table 2).

Table 2 Clinical and laboratory findings in 29 patients with psoriasis that completed 6 months of therapy with adalimumab. Differences between data found immediately before the onset of adalimumab therapy (basal results - time 0) and those observed at month 6

Variable	Basal (time 0) Mean ± SD	At month 6 Mean ± SD	*P*-value
HOMA	2.2 ± 1.5	1.7 ± 1.3	0.13
QUICKI	0.35 ± 0.04	0.37 ± 0.04	0.008
Fasting serum glucose (mg/dL)	84.3 ± 8.9	82.5 ± 7.8	0.33
Glycated haemoglobin (%)	5.3 ± 0.3	5.4 ± 1.7	0.62
Insulin (U/mL)	10.2 ± 6.3	8.3 ± 5.5	0.10
Ratio insulin/glucose	0.12 ± 0.07	0.10 ± 0.06	0.07
Serum creatinine (mg/dL)	0.77 ± 0.12	0.77 ± 0.13	0.97
Total cholesterol (mg/dL)	196.9 ± 38.5	202.9 ± 36.6	0.19
HDL-cholesterol (mg/dL)	53.2 ± 14.9	52.9 ± 14.3	0.89
LDL-cholesterol (mg/dL)	120.7 ± 28.4	127.0 ± 27.9	0.13
Triglycerides (mg/dL)	118.2 ± 56.3	115.2 ± 53.3	0.71
Apo-A1 (mg/dL)	161.6 ± 28.4	160.7 ± 29.4	0.85
Apo-B (mg/dL)	100.0 ± 26.8	100.0 ± 23.4	0.99
Lpa (mg/dL)	20.0 ± 23.3	15.4 ± 14.8	0.21
Total cholesterol/ HDL-cholesterol	3.87 ± 0.95	4.01 ± 0.98	0.25
Apo-B/Apo-A1	0.63 ± 0.16	0.64 ± 0.18	0.73
Homocysteine (mol/L)	15.9 ± 7.5	14.4 ± 9.8	0.11
ESR (mm/1st hour)	13.4 ± 12.8	8.3 ± 7.7	0.01
Ultra-sensitive CRP (mg/dL)	0.36 ± 0.33	0.19 ± 0.17	0.008
BMI (kg/m^2)	27.5 ± 3.7	27.6 ± 3.7	0.59
Systolic blood pressure (mmHg)	120.7 ± 12.5	118.4 ± 12.4	0.19
Diastolic blood pressure (mmHg)	74.4 ± 6.8	74.2 ± 6.4	0.86
BSA (%)	37.9 ± 16.3	3.1 ± 5.5	<0.001
PASI (0–72)	18.9 ± 7.8	1.3 ± 2.1	<0.001
NAPSI hands (0–80)	5.4 ± 10.5	1.5 ± 3.9	0.04
PGA psoriasis (0–6)	3.9 ± 0.6	0.7 ± 0.6	<0.001
PASE total score (15–75)	32.5 ± 15.9	25.2 ± 13.0	0.005
PASE functional (8–40)	15.9 ± 8.7	12.1 ± 6.2	0.005
PASE symptoms (7–35)	16.6 ± 7.7	13.1 ± 7.3	0.007

Apo-A1, apolipoprotein A1; Apo-B, apolipoprotein B; BMI, body mass index; BSA, body surface area; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; Lpa, lipoprotein a; NAPSI, Nail Psoriasis Severity Index; PASE, psoriatic arthritis screening and evaluation questionnaire; PASI, Psoriasis Area and Severity Index; PGA, physician global assessment; SD, standard deviation.

In a further step, we analysed whether there was a correlation of insulin sensitivity (QUICKI) prior to adalimumab and after 6 months on treatment with continuous variables adjusting for age at the time of the study, sex and disease duration. With respect to this, we observed a negative and significant correlation between basal CRP levels and insulin sensitivity before the onset of adalimumab. This negative correlation was marginally significant after 6 months of adalimumab therapy (Table 3). Moreover, a statistically significant negative correlation between BMI and insulin sensitivity was observed at time 0 (immediately before the onset of adalimumab therapy) ($r = -0.49$; $P = 0.01$) and after 6 months of biological therapy ($r = -0.69$; $P < 0.001$). In keeping with that, we also disclosed a statistically significant negative correlation between abdominal perimeter determined by waist circumference values and insulin sensitivity before the onset of adalimumab therapy (Table 3). As observed for BMI, this negative correlation was also stronger after 6 months of biological therapy ($r = -0.69$; $P = 0.001$) (Table 3). Finally, a negative and marginally significant correlation was observed between BSA and insulin sensitivity after 6 months of treatment with adalimumab (Table 3).

Table 3 Partial correlation of insulin sensitivity (QUICKI) prior to adalimumab (time 0) and after 6 months of therapy with this biological agent with selected continuous variables adjusted for age at the time of the study, sex and disease duration in 29 patients with psoriasis

Variable	Time 0		Time 6 months	
	r	*P*	*r*	*P*
Systolic BP	−0.11	0.55	−0.34	0.09
Diastolic BP	0.0005	0.99	−0.17	0.40
Total cholesterol (mg/dL)	0.13	0.48	−0.19	0.33
HDL-cholesterol (mg/dL)	0.22	0.23	−0.06	0.74
LDL-cholesterol (mg/dL)	0.14	0.44	−0.21	0.29
Triglycerides (mg/dL)	−0.28	0.12	−0.02	0.91
Apo-A1 (mg/dL)	0.10	0.57	−0.07	0.70
Apo-B (mg/dL)	0.12	0.53	−0.18	0.36
Lpa (mg/dL)	0.02	0.89	−0.28	0.17
Total cholesterol/HDL-cholesterol	−0.19	0.29	−0.14	0.49
Apo-B/Apo-A1	0.02	0.91	−0.17	0.39
Homocysteine (μmol/L)	0.20	0.32	−0.04	0.84
ESR (mm/1st hour)	0.27	0.14	0.09	0.63
Ultra-sensitive CRP (mg/dL)	−0.39	0.02	−0.35	0.07
BMI (kg/m^2)	−0.49	0.01	−0.69	<0.001
Waist circumference	−0.45	0.01	−0.59	0.001
BSA	−0.25	0.18	−0.38	0.05
PASI	−0.21	0.26	−0.26	0.20
NAPSI hands	−0.009	0.95	−0.18	0.39
PGA psoriasis	−0.24	0.19	−0.21	0.30
PASE total score	0.20	0.28	−0.13	0.51
PASE functional	0.12	0.49	−0.18	0.36
PASE symptoms	0.27	0.14	−0.08	0.67

Discussion

In this study, we disclosed that non-diabetic patients with moderate to severe psoriasis on treatment with adalimumab experience an improvement of insulin sensitivity. These observations

are in keeping with the data reported by Marra *et al.* that showed an improvement of insulin sensitivity in nine psoriatic patients treated with etanercept for 24 weeks.[38]

More than 20 years ago, Scandinavian investigators disclosed the presence of glucose intolerance in patients with RA and other chronic inflammatory diseases. The degree of the impaired glucose handling was related to the severity of inflammatory activity as defined by acute phase reactants.[39] In patients with active RA, the impaired glucose handling combined with hyperinsulinaemia was directly related to peripheral insulin resistance.[40] Later on, Paolisso *et al.*[41] confirmed the presence of insulin resistance in different chronic inflammatory diseases and found that insulin resistance was mainly confined to muscular rather than hepatic site. Dessein *et al.*[42] reported that the acute phase response predicts insulin resistance in RA.

Tumour necrosis factor-α production is increased under chronic hyperglycaemia and it has ominous effects on insulin sensitivity.[43] TNF-α is also an important mediator of insulin resistance in obesity and diabetes through its ability to decrease the tyrosine kinase activity of the insulin receptor, and it also directly impedes insulin–glucose-mediated uptake in the skeletal muscle.[44] Interestingly, both short-term and persistent beneficial effect of adalimumab on endothelial function has been reported in patients with RA.[29,45] This is of potential relevance as the use of anti-TNF-α therapy has been associated with a decrease of mortality in RA patients, mainly due to a reduction in the incidence of cardiovascular events.[46]

Psoriasis bears similarities with inflammatory arthritis such as RA. In this regard, both conditions are associated with increased prevalence of the metabolic syndrome, an impaired aortic elasticity, echocardiographic abnormalities and an increased carotid artery intima-media thickness.[25–27,47–51]As observed in RA, Wu *et al.* found a significant reduction in myocardial infarction risk and its incident rate among psoriatic patients treated with TNF-α inhibitors.[52,53]

Regarding lipid profile, we did not find a significant change of the lipid levels after 6 months of treatment with adalimumab. Only a non-significant reduction in Lpa levels was observed after 6 months of adalimumab therapy. These results are in agreement with data on lipids reported by Bacchetti *et al.*[54] who only found a reduction of Lpa levels in psoriatic patients after 24 weeks of treatment with etanercept. Since high serum Lpa is an independent risk factor for atherosclerotic disease, its reduction may have a beneficial effect on cardiovascular risk.[55]

Although we recognize that long-term data are required to validate the improvement in insulin sensitivity found in our study, and possibly to detect any reduction in cardiovascular outcomes in psoriatic patients undergoing adalimumab therapy, our prospective study supports a beneficial effect of the anti-TNF-α blockade on the mechanisms associated with the development of metabolic syndrome and atherosclerosis in patients with psoriasis.

References

1 Nestle FO, Kaplan DH, Barker J. Psoriasis. *N Engl J Med* 2009; **361**: 496–509.
2 Coumbe AG, Pritzker MR, Duprez DA. Cardiovascular risk and psoriasis: beyond the traditional risk factors. *Am J Med* 2014; **127**: 12–18.
3 Maradit-Kremers H, Nicola PJ, Crowson CS, Ballman KV, Gabriel SE. Cardiovascular death in rheumatoid arthritis: a population-based study. *Arthritis Rheum* 2005; **52**: 722–732.
4 Gladman DD. Mortality in psoriatic arthritis. *Clin Exp Rheumatol* 2008; **26**: S62–S65.
5 Zochling J, Braun J. Mortality in ankylosing spondylitis. *Clin Exp Rheumatol* 2008; **26**: S80–S84.
6 Gelfand JM, Troxel AB, Lewis JD *et al.* The risk of mortality in patients with psoriasis: results from a population-based study. *Arch Dermatol* 2007; **143**: 1493–1499.
7 Prodanovich S, Kirsner RS, Kravetz JD, Ma F, Martinez L, Federman DG. Association of psoriasis with coronary artery, cerebrovascular, and peripheral vascular diseases and mortality. *Arch Dermatol* 2009; **145**: 700–703.
8 Ahlehoff O, Gislason GH, Jorgensen CH *et al.* Psoriasis and risk of atrial fibrillation and ischaemic stroke: a Danish nationwide cohort study. *Eur Heart J* 2012; **33**: 2054–2064.
9 Gelfand JM, Dommasch ED, Shin DB *et al.* The risk of stroke in patients with psoriasis. *J Invest Dermatol* 2009; **129**: 2411–2418.
10 Armstrong AW, Harskamp CT, Armstrong EJ. The association between psoriasis and hypertension: a systematic review and meta-analysis of observational studies. *J Hypertens* 2013; **31**: 433–443.
11 Armstrong AW, Harskamp CT, Armstrong EJ. The association between psoriasis and obesity: a systematic review and meta-analysis of observational studies. *Nutr Diabetes* 2012; **2**: e54.
12 Khalid U, Hansen PR, Gislason GH *et al.* Psoriasis and new-onset diabetes. A Danish nationwide cohort study. *Diabetes Care* 2013; **36**: 2402–2407.
13 Akhyani M, Ehsani AH, Robati RM, Robati AM. The lipid profile in psoriasis: a controlled study. *J Eur Acad Dermatol Venerol* 2007; **21**: 1330–1332.
14 Neimann AL, Shin DB, Wang X, Margolis DJ, Troxel AB, Gelfand JM. Prevalence of cardiovascular risk factors in patients with psoriasis. *J Am Acad Dermatol* 2006; **55**: 829–835.
15 Yeung H, Takeshita J, Mehta NN *et al.* Psoriasis severity and the prevalence of major medical comorbidity. A population-based study. *JAMA Dermatol* 2013; **149**: 1173–1179.
16 Ahlehoff O, Gislason GH, Charlot M *et al.* Psoriasis is associated with clinically significant cardiovascular risk: a Danish nationwide cohort study. *J Intern Med* 2011; **270**: 147–157.
17 Mehta NN, Yu Y, Pinnelas R *et al.* Attributable risk estimate of severe psoriasis on major cardiovascular events. *Am J Med* 2011; **124**: 775.e1–e6.
18 Balci DD, Balci A, Karazincir S *et al.* Increased carotid intima-media thickness and impaired endothelial function in psoriasis. *J Eur Acad Dermatol Venerol* 2009; **23**: 1–6.
19 Gonzalez-Juanatey C, Llorca J, Testa A, Revuelta J, Garcia-Porrua C, Gonzalez-Gay MA. Increased prevalence of severe subclinical atherosclerotic findings in long-term treated rheumatoid arthritis patients without clinically evident atherosclerotic disease. *Medicine (Baltimore)* 2003; **82**: 407–413.
20 Gonzalez-Juanatey C, Vazquez-Rodriguez TR, Miranda-Filloy JA *et al.* The high prevalence of subclinical atherosclerosis in patients with ankylosing spondylitis without clinically evident cardiovascular disease. *Medicine (Baltimore)* 2009; **88**: 358–365.
21 Gonzalez-Juanatey C, Llorca J, Amigo-Diaz E, Dierssen T, Martin J, Gonzalez-Gay MA. High prevalence of subclinical atherosclerosis in psoriatic arthritis patients without clinically evident cardiovascular disease or classic atherosclerosis risk factors. *Arthritis Rheum* 2007; **57**: 1074–1080.
22 Gonzalez-Gay MA, Gonzalez-Juanatey C, Martin J. Rheumatoid arthritis: a disease associated with accelerated atherogenesis. *Semin Arthritis Rheum* 2005; **35**: 8–17.

23 Ferraz-Amaro I, Gonzalez-Juanatey C, Lopez-Mejias R, Riancho-Zarrabeitia L, González-Gay MA. Metabolic syndrome in rheumatoid arthritis. *Mediators Inflamm* 2013; **2013**: 710928.
24 Boehncke S, Thaci D, Beschmann H *et al.* Psoriasis patients show signs of insulin resistance. *Br J Dermatol* 2007; **157**: 1249–1251.
25 Sommer DM, Jenisch S, Suchan M, Christophers E, Weichenthal M. Increased prevalence of the metabolic syndrome in patients with moderate to severe psoriasis. *Arch Dermatol Res* 2006; **298**: 321–328.
26 Love TJ, Qureshi AA, Karlson EW, Gelfand JM, Choi HK. Prevalence of the metabolic syndrome in psoriasis: results from the National Health and Nutrition Examination Survey, 2003-2006. *Arch Dermatol* 2011; **147**: 419–424.
27 Langan SM, Seminara NM, Shin DB *et al.* Prevalence of metabolic syndrome in patients with psoriasis: a population-based study in the United Kingdom. *J Invest Dermatol* 2012; **132**: 556–562.
28 Gonzalez-Gay MA, Gonzalez-Juanatey C, Vazquez-Rodriguez TR, Miranda-Filloy JA, Llorca J. Insulin resistance in rheumatoid arthritis: the impact of the anti-TNF-alpha therapy. *Ann N Y Acad Sci* 2010; **1193**: 153–159.
29 Gonzalez-Juanatey C, Vazquez-Rodriguez TR, Miranda-Filloy JA *et al.* Anti-TNF-alpha-adalimumab therapy is associated with persistent improvement of endothelial function without progression of carotid intima-media wall thickness in patients with rheumatoid arthritis refractory to conventional therapy. *Mediators Inflamm* 2012; **2012**: 674265.
30 Puig L, Bordas X, Carrascosa JM *et al.* Consensus document on the evaluation and treatment of moderate-to-severe psoriasis. Spanish psoriasis group of the Spanish Academy of Dermatology and Venereology. *Actas Dermosifiliogr* 2009; **100**: 277–286.
31 Definition and Diagnosis of Diabetes Mellitus and Intermediate Hyperglycaemia. Report of a WHO/IDF Consultation. 2006. ISBN: 978 92 4 159493 6
32 Feldman SR, Krueger GG. Psoriasis assessment tools in clinical trials. *Ann Rheum Dis* 2005; **64**(Suppl. 2): 65–68, discussion 69–73.
33 Husni ME, Meyer KH, Cohen DS, Mody E, Qureshi AA. The PASE questionnaire: pilot testing a psoriatic arthritis screening and evaluation tool. *J Am Acad Dermatol* 2007; **57**: 581–587.
34 Domingez PL, Husni ME, Holt EW, Tyler S, Qureshi AA. Validity, reliability and sensitivity to change properties of the psoriatic arthritis screening evaluation questionnaire. *Arch Der Res* 2009; **301**: 573–579.
35 Rich P, Scher RK. Nail Psoriasis Severity Index: a useful tool for evaluation of nail psoriasis. *J Am Acad Dermatol* 2003; **49**: 206–212.
36 Katz A, Nambi SS, Mather K *et al.* Quantitative insulin sensitivity check index: a simple, accurate method for assessing insulin sensitivity in humans. *J Clin Endocrinol Metab* 2000; **85**: 2402–2410.
37 Gordillo-Moscoso A, Valadez-Castillo JF, Mandeville PB, Hernandez-Sierra JF. Comparison of equivalence and determination of diagnostic utility of minmod and clamp methods for insulin resistance in diabetes free subjects: a meta-analysis. *Endocrine* 2004; **25**: 259–263.
38 Marra M, Campanati A, Testa R *et al.* Effect of etanercept on insulin sensitivity in nine patients with psoriasis. *Int J Immunopathol Pharmacol* 2007; **20**: 731–736.
39 Hallgren R, Berne C. Glucose intolerance in patients with chronic inflammatory diseases is normalized by glucocorticoids. *Acta Med Scand* 1983; **213**: 351–355.
40 Svenson KL, Pollare T, Lithell H, Hällgren R. Impaired glucose handling in active rheumatoid arthritis: relationships to peripheral insulin resistance. *Metabolism* 1988; **37**: 125–130.
41 Paolisso G, Valentini G, Giuliano D *et al.* Evidence of peripheral impaired glucose handling in patients with connective tissue diseases. *Metabolism* 1991; **40**: 902–907.
42 Dessein PH, Joffe BI, Stanwix A, Botha AS, Moomal Z. The acute phase response does not fully predict the presence of insulin resistance and dyslipidemia in inflammatory arthritis. *J Rheumatol* 2002; **29**: 462–466.
43 Fukuzawa M, Satoh J, Qiang X *et al.* Inhibition of tumor necrosis factor-alpha with anti-diabetic agents. *Diabetes Res Clin Pract* 1999; **43**: 147–154.
44 Hotamisligil GS, Peraldi P, Budavari A, Ellis R, White MF, Spiegelman BM. IRS-1-mediated inhibition of insulin receptor tyrosine kinase activity in TNF-alpha- and obesity-induced insulin resistance. *Science* 1996; **271**: 665–668.
45 Gonzalez-Juanatey C, Llorca J, Sanchez-Andrade A, Garcia-Porrua C, Martin J, Gonzalez-Gay MA. Short-term adalimumab therapy improves endo-thelial function in patients with rheumatoid arthritis refractory to infliximab. *Clin Exp Rheumatol* 2006; **24**: 309–312.
46 Barnabe C, Martin BJ, Ghali WA. Systematic review and meta-analysis: anti-tumor necrosis factor α therapy and cardiovascular events in rheumatoid arthritis. *Arthritis Care Res (Hoboken)* 2011; **63**: 522–529.
47 Dessein PH, Joffe BI, Stanwix AE. Inflammation, insulin resistance, and aberrant lipid metabolism as cardiovascular risk factors in rheumatoid arthritis. *J Rheumatol* 2003; **30**: 1403–1405.
48 Bicer A, Acikel S, Kilic H *et al.* Impaired aortic elasticity in patients with psoriasis. *Acta Cardiol* 2009; **64**: 597–602.
49 Mäki-Petäjä KM, Hall FC, Booth AD *et al.* Rheumatoid arthritis is associated with increased aortic pulse-wave velocity, which is reduced by anti-tumor necrosis factor-alpha therapy. *Circulation* 2006; **114**: 1185–1192.
50 Biyik I, Narin A, Bozok MA, Ergene O. Echocardiographic and clinical abnormalities in patients with psoriasis. *J Int Med Res* 2006; **34**: 632–639.
51 Gonzalez-Juanatey C, Testa A, Garcia-Castelo A *et al.* Echocardiographic and Doppler findings in long-term treated rheumatoid arthritis patients without clinically evident cardiovascular disease. *Semin Arthritis Rheum* 2004; **33**: 231–238.
52 Dixon WG, Watson KD, Lunt M *et al.* Reduction in the incidence of myocardial infarction in patients with rheumatoid arthritis who respond to anti-tumor necrosis factor alpha therapy: results from the British Society for Rheumatology Biologics Register. *Arthritis Rheum* 2007; **56**: 2905–2912.
53 Wu JJ, Poon KY, Channual JC, Shen AY. Association between tumor necrosis factor inhibitor therapy and myocardial infarction risk in patients with psoriasis. *Arch Dermatol* 2012; **148**: 1244–1250.
54 Bacchetti T, Campanati A, Ferretti G, Simonetti O, Liberati G, Offidani AM. Oxidative stress and psoriasis: the effect of antitumour necrosis factor-α inhibitor treatment. *Br J Dermatol* 2013; **168**: 984–989.
55 Nordestgaard BG, Chapman MJ, Ray K *et al.* Lipoprotein(a) as a cardiovascular risk factor: current status. *Eur Heart J* 2010; **31**: 2844–2853.

DOI: 10.1111/jdv.13131 JEADV

ORIGINAL ARTICLE

Relationship of Leptin with adiposity and inflammation and Resistin with disease severity in Psoriatic patients undergoing anti-TNF-alpha therapy

T. Pina,[1] F. Genre,[1] R. Lopez-Mejias,[1] S. Armesto,[2] B. Ubilla,[1] V. Mijares,[1] T. Dierssen-Sotos,[3,4] M.A. Gonzalez-Lopez,[2] M.C. Gonzalez-Vela,[5] R. Blanco,[1] J.L. Hernández,[6] J. Llorca,[3,4], M.A. Gonzalez-Gay[1,*]

[1]Epidemiology, Genetics and Atherosclerosis Research Group on Systemic Inflammatory Diseases, Rheumatology Division, Hospital Universitario Marqués de Valdecilla, IDIVAL, Santander, Spain
[2]Dermatology Division, Hospital Universitario Marqués de Valdecilla, IDIVAL, Santander, Spain
[3]Department of Epidemiology and Computational Biology, School of Medicine, University of Cantabria, Santander, Spain
[4]CIBER Epidemiología y Salud Pública (CIBERESP), IDIVAL, Santander, Spain
[5]Pathology Division, Hospital Universitario Marqués de Valdecilla, University of Cantabria, Santander, Spain
[6]Department of Internal Medicine, Hospital Universitario Marqués de Valdecilla, IDIVAL, Santander, Spain
*Correspondence: M.A. González-Gay. E-mail: miguelaggay@hotmail.com

Abstract

Background Altered secretion patterns of proinflammatory adipokines may influence the increased risk of cardiovascular mortality observed in patients with chronic inflammatory diseases.

Objective To determine whether two adipokines, leptin and resistin, correlate with metabolic syndrome features and disease severity in psoriatic patients who underwent anti-TNF-α therapy.

Methods Prospective study of consecutive non-diabetic patients with moderate-to-severe psoriasis who completed 6 months of therapy with anti-TNF-α- adalimumab. Patients with kidney disease, hypertension or body mass index ≥35 Kg/m^2 were excluded. Metabolic and clinical evaluation was performed at the onset of anti-TNF-α treatment and at month 6.

Results Twenty-nine patients were assessed. A correlation between adiposity and leptin was observed (waist circumference and leptin levels after 6 months of therapy: $r = 0.43$; $P = 0.030$). Leptin concentration also correlated with blood pressure before adalimumab onset (systolic: $r = 0.48$; $P = 0.013$ and diastolic blood pressure: $r = 0.50$; $P = 0.010$). A marginally significant negative correlation between insulin sensitivity (QUICKI) and leptin levels was also observed. CRP levels correlated with leptin prior to the onset of adalimumab ($r = 0.45$; $P = 0.020$) and with resistin both before ($r = 0.45$; $P = 0.020$) and after 6 months of therapy ($r = 0.55$; $P = 0.004$). A positive association between parameters of disease activity such as BSA ($r = 0.60$; $P = 0.001$) and PASI ($r = 0.63$; $P = 0.001$) prior to the onset of adalimumab therapy and resistin concentrations was also disclosed. No significant changes in leptin and resistin concentrations following the 6-month treatment with adalimumab were seen.

Conclusion In patients with moderate-to-severe psoriasis leptin correlates with metabolic syndrome features and inflammation whereas resistin correlate with inflammation and disease severity.

Received: 2 February 2015; Accepted: 9 March 2015

Funding sources

The study was supported by a research grant from Abbvie Inc.

Conflicts of interest

The authors had sole responsibility for data analysis and manuscript preparation. The opinions expressed in this paper are those of the authors and do not necessarily represent those of Abbvie Inc.

Competing interests

MAG-G has received the grant funding from Abbvie Inc, as outlined above.

Introduction

Patients with psoriasis have an increased risk for metabolic syndrome. A national sample of more than 6500 people from the USA confirmed the higher prevalence of metabolic syndrome among patients with psoriasis when compared with controls.[1] This is of great relevance due to the role of this syndrome as a risk factor for cardiovascular disease incidence and mortality.[2] In this regard, different features of the metabolic syndrome such as insulin resistance, hypertension, abnormalities of lipids and obesity are present in patients with psoriasis.[3] Nevertheless, psoriasis by itself is an independent risk factor for cardiovascular disease.[3]

As observed in other chronic inflammatory diseases like rheumatoid arthritis,[4] inflammation plays a pivotal role in the development of accelerated atherosclerosis in psoriasis patients. A chronic proinflammatory state was found to be responsible for abnormally increased carotid artery intima-media thickness, a surrogate marker of atherosclerotic disease, in patients with psoriasis without traditional cardiovascular risk factors.[5]

Adipokines are pleiotropic molecules that contribute to the so-called low-grade inflammatory state of obese subjects. These molecules create a cluster of metabolic aberrations that are implicated in the pathogenesis of autoimmune and inflammatory diseases. The presence of a metabolic syndrome and the altered secretion patterns of proinflammatory adipokines present in patients with chronic inflammatory diseases may influence the increased risk of cardiovascular disease observed in patients with these conditions.[6] In patients with chronic inflammatory diseases, some adipokines such as leptin or resistin have been found to be associated with metabolic syndrome components and inflammation.[7] In patients with psoriasis, a recent study has disclosed a positive correlation of carotid intima-media thickness of the common carotid artery with serum leptin and resistin.[8]

Tumour necrosis factor-α (TNF-α) is a proinflammatory cytokine that is upregulated in psoriatic skin and represents a prominent target in psoriasis treatment.[9] Our group has reported beneficial effects of TNF-α blockade on metabolic syndrome features such as insulin resistance, even though in these studies psoriatic patients with diabetes, hypertension or severe obesity were excluded.[10,11]

Taking into account these considerations, in this study, we assessed the effect of TNF-α blockade on two adipokines associated with metabolic syndrome and inflammation in a series of non-diabetic psoriatic patients with moderate-to-severe psoriasis. We also aimed to determine if leptin and resistin levels correlate with metabolic syndrome features, inflammation and disease severity in these patients. For this purpose, we prospectively assessed a series of patients with psoriasis who underwent adalimumab therapy because of disease severity.

Materials and methods

Patients and treatment

We consecutively enrolled patients with moderate-to-severe psoriasis over an 18-month period from the Dermatology outpatient clinics of the University Hospital Marques de Valdecilla (Santander, Northern Spain). Arthralgia was often described by the patients but none of them had a clinical pattern of psoriatic arthritis. Recruitment protocol has been previously described.[10,11] Briefly, psoriatic patients with diabetes, kidney disease, hypertension or body mass index $\geq$35 Kg/m^2 were excluded. Patients received subcutaneous injections of adalimumab (Humira, Abbot Laboratories S.A., Madrid, Spain) 80 mg at week 0 followed by 40 mg every other week, starting 1 week after the initial dose. The study protocol was approved by the local institutional ethics committee of Cantabria (Spain), and it was in accordance with the ethical standards outlined in the Declaration of Helsinki. Patients gave informed consent to participate in this study.

Evaluation of disease severity

At the time of enrolment all patients underwent evaluation of their demographical and clinical characteristics. At baseline (before adalimumab) and after 6 months of therapy all patients were assessed for disease activity, including the per cent of body surface area affected (BSA), Psoriasis Area and Severity Index (PASI), Psoriatic Arthritis Screening and Evaluation questionnaire (PASE), Nail Psoriasis Severity Index (NAPSI) and physician's global assessment of disease severity (PGA). Moderate-to-severe psoriasis was defined if BSA was $\geq$10% and/or PASI $\geq$ 10.

Metabolic and serological assessments

Blood samples, for routine biochemical parameters and specific determinations, were taken after a 12-h overnight fast between 08:00 am and 10:00 am for two separate visits: prior to starting adalimumab (at time 0) and 6 months after the onset of treatment. Glucose, creatinine, total cholesterol, HDL-cholesterol and triglycerides were measured by standard automated methods on an ADVIA 2400 Chemistry System from Siemens (Siemens Medical Solutions Diagnostics, Los Angeles, CA USA), using the reagents supplied by Siemens. LDL-cholesterol was calculated by the Friedewald equation. Apolipoprotein (apo)-A, Apo-B, lipoprotein a (Lpa), homocysteine and ultra-sensitive C-reactive protein (usCRP) were analysed by immunonephelometry (Behring Nephelometer Analyzer II, Behring Diagnostics, Marburg, Germany). Insulin was quantified by specific automated immunoassay (Liaison, DiaSorin, Stillwater, Minnesota). Erythrocyte sedimentation rate (ESR) was determined using the Westergren method. The Homeostasis Model Assessment (HOMA) and the Quantitative Insulin

Sensitivity Check Index (QUICKI) were used as noninvasive surrogate markers of insulin resistance and insulin sensitivity, respectively. Leptin serum levels were determined by a commercially available ELISA (Linco Research, St. Charles, MO, USA; Human Leptin ELISA Kit, EZHL-80SK; assay sensitivity = 0.135 ng/mL ±2 SD; intra-and interassay coefficients of variation were 3.7% and 4%, respectively) according to the manufacturer's instructions.[12] Serum resistin was measured by ELISA kit (Linco Research; the assay sensitivity was 0.16 ng/mL and the intra- and interassay coefficients of variation were <5% and <7%, respectively).[13]

Statistical analysis

Results were reported as mean ± standard deviation (SD) or as median and interquartile range (IQR). For the comparison between groups, Student's *t*-test or Mann–Whitney *U*-test were used. Correlation of adipokine levels prior to adalimumab (at time 0) and after 6 months of treatment with selected continuous variables was performed adjusting for age at the time of the study, sex and disease duration via estimation of the Pearson partial correlation coefficient (*r*). Statistical analysis was performed using STATA 12/SE (StataCorp, College Station, TX, USA). Differences were considered statistically significant at $P < 0.05$.

Results

Twenty-nine patients completed 6 months of therapy with adalimumab and were suitable for the comparative analyses. Table 1 summarizes the epidemiological features of these 29 patients at the onset of adalimumab therapy.

Table 1 Epidemiological features in 29 patients with psoriasis who completed 6 months of therapy with adalimumab

Variable	
Men/Women, *n* (%)	14 (48)/15 (52)
Age at the time of the study (years); mean ± SD	38.6 ± 10.7
Disease duration (years); mean ± SD	18.2 ± 12.1
Classic cardiovascular risk factors, *n* (%)	
Current smokers	10 (34)
Ever smoked	14 (48)
Obese (BMI > 30 and <35 kg/m^2)	7 (24)
Dyslipidemia	13 (44)
BMI (kg/m^2); mean ± SD	27.5 ± 3.7
Waist circumference (cm); mean ± SD	96.1 ± 10.8
BSA	37.9 ± 16.3%
PASI	18.9 ± 7.8
ESR (mm/1st h)	13.4 ± 12.8
CRP (mg/dL)	0.36 ± 0.33

BSA, Per cent of body surface area affected; PASI, Psoriasis Area and Severity Index; ESR, Erythrocyte sedimentation rate; CRP, Ultra-sensitive C-reactive protein.

Relationships of demographical features, inflammation and adiposity with circulating leptin and resistin concentrations

At the onset of anti-TNF-α therapy significant differences in leptin concentrations between women (11.6 ± 4.4 ng/mL) and men (4.7 ± 4.7 ng/mL) were observed ($P < 0.001$). These differences were still present after 6 months of biological therapy (Table 2). However, we did not find differences in resistin levels according to sex. When patients were stratified according to sex, we observed that leptin was associated with obesity in men but not in women (data not shown).

A statistically significant positive correlation between CRP levels and resistin serum levels obtained before the onset of adalimumab therapy ($r = 0.45$; $P = 0.020$) and after 6 months of treatment with this biological drug ($r = 0.55$; $P = 0.004$) was seen (Table 3). A significant correlation between leptin and CRP levels prior to the onset of adalimumab therapy was also found ($r = 0.45$; $P = 0.020$). However, such a significant correlation was no longer evident after 6 months of treatment with this drug (Table 3).

Although in this study patients with severe obesity were excluded, a significant correlation between adiposity and leptin was observed regardless of the biological therapy use (Table 3). In this regard, after 6 months of therapy, the administration of adalimumab did not modify the baseline significant correlation between waist circumference and leptin levels ($r = 0.43$; $P = 0.030$). In contrast, no correlation between resistin levels and adiposity was disclosed (Table 3).

Relationships of leptin and resistin concentrations with metabolic syndrome features other than adiposity

Despite exclusion of patients with hypertension, a significant correlation between leptin levels and systolic ($r = 0.48$; $P = 0.013$) and diastolic ($r = 0.50$; $P = 0.010$) blood pressure prior to the onset of adalimumab therapy was seen (Table 3). This correlation was no longer statistically significant after 6 months of adalimumab therapy (Table 3). Also, a marginally significant negative correlation between insulin sensitivity (QUICKI) and leptin levels both before ($r = -0.38$; $P = 0.058$) and after 6 months of adalimumab therapy ($r = -0.39$; $P = 0.052$) was observed (Table 3). However, no significant correlation between leptin concentrations with the lipid profile was seen (Table 3).

Unlike leptin, resistin levels were not associated with blood pressure levels or other features of metabolic syndrome (Table 3).

To establish whether correlations between baseline levels of leptin and resistin and changes in various parameters after the 6 months period of therapy with adalimumab might exist, we assessed a partial correlation of leptin and resistin serum levels prior to adalimumab (time 0) and 6-month change in selected continuous variables adjusted for age at the time of the study, sex and disease duration in our series of 29 patients with

Table 2 Differences in serum levels of leptin and resistin immediately before the onset of adalimumab therapy (basal results – time 0) and those observed at month 6 according to categorical variables in 29 patients with moderate-to-severe psoriasis*

Variable	Category	Leptin (ng/mL)				Resistin (ng/mL)			
		Time 0		Time 6 months		Time 0		Time 6 months	
		Mean ± SD	*P*	Mean ± SD	*P*	Mean ± SD	*P*	Mean ± SD	*P*
Sex	Women	11.6 ± 4.4	<0.001	12.3 ± 4.7	<0.001	7.3 ± 3.9	0.680	7.2 ± 3.6	0.931
	Men	4.7 ± 4.7		5.0 ± 3.4		7.8 ± 2.5		7.1 ± 4.9	
Dyslipidemia	Yes	8.7 ± 5.3	0.722	10.1 ± 6.2	0.237	8.4 ± 4.1	0.200	8.5 ± 5.4	0.112
	No	7.9 ± 6.1		7.6 ± 4.8		6.9 ± 2.3		6.0 ± 2.5	
Obesity	Yes	10.6 ± 6.9	0.226	11.2 ± 6.1	0.184	9.0 ± 4.8	0.190	6.8 ± 1.8	0.844
	No	7.6 ± 5.2		8.0 ± 5.2		7.1 ± 2.6		7.2 ± 4.7	
Smoking	Yes	8.9 ± 7.0	0.671	8.9 ± 6.1	0.942	7.0 ± 2.2	0.512	8.3 ± 5.9	0.287
	No	7.9 ± 5.0		8.7 ± 5.3		7.9 ± 3.7		6.5 ± 2.9	

*Comparisons at time 0 and after 6 months of adalimumab therapy represent differences according to sex (women vs. men) or according to the presence or absence of any of the following traditional cardiovascular risk factors (dyslipidemia, obesity and smoking).

Table 3 Partial correlation of leptin and resistin serum levels prior to adalimumab (time 0) and after 6 months of therapy with this biological agent with selected continuous variables adjusted for age at the time of the study, sex and disease duration in 29 patients with moderate-to-severe psoriasis

Variables	Leptin				Resistin			
	Time 0		Time 6 months		Time 0		Time 6 months	
	r	*P*	*r*	*P*	*r*	*P*	*r*	*P*
HOMA	0.30	0.132	0.37	0.061	0.15	0.452	0.01	0.967
QUICKI	−0.38	0.058	−0.39	0.052	−0.17	0.395	0.21	0.309
Systolic BP	**0.48**	**0.013**	0.33	0.112	0.34	0.087	0.27	0.200
Diastolic BP	**0.50**	**0.010**	0.29	0.176	0.08	0.681	0.13	0.544
Total cholesterol	0.02	0.939	−0.05	0.792	−0.04	0.842	0.00	0.999
HDL-cholesterol	0.03	0.894	−0.01	0.969	−0.31	0.119	0.07	0.731
LDL-cholesterol	0.06	0.770	−0.05	0.795	0.03	0.890	−0.05	0.814
Triglycerides	−0.16	0.424	−0.04	0.833	0.10	0.634	0.06	0.789
Apo-A1	0.10	0.649	0.05	0.807	−0.19	0.365	0.21	0.296
Apo-B	0.05	0.809	−0.05	0.801	0.14	0.491	−0.01	0.959
Lpa	−0.02	0.915	−0.11	0.612	0.38	0.058	0.11	0.602
Total cholesterol/HDL-cholesterol	0.07	0.739	−0.05	0.814	0.24	0.244	−0.11	0.610
Apo-B/Apo-A1	0.12	0.583	−0.11	0.601	0.28	0.181	−0.17	0.400
Homocysteine	0.02	0.938	0.17	0.393	−0.03	0.909	−0.11	0.608
ESR	0.03	0.867	−0.28	0.170	0.28	0.171	0.08	0.695
Ultra-sensitive CRP	**0.45**	**0.020**	0.15	0.456	**0.45**	**0.020**	**0.55**	**0.004**
Body mass index	0.35	0.084	**0.55**	**0.003**	0.19	0.344	−0.09	0.654
Waist circumference	**0.43**	**0.029**	**0.43**	**0.030**	0.14	0.482	−0.16	0.425
BSA	−0.31	0.126	0.39	0.056	**0.60**	**0.001**	−0.17	0.430
PASI	−0.01	0.953	0.34	0.100	**0.63**	**0.001**	0.01	0.945
NAPSI hands	−0.19	0.358	0.38	0.069	0.35	0.079	0.03	0.905
PGA psoriasis	−0.34	0.085	0.29	0.166	**0.45**	**0.021**	−0.36	0.073
PASE total score	−0.21	0.313	0.13	0.519	0.14	0.500	−0.09	0.678
PASE functional	−0.22	0.289	0.15	0.464	0.15	0.453	−0.10	0.619
PASE symptoms	−0.19	0.355	0.11	0.589	0.12	0.568	−0.07	0.746
Leptin (time 0)	-	-	-	-	−0.08	0.694	0.02	0.930
Resistin (time 0)	−0.08	0.694	0.02	0.930	-	-	-	-

Significant results are highlighted in bold.

Table 4 Partial correlation of leptin and resistin serum levels prior to adalimumab (time 0) and 6-month change in selected continuous variables adjusted for age at the time of the study, sex and disease duration in 29 patients with moderate-to-severe psoriasis. Change in any variable is calculated as level at 6 month minus level at time 0

Change in	Leptin		Resistin	
	r	*P*	*r*	*P*
HOMA	−0.06	0.76	0.22	0.28
QUICKI	−0.04	0.84	−0.14	0.48
Systolic BP	−0.07	0.75	−0.06	0.79
Diastolic BP	−0.32	0.13	−0.18	0.40
Total cholesterol	−0.33	0.11	0.33	0.10
HDL-cholesterol	−0.19	0.36	0.33	0.10
LDL-cholesterol	−0.23	0.26	0.30	0.14
Triglycerides	−0.02	0.93	−0.29	0.15
Apo-A1	−0.18	0.39	0.15	0.47
Apo-B	−0.28	0.17	−0.12	0.58
Lpa	−0.04	0.84	−0.37	0.07
Total cholesterol/HDL-cholesterol	−0.08	0.69	−0.16	0.43
Apo-B/Apo-A1	−0.24	0.25	−0.18	0.40
Homocysteine	−0.15	0.50	−0.30	0.18
ESR	−0.07	0.75	−0.17	0.39
Ultra-sensitive CRP	−0.29	0.15	−0.31	0.12
Body mass index	0.19	0.36	−0.31	0.12
Waist circumference	0.28	0.17	−0.16	0.43
BSA	**0.40**	**0.05**	**−0.65**	**<0.001**
PASI	0.07	0.73	**−0.69**	**<0.001**
NAPSI hands	0.28	0.18	−0.30	0.16
PGA psoriasis	0.35	0.09	**−0.45**	**0.03**
PASE total score	0.13	0.53	−0.14	0.50
PASE functional	0.11	0.58	−0.09	0.67
PASE symptoms	0.14	0.49	−0.19	0.35

Significant results are highlighted in bold.

moderate-to-severe psoriasis. The change in any variable was calculated as level at 6 month minus level at time 0. Interestingly, as shown in Table 4, a negative association between baseline levels of resistin and 6-month disease activity parameters was found (BSA: $r = -0.65$; $P < 0.001$; PASI: $r = -0.69$; $P < 0.001$).

Relationships of leptin and resistin concentrations with disease severity

Circulating leptin concentrations did not correlate with disease severity data (Table 3). In contrast, a statistically significant positive association between parameters of disease activity, such as BSA ($r = 0.60$; $P = 0.001$), PASI ($r = 0.63$; $P = 0.001$) and PGA ($r = 0.45$; $P = 0.021$) and resistin concentrations obtained prior to the onset of adalimumab therapy was found (Table 3). Probably due to the influence of anti-TNF-α therapy, these associations were not observed in these series of patients after 6 months of therapy with adalimumab (Table 3).

Changes in leptin and resistin concentrations upon anti-TNF-α therapy

No significant changes in leptin and resistin concentrations were found, when levels of these adipokines obtained immediately before the onset of adalimumab therapy (basal results – time 0) and those observed at month 6 were compared (Table 5). Also, leptin concentrations were not correlated with resistin levels obtained before the onset of biological therapy (Table 3). It was also the case for potential correlation between the levels of these two adipokines observed after 6 months of adalimumab therapy.

Discussion

This study shows that in non-diabetic patients with moderate-to-severe psoriasis leptin levels correlate with metabolic syndrome features and inflammation whereas resistin levels correlate with disease activity and inflammation.

White adipose tissue-derived cytokines mediate between obesity-related exogenous factors such as nutrition and lifestyle and the molecular events that lead to the development of metabolic syndrome, inflammation and cardiovascular disease.[14] A complex adipokine-mediated interaction among white adipose tissue and cardiovascular disease has been observed in other chronic inflammatory diseases such as rheumatoid arthritis.[15,16]

Leptin is an adipokine implicated in the regulation of bodyweight by inhibiting food intake and stimulating energy expenditure.[17] This is also a proinflammatory adipocyte-derived factor that operates in the cytokine network by linking immune and inflammatory processes to the neuroendocrine system.[17,18] This adipokine regulates and participates both in immune homoeostasis and in inflammatory processes. Leptin levels are mostly dependent on the amount of body fat, but its synthesis is also regulated by inflammatory mediators such as TNF-α and interleukin (IL)-1.[19] High leptin levels may play a relevant role in obesity-associated cardiovascular diseases including atherosclerosis. Elevated serum concentration of leptin has been found in

Table 5 Differences between basal (time 0) and after 6 months of treatment with adalimumab in serum concentrations of leptin and resistin

		Basal (time 0)	6 months	*P*-value
Leptin	Mean ± SD (ng/mL)	8.28 ± 5.66	8.75 ± 5.49	0.458
	Median (IQ range)	7.65 (3.50–9.91)	7.69 (4.69–13.24)	
Resistin	Mean ± SD (ng/mL)	7.56 ± 3.26	7.13 ± 4.19	0.597
	Median (IQ range)	7.06 (4.79–9.46)	6.48 (4.64–7.64)	

patients with myocardial infarction and stroke independently of traditional cardiovascular risk factors and obesity status.[20] Moreover; it has been proposed that leptin plays a pathogenic role in atheromatous plaques, due to its positive association with CRP and soluble IL-6 receptor.[21]

We disclosed a significant correlation between baseline serum levels of leptin and CRP in patients with moderate-to- severe psoriasis. It was not found after 6 months of treatment with adalimumab. It is possible that the correlation between leptin and CRP at time 0 could be the result of the proinflammatory state associated with moderate-to-severe psoriasis before the onset of the biological treatment. It is noteworthy that we observed a reduction in inflammation manifested by a significant reduction in the levels of CRP after 6 months of treatment with adalimumab. This low level of inflammation following biological therapy might account for the lack of correlation between leptin and CRP at month 6.

Plasma leptin concentration is directly related to the degree of obesity and it is higher in women than in men of the same BMI.[22] As previously observed in patients with AS,[12] in this study, we also confirmed the presence of higher levels of leptin in women than in men. In keeping with what was reported in the general population, BMI and especially central adiposity were also related to leptin concentrations in our series of patients with moderate-to-severe psoriasis. In this regard, a statistically significant positive correlation between waist circumference and leptin was observed both before the onset and after 6 months of adalimumab therapy. In addition, in our series of psoriatic patients, although the correlation between BMI and leptin prior to the commencement of adalimumab was only marginally significant, this correlation turned out to be statistically significant after 6 months of anti-TNF-α therapy. Leptin levels also correlated positively with BMI in 58 patients with rheumatoid arthritis treated with anti-TNF-α therapy for 6 months.[23] Nevertheless, as observed in our patients with psoriasis, no clear correlation between serum concentrations of leptin and disease activity was found in patients with rheumatoid arthritis.[23] These findings were also in keeping with former results from our group in patients with severe rheumatoid arthritis undergoing periodical treatment with anti-TNF-α-therapy and ongoing disease activity.[24] Leptin levels in patients with moderate-to-severe psoriasis were related to other features of metabolic syndrome such as blood pressure. In addition, a marginally significant correlation with insulin resistance was also observed in these patients.

It has been proposed that the potential effect of leptin on coronary atherosclerosis in patients with rheumatoid arthritis may be mediated through interactions with cardiovascular risk factors.[25] In line with these observations, Dessein *et al.*[26] have shown that the effect of leptin on carotid artery plaque is dependent on the number of major conventional risk factors. Therefore, our results in patients with moderate-to-severe psoriasis highlight the potential relevance of leptin in the complex mechanism associated with accelerated atherosclerosis in psoriasis.

In this study, we observed that resistin serum levels correlated positively with CRP and disease activity. These results are in accordance with a former study of our group that disclosed a positive correlation between markers of inflammation, in particular with CRP, and resistin levels in a series of patients with rheumatoid arthritis in treatment with the anti-TNF-α monoclonal antibody-infliximab for severe disease refractory to methotrexate.[27]

Since a strong correlation between systemic inflammation and cardiovascular disease has been observed in chronic inflammatory diseases such as rheumatoid arthritis,[28] we might be tempted to speculate about the potential implication of resistin as a marker of cardiovascular disease morbidity and mortality in patients with other chronic inflammatory diseases. However, as recently pointed out by Dessein *et al.*,[29] whether resistin enhances cardiovascular risk in these conditions is currently uncertain. With respect to this, resistin concentrations were found to be unrelated to coronary artery calcification score and carotid intima-media wall thickness in rheumatoid arthritis.[25,30]

A potential limitation of our study is the relatively small sample size. Nevertheless, data on leptin and resistin in patients with psoriasis undergoing adalimumab therapy are scarce. In this regard, in a study that included 10 Japanese patients with severe psoriasis treated with adalimumab, a statistically significant decrease in PASI score following this biological agent was observed.[31] At 12 weeks, serum levels of leptin and resistin were not significantly different compared with the pretreatment levels. However, at 6 months serum levels of leptin and resistin were significantly decreased in these series of adalimumab-treated patients.[31] In contrast, although a statistically significant reduction in PASI was found in our series of 29 Caucasian individuals with moderate-to-severe psoriasis treated with adalimumab, we could not find significant decrease in these adipokines at 6 months. It is possible that the different genetic background of our population and the higher number of cases included in our series might explain the differences with respect to the former study in Japanese individuals.[31]

We previously reported a decrease in resistin levels following a single infliximab infusion in patients with rheumatoid and ongoing severe/very active disease despite periodic treatment with this anti-TNF-α agent.[27] It was not the case for ankylosing spondylitis patients undergoing infliximab therapy who had lower inflammatory burden than those with rheumatoid arthritis.[13] With respect to this, in patients with rheumatoid arthritis and in those from this study with moderate-to-severe psoriasis we observed a positive correlation between C-reactive protein (CRP) and resistin.[27] However, we feel that the decrease in resistin levels following anti-TNF-α therapy may be influenced by the degree of severity of the baseline inflammatory burden. As shown in Table 1, in this study patients with

psoriasis showed mild increase in CRP levels prior to the onset of adalimumab therapy. Because of that, the expected decrease in resistin levels failed to achieve statistical significance (baseline resistin 7.56 ± 3.26 ng/mL vs. 7.13 ± 4.19 at month 6), although the mean CRP fell from 0.36 ± 0.33 mg/dL to 0.19 ± 0.17 mg/dL ($P = 0.008$) after 6 months of therapy with adalimumab.

With respect to potential variations in leptin levels following adalimumab therapy, we did not observe significant changes in leptin serum levels in our series of psoriatic patients treated with adalimumab for 6 months. These findings are in line with a former report in which, we did not observe a significant change in leptin concentrations following an infliximab infusion in rheumatoid arthritis patients with severe disease.[24] Similarly, in another study, long-term TNF-α blockade in patients with rheumatoid arthritis did not have influence on circulating leptin concentrations.[23]

In conclusion, in patients with moderate-to-severe psoriasis leptin concentrations correlate with metabolic syndrome and inflammation whereas resistin levels correlate with inflammation and disease severity. However, long-term TNF-α blockade does not yield significant changes in the levels of these adipokines.

References

1 Love TJ, Qureshi AA, Karlson EW, Gelfand JM, Choi HK. Prevalence of the metabolic syndrome in psoriasis: results from the National Health and Nutrition Examination Survey, 2003–2006. *Arch Dermatol* 2011; **147**: 419–424.

2 Galassi A, Reynolds K, He J. Metabolic syndrome and risk of cardiovascular disease: a meta-analysis. *Am J Med* 2006; **119**: 812–819.

3 Coumbe AG, Pritzker MR, Duprez DA. Cardiovascular risk and psoriasis: beyond the traditional risk factors. *Am J Med* 2014; **127**: 12–18.

4 Gonzalez-Gay MA, Gonzalez-Juanatey C, Martin J. Rheumatoid arthritis: a disease associated with accelerated atherogenesis. *Semin Arthritis Rheum* 2005; **35**: 8–17.

5 El-Mongy S, Fathy H, Abdelaziz A *et al.* Subclinical atherosclerosis in patients with chronic psoriasis: a potential association. *J Eur Acad Dermatol Venereol* 2010; **24**: 661–666.

6 Abella V, Scotece M, Conde J *et al.* Adipokines, metabolic syndrome and rheumatic diseases. *J Immunol Res* 2014; **2014**: 343746.

7 Ferraz-Amaro I, González-Juanatey C, López-Mejias R, Riancho-Zarrabeitia L, González-Gay MA. Metabolic syndrome in rheumatoid arthritis. *Mediators Inflamm* 2013; **2013**: 710928.

8 Robati RM, Partovi-Kia M, Haghighatkhah HR, Younespour S, Abdollahimajd F. Increased serum leptin and resistin levels and increased carotid intima-media wall thickness in patients with psoriasis: is psoriasis associated with atherosclerosis? *J Am Acad Dermatol* 2014; **71**: 642–648.

9 Jakobsen M, Stenderup K, Rosada C *et al.* Amelioration of psoriasis by anti-TNF-alpha RNAi in the xenograft transplantation model. *Mol Ther* 2009; **17**: 1743–1753.

10 Pina T, Armesto S, Lopez-Mejias R *et al.* Anti-TNF-α therapy improves insulin sensitivity in non-diabetic patients with psoriasis: a 6-month prospective study. *J Eur Acad Dermatol Venereol* 2014; doi:10.1111/jdv.12814. [Epub ahead of print]

11 Pina T, Genre F, Lopez-Mejias R *et al.* Anti-TNF-α therapy reduces retinol-binding protein 4 serum levels in non-diabetic patients with psoriasis: a 6-month prospective study. *J Eur Acad Dermatol Venereol* 2015; doi: 10.1111/jdv.13005. [Epub ahead of print]

12 Miranda-Filloy JA, López-Mejias R, Genre F *et al.* Leptin and visfatin serum levels in non-diabetic ankylosing spondylitis patients undergoing TNF-α antagonist therapy. *Clin Exp Rheumatol* 2013; **31**: 538–545.

13 Miranda-Filloy JA, López-Mejias R, Genre F *et al.* Adiponectin and resistin serum levels in non-diabetic ankylosing spondylitis patients undergoing TNF-α antagonist therapy. *Clin Exp Rheumatol* 2013; **31**: 365–371.

14 Gualillo O, González-Juanatey JR, Lago F. The emerging role of adipokines as mediators of cardiovascular function: physiologic and clinical perspectives. *Trends Cardiovasc Med* 2007; **17**: 275–283.

15 Gómez R, Conde J, Scotece M, Gómez-Reino JJ, Lago F, Gualillo O. What's new in our understanding of the role of adipokines in rheumatic diseases? *Nat Rev Rheumatol* 2011; **7**: 528–536.

16 Otero M, Lago R, Gomez R *et al.* Changes in plasma levels of fat-derived hormones adiponectin, leptin, resistin and visfatin in patients with rheumatoid arthritis. *Ann Rheum Dis* 2006; **65**: 1198–1201.

17 Tilg H, Moschen AR. Adypocytokines: mediators linking adipose tissue, inflammation and immunity. *Nat Rev Immunol* 2006; **6**: 772–783.

18 Otero M, Lago R, Gómez R, Lago F, Gómez-Reino JJ, Gualillo O. Leptin: a metabolic hormone that functions like a proinflammatory adipokine. *Drug News Perspect* 2006; **19**: 21–26.

19 Beltowski J. Leptin and atherosclerosis. *Atherosclerosis* 2006; **189**: 47–60.

20 Sierra-Johnson J, Romero-Corral A, Lopez-Jimenez F *et al.* Relation of increased leptin concentrations to history of myocardial infarction and stroke in the United States population. *Am J Cardiol* 2007; **100**: 234–239.

21 Karaduman M, Oktenli C, Musabak U *et al.* Leptin, soluble interleukin-6 receptor, C-reactive protein and soluble vascular cell adhesion molecule-1 levels in human coronary atherosclerotic plaque. *Clin Exp Immunol* 2006; **143**: 452–457.

22 Nicklas BJ, Katzel LI, Ryan AS, Dennis KE, Goldberg AP. Gender differences in the response of plasma leptin concentrations to weight loss in obese older individuals. *Obes Res* 1997; **5**: 62–68.

23 Popa C, Netea MG, de Graaf J *et al.* Circulating leptin and adiponectin concentrations during tumor necrosis factor blockade in patients with active rheumatoid arthritis. *J Rheumatol* 2009; **36**: 724–730.

24 Gonzalez-Gay MA, Garcia-Unzueta MT, Berja A *et al.* Anti-TNF-alpha therapy does not modulate leptin in patients with severe rheumatoid arthritis. *Clin Exp Rheumatol* 2009; **27**: 222–228.

25 Rho YH, Chung CP, Solus JF *et al.* Adipocytokines, insulin resistance, and coronary atherosclerosis in rheumatoid arthritis. *Arthritis Rheum* 2010; **62**: 1259–1264.

26 Dessein PH, Tsang L, Woodiwiss AJ, Solomon A. Effect of traditional cardiovascular risk factors on the independent relationship of leptin with atherosclerosis in rheumatoid arthritis. *J Rheumatol* 2014; **41**: 2087–2089.

27 Gonzalez-Gay MA, Garcia-Unzueta MT, Gonzalez-Juanatey C *et al.* Anti-TNF-alpha therapy modulates resistin in patients with rheumatoid arthritis. *Clin Exp Rheumatol* 2008; **26**: 311–316.

28 Gonzalez-Gay MA, Gonzalez-Juanatey C, Lopez-Diaz MJ *et al.* HLA-DRB1 and persistent chronic inflammation contribute to cardiovascular events and cardiovascular mortality in patients with rheumatoid arthritis. *Arthritis Rheum* 2007; **57**: 125–132.

29 Dessein PH, Tsang L, Woodiwiss AJ, Hsu HC, Norton GR, Solomon A. Leukocyte count influences the relationship of circulating resistin concentrations with advanced atherosclerosis in rheumatoid arthritis. *Clin Exp Rheumatol* 2014; **32**: 989–990.

30 Gonzalez-Gay MA, Gonzalez-Juanatey C, Rodriguez-Rodriguez L, Miranda-Filloy JA, Martin J, Llorca J. Lack of association between adipokines and ghrelin and carotid intima-media thickness in patients with severe rheumatoid arthritis. *Clin Exp Rheumatol* 2011; **29**: 358–359.

31 Takahashi H, Tsuji H, Ishida-Yamamoto A, Iizuka H. Serum level of adiponectin increases and those of leptin and resistin decrease following the treatment of psoriasis. *J Dermatol* 2013; **40**: 475–476.

DOI: 10.1111/jdv.13005 JEADV

SHORT REPORT

Anti-TNF-α therapy reduces retinol-binding protein 4 serum levels in non-diabetic patients with psoriasis: a 6-month prospective study

T. Pina,[1] F. Genre,[1] R. Lopez-Mejias,[1] S. Armesto,[2] B. Ubilla,[1] V. Mijares,[1] T. Dierssen-Sotos,[3] A. Corrales,[1] M.A. Gonzalez-Lopez,[2] M.C. Gonzalez-Vela,[4] R. Blanco,[1] J. Llorca,[3] M.A. Gonzalez-Gay[1,*]

[1]Epidemiology, Genetics and Atherosclerosis Research Group on Systemic Inflammatory Diseases, Rheumatology Division, Hospital Universitario Marques de Valdecilla, IDIVAL, Santander, Spain
[2]Dermatology Division, Hospital Universitario Marques de Valdecilla, IDIVAL, Santander, Spain
[3]Department of Epidemiology and Computational Biology, School of Medicine, University of Cantabria, and CIBER Epidemiología y Salud Pública (CIBERESP), IDIVAL, Santander, Spain
[4]Pathology Division, Hospital Universitario Marques de Valdecilla, University of Cantabria, Santander, Spain
*Correspondence: M.A. González-Gay. E-mail: miguelaggay@hotmail.com

Abstract

Background Retinol-binding protein-4 (RBP4), an adipokine considered as an emerging cardiometabolic risk factor, is increased in patients with moderate-to-severe psoriasis.

Objective In this study, we aimed to establish the effect of anti-TNF-α therapy on RBP4 levels in patients with moderate-to-severe psoriasis. We also assessed if RBP4 levels correlate with metabolic syndrome features and disease severity in these patients.

Methods Prospective study on a series of consecutive non-diabetic patients with moderate-to-severe psoriasis who completed 6 months of therapy with adalimumab. Patients with kidney disease, hypertension or body mass index ≥ 35 kg/m^2 were excluded. Metabolic and clinical evaluation was performed at the onset of treatment (time 0) and at month 6.

Results Twenty-nine patients were assessed. Statistically significant reduction (P = 0.0001) of RBP4 levels was observed after 6 months of therapy (RBP4 at time 0: 55.7 ± 21.4 μg/mL, vs. 35.6 ± 29.9 μg/mL at month 6). No significant correlation between basal RBP4 levels and metabolic syndrome features or disease severity was found. Nevertheless, although RBP4 levels did not correlate with insulin resistance, a negative and significant correlation between RBP4 levels obtained after 6 months of adalimumab therapy and other metabolic syndrome features such as abdominal perimeter and body mass index were observed. At that time, a negative and significant correlation between RBP4 levels and disease activity scores and ultrasensitive CRP levels was also disclosed.

Conclusion Our results support an influence of the anti-TNF-α blockade on RBP4 serum levels. This finding is of potential relevance due to increased risk of cardiovascular disease in patients with psoriasis.

Received: 4 December 2014; Accepted: 7 January 2015

Conflict of interest

The authors had sole responsibility for data analysis and manuscript preparation. The opinions expressed in this paper are those of the authors and do not necessarily represent those of Abbvie Inc.

Funding sources

The study was supported by a research grant from Abbvie Inc.

Introduction

Patients with moderate-to-severe psoriasis are at a two-fold risk of myocardial infarction, stroke and death, playing accelerated atherosclerosis the major role in the increased mortality observed.[1–3] Endothelial dysfunction, an early step in the atherogenesis process, is linked to the presence of chronic inflammation, insulin resistance and metabolic syndrome.[4] Psoriasis is a systemic chronic inflammatory condition associated with metabolic syndrome, and accordingly with endothelial dysfunction.[3,5–8]

Competing Interests

MAG-G has received the grant funding from Abbvie Inc., as outlined above

Retinol-binding protein-4 (RBP4) is an adipokine with a major impact in the development of insulin resistance that has been found to be positively correlated with carotid intima-media thickness as a measure of subclinical atherosclerosis.[9,10] In accordance, a close association of RBP4 and cardiovascular disease has been reported.[11] RBP4 has been associated with insulin resistance in obese and diabetic patients.[9,12] However, no correlation between RBP4 and insulin resistance was found in patients with rheumatoid arthritis (RA), a disease that constitutes the prototype of chronic inflammatory disease associated with increased risk of cardiovascular disease.[13]

Interestingly, circulating levels of RBP4 are increased in patients with moderate-to-severe psoriasis, and they correlate with disease activity.[14] Furthermore, a significant reduction of RBP4 levels following an infusion with the chimeric anti-TNF-α monoclonal antibody-infliximab has been reported in non-diabetic patients with ankylosing spondylitis.[15]

Previously, in a prospective study of psoriatic patients with active disease, we disclosed a beneficial effect of adalimumab, a fully human monoclonal antibody targeted against TNF-α, on the mechanism associated with accelerated atherogenesis, specifically on insulin resistance.[16]

Taken together all these considerations, in this study we aimed to establish for the first time the effect of anti-TNF-α therapy on RBP4 levels in patients with moderate-to-severe psoriasis. We also aimed to determine if RBP4 levels correlate with metabolic syndrome features and disease severity in anti-TNF-α therapy treated patients with moderate–severe psoriasis without diabetes or severe obesity. For this purpose, we prospectively assessed a series of patients with psoriasis who required adalimumab therapy because of disease severity.

Materials and methods

Patients and treatment

We consecutively enrolled patients with moderate-to-severe psoriasis over an 18-month period from the Dermatology outpatient clinics of the University Hospital Marques de Valdecilla (Santander, Northern Spain). Recruitment protocol has been previously described.[16] Psoriatic patients with diabetes, kidney disease, hypertension or body mass index $\geq$ 35 kg/m^2 were excluded. Patients received subcutaneous injections of adalimumab (Humira, Abbot Laboratories S.A., Madrid, Spain) 80 mg at week 0 followed by 40 mg every other week, starting 1 week after the initial dose. At the time of enrolment, all patients underwent evaluation of their demographic and clinical characteristics. At baseline (before adalimumab) and after 6 months of therapy, all patients were assessed for disease activity, including the per cent of body surface area affected (BSA), Psoriasis Area and Severity Index (PASI), Psoriatic Arthritis Screening and Evaluation questionnaire (PASE), Nail Psoriasis Severity Index (NAPSI) and physician's global assessment of disease severity (PGA).

The study protocol was approved by the local institutional ethics committee, and it was in accordance with the ethical standards outlined in the Declaration of Helsinki. Patients gave informed consent to participate in this study.

Metabolic and serological assessments

Blood samples, for routine biochemical parameters and specific determinations, were taken after a 12-h overnight fast between 08:00 am and 10:00 am for two separate visits: prior to starting adalimumab (at time 0) and 6 months after initiation of treatment. Glucose, creatinine, total cholesterol, HDL-cholesterol and triglycerides were measured by standard automated methods on an ADVIA 2400 Chemistry System from Siemens (Siemens Medical Solutions Diagnostics, Los Angeles, CA, USA), using the reagents supplied by Siemens. LDL-cholesterol was calculated by the Friedewald equation. Apolipoprotein (apo)-A, Apo-B, lipoprotein a (Lpa), homocysteine and ultrasensitive C-reactive protein (usCRP) were analysed by immunonephelometry (Behring Nephelometer Analyzer II, Behring Diagnostics, Marburg, Germany). Glycated haemoglobin (HbA1c) was measured by high-performance liquid chromatography (DiamatTM, Bio-Rad, München, Germany). Insulin was quantified by specific automated immunoassay (Liaison, DiaSorin, Stillwater, MN, USA). Erythrocyte sedimentation rate (ESR) was determined using the Westergren method. The Homeostasis Model Assessment (HOMA) for insulin resistance and the Quantitative Insulin Sensitivity Check Index (QUICKI) were used as non-invasive surrogate markers of insulin resistance and insulin sensitivity respectively. RBP4 serum levels were measured by ELISA (Phoenix Pharmaceuticals, EK-028-28).

Statistical analysis

Statistical analysis was performed using STATA 12/SE (StataCorp, College Station, TX, USA). Results were reported as mean $\pm$ standard deviation (SD). For the comparison of normally distributed variables between groups, Student's *t*-test was used. Correlation of RBP4 levels prior to adalimumab (at time 0) and after 6 months of treatment with selected continuous variables was performed adjusting by age, sex and disease duration via estimation of the Pearson partial correlation coefficient (r). Differences were considered statistically significant at $P < 0.05$.

Results

Twenty-nine patients completed 6 months of therapy with adalimumab and were suitable for the comparative analyses. Table 1 summarizes the epidemiological features of these 29 patients at the onset of adalimumab therapy. Figure 1 shows the differences in RBP4 serum levels before and after 6 months of treatment with adalimumab. Anti-TNF-α adalimumab therapy yielded a

Table 1 Epidemiological features in 29 non-diabetic patients with psoriasis who completed 6 months of therapy with adalimumab

Variable	
Men/Women, *n* (%)	14 (48)/15 (52)
Age at the time of the study (years); mean ± SD	38.6 ± 10.7
Disease duration (years); mean ± SD	18.2 ± 12.1
Classic cardiovascular risk factors, *n* (%)	
Current smokers	10 (34)
Ever smoked	14 (48)
Obese (BMI > 30 and <35 kg/m^2)	7 (24)
Dyslipidaemia	13 (44)
BMI (kg/m^2); mean ± SD	27.5 ± 3.7
Waist circumference (cm); mean ± SD	96.1 ± 10.8

significant reduction of RBP4 serum levels. The mean ± SD RBP4 values decreased from 55.7 ± 21.4 μg/mL before adalimumab, to 35.6 ± 29.9 μg/mL after 6 months of treatment with this biologic therapy ($P = 0.0001$).

In a further step, we assessed if RBP4 levels correlate with metabolic syndrome features and disease severity in these patients (Table 2). With respect to this, no significant correlation between basal RBP4 levels obtained prior to the onset of adalimumab therapy and metabolic syndrome features or disease severity was found. Nevertheless, although in patients with moderate-to-severe psoriasis RBP4 levels did not correlate with insulin resistance, a negative and significant correlation between RBP4 levels obtained after 6 months of adalimumab therapy and other metabolic syndrome features such as abdominal perimeter and body mass index was observed. Also, after 6 months of treatment with adalimumab, a negative and significant correlation was observed between RBP4 levels and disease activity scores such as BSA and PASI. Finally, following adalimumab therapy an inverse correlation between RBP4 and usCRP levels was also disclosed (Table 2).

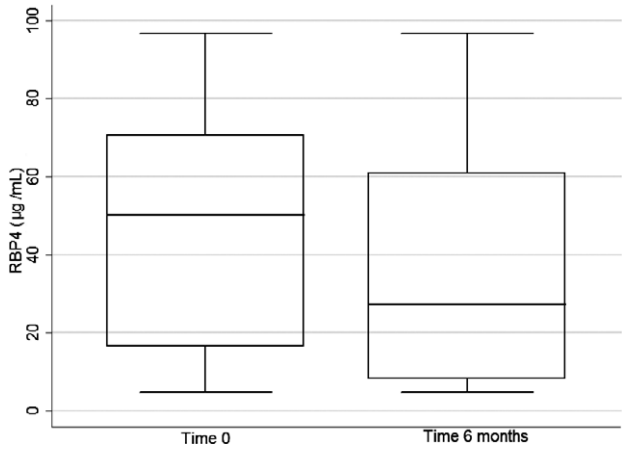

Figure 1 Box plot showing differences between basal (time 0) and after 6 months of adalimumab therapy in retinol-binding protein (RBP-4) serum concentration.

Table 2 Partial correlation of RBP-4 levels prior to adalimumab (time 0) and after 6 months of therapy with this biologic agent with selected continuous variables adjusted for age at the time of the study, sex and disease duration in 29 patients with moderate-to-severe psoriasis

Variable	Time 0		Time 6 months	
	r	*P*	*r*	*P*
HOMA	−0.07	0.751	−0.24	0.240
QUICKI	0.25	0.217	0.38	0.054
Systolic BP	−0.09	0.661	−0.23	0.283
Diastolic BP	−0.004	0.983	−0.13	0.533
Total cholesterol	0.07	0.741	−0.04	0.854
HDL-cholesterol	−0.19	0.359	0.01	0.981
LDL-cholesterol	0.14	0.487	−0.01	0.965
Triglycerides	0.07	0.717	−0.10	0.632
Apo-A1	−0.06	0.789	−0.07	0.742
Apo-B	0.16	0.455	−0.10	0.613
Lpa	0.03	0.887	0.25	0.231
Total cholesterol/ HDL-cholesterol	0.19	0.352	−0.10	0.644
Apo-B/Apo-A1	0.19	0.361	−0.06	0.764
Homocysteine	0.40	0.064	−0.22	0.291
ESR	0.36	0.072	0.21	0.296
Ultra-sensitive CRP	0.27	0.188	**−0.41**	**0.036**
Body mass index	−0.02	0.918	**−0.49**	**0.012**
Waist circumference	−0.10	0.626	**−0.40**	**0.046**
BSA	−0.10	0.629	**−0.51**	**0.009**
PASI	−0.09	0.670	**−0.49**	**0.013**
NAPSI hands	0.27	0.188	−0.08	0.723
PGA psoriasis	−0.39	0.050	−0.26	0.212
PASE total score	0.36	0.073	0.09	0.650
PASE functional	0.37	0.060	0.07	0.748
PASE symptoms	0.33	0.100	0.11	0.579

Significant results are highlighted in bold.

Discussion

This study shows that non-diabetic patients with moderate-to-severe psoriasis undergoing treatment with adalimumab experience a reduction of RBP4 serum levels.

Circulating RBP4 levels have been found to be positively correlated with serum levels of TNF-α in diabetic patients with coronary heart disease.[17] In keeping with that, Erikstrup *et al.*[18] reported a positive correlation between adipose tissue RBP mRNA levels and TNF-α mRNA levels of plasma and skeletal muscle origin. Our results are in agreement with these findings. However, they are in contrast with data reported by Sell and Eckel who found that TNF-α strongly down-regulates RBP4 production in adipocytes, a completely unexpected effect as TNF-α-treated adipocytes are insulin resistant.[19]

TNF-α is an important mediator of insulin resistance in obesity and diabetes through its ability to decrease the tyrosine kinase activity of the insulin receptor, and it also directly impedes insulin–glucose-mediated uptake in the skeletal muscle.[20] To our surprise, in patients with moderate-to-severe psoriasis undergoing adalimumab therapy, the reduction of RBP4 levels following 6-month treatment with this biologic agent did not correlate with insulin resistance. An explanation for that may be that our cohort did not include patients with diabetes or severe obesity. In addition, it is striking that, whereas prior to TNF-α blockade no relations between RBP4 concentrations and clinical features and metabolic risk factors were found, subsequent to the intervention the levels of the respective adipokine correlated inversely with CRP concentrations, anthropometric measures and BSA and PASI. In this regard, paradoxical adipokine–cardiovascular disease risk relations were recently reported in treated RA patients as relates to both total and high molecular weight adiponectin as well as RBP4 concentrations.[21,22] Such associations were also reported in non-RA subjects,[23] and are thought to represent a compensatory change in adipokine production in the presence of chronic vascular disease and aimed at reducing metabolic risk. In this regard, Dessein *et al.*[21] disclosed a direct relation of RBP4 levels with atherosclerosis in black but not white Africans with treated RA.

We cannot exclude that the reduction of RBP4 levels mediated by the anti-TNF-α- adalimumab therapy may be independent to the effect of this biologic agent to decrease the inflammatory burden. In this regard, our results in patients with moderate-to-severe psoriasis are in keeping with recent findings reported in patients with RA.[13] With respect to this, in RA patients with active disease no correlation between RBP4 and insulin resistance was found.

We realize that long-term studies including large cohorts of patients with psoriasis undergoing anti-TNF-α therapy may be required to establish the biologic implication of the reduction of RBP4 levels on the risk of cardiovascular events. Nevertheless, our prospective exploratory study provides new information on the complex mechanisms associated with the development of metabolic syndrome and atherosclerosis in patients with psoriasis.

References

1 Gelfand JM, Troxel AB, Lewis JD *et al.* The risk of mortality in patients with psoriasis: results from a population-based study. *Arch Dermatol* 2007; **143**: 1493–1499.

2 Prodanovich S, Kirsner RS, Kravetz JD, Ma F, Martinez L, Federman DG. Association of psoriasis with coronary artery, cerebrovascular, and peripheral vascular diseases and mortality. *Arch Dermatol* 2009; **145**: 700–703.

3 Balci DD, Balci A, Karazincir S *et al.* Increased carotid intima-media thickness and impaired endothelial function in psoriasis. *J Eur Acad Dermatol Venerol* 2009; **23**: 1–6.

4 Gonzalez-Gay MA, Gonzalez-Juanatey C, Martin J. Rheumatoid arthritis: a disease associated with accelerated atherogenesis. *Semin Arthritis Rheum* 2005; **35**: 8–17.

5 Boehncke S, Thaci D, Beschmann H *et al.* Psoriasis patients show signs of insulin resistance. *Br J Dermatol* 2007; **157**: 1249–1251.

6 Sommer DM, Jenisch S, Suchan M, Christophers E, Weichenthal M. Increased prevalence of the metabolic syndrome in patients with moderate to severe psoriasis. *Arch Dermatol Res* 2006; **298**: 321–328.

7 Love TJ, Qureshi AA, Karlson EW, Gelfand JM, Choi HK. Prevalence of the metabolic syndrome in psoriasis: results from the National Health and Nutrition Examination Survey, 2003–2006. *Arch Dermatol* 2011; **147**: 419–424.

8 Langan SM, Seminara NM, Shin DB *et al.* Prevalence of metabolic syndrome in patients with psoriasis: a population-based study in the United Kingdom. *J Invest Dermatol* 2012; **132**: 556–562.

9 Yang Q, Graham TE, Mody N *et al.* Serum retinol binding protein 4 contributes to insulin resistance in obesity and type 2 diabetes. *Nature* 2005 Jul 21; **436**: 356–362.

10 Bobbert T, Raila J, Schwarz F *et al.* Relation between retinol, retinol-binding protein 4, transthyretin and carotid intima media thickness. *Atherosclerosis* 2010; **213**: 549–551.

11 Cabré A, Lázaro I, Girona J *et al.* Retinol-binding protein 4 as a plasma biomarker of renal dysfunction and cardiovascular disease in type 2 diabetes. *J Intern Med* 2007; **262**: 496–503.

12 Graham TE, Yang Q, Blüher M *et al.* Retinol-binding protein 4 and insulin resistance in lean, obese, and diabetic subjects. *N Engl J Med* 2006; **354**: 2552–2563.

13 Ferraz-Amaro I, González-Gay MA, Diaz-González F. Retinol-binding protein 4 in rheumatoid arthritis-related insulin resistance and β-cell function. *J Rheumatol* 2014; **41**: 658–665.

14 Romaní J, Caixàs A, Ceperuelo-Mallafré V *et al.* Circulating levels of lipocalin-2 and retinol-binding protein-4 are increased in psoriatic patients and correlated with baseline PASI. *Arch Dermatol Res* 2013; **305**: 105–112.

15 Genre F, López-Mejías R, Miranda-Filloy JA *et al.* Antitumour necrosis factor α treatment reduces retinol-binding protein 4 serum levels in non-diabetic ankylosing spondylitis patients. *Ann Rheum Dis* 2014; **73**: 941–943.

16 Pina T, Armesto S, Lopez-Mejias R *et al.* Anti-TNF-α therapy improves insulin sensitivity in non-diabetic patients with psoriasis: a 6-month prospective study. *J Eur Acad Dermatol Venereol* 2014;. doi:10.1111/jdv.12814.

17 Al-Daghri NM, Al-Attas OS, Alokail M, Draz HM, Bamakhramah A, Sabico S. Retinol binding protein-4 is associated with TNF-alpha and not insulin resistance in subjects with type 2 diabetes mellitus and coronary heart disease. *Dis Markers* 2009; **26**: 135–140.

18 Erikstrup C, Mortensen OH, Nielsen AR *et al.* RBP-to-retinol ratio, but not total RBP, is elevated in patients with type 2 diabetes. *Diabetes Obes Metab* 2009; **11**: 204–212.

19 Sell H, Eckel J. Regulation of retinol binding protein 4 production in primary human adipocytes by adiponectin, troglitazone and TNF-alpha. *Diabetologia* 2007; **50**: 2221–2223.

20 Hotamisligil GS, Peraldi P, Budavari A, Ellis R, White MF, Spiegelman BM. IRS-1-mediated inhibition of insulin receptor tyrosine kinase activity in TNF-alpha- and obesity-induced insulin resistance. *Science* 1996; **271**: 665–668.

21 Dessein PH, Woodiwiss AJ, Norton GR, Tsang L, Solomon A. Independent associations of total and high molecular weight adiponectin with cardiometabolic risk and surrogate markers of enhanced early atherogenesis in black and white patients with rheumatoid arthritis: a cross-sectional study. *Arthritis Res Ther* 2013; **15**: R128.

22 Dessein PH, Tsang L, Norton GR, Woodiwiss AJ, Solomon A. Retinol binding protein 4 concentrations relate to enhanced atherosclerosis in obese patients with rheumatoid arthritis. *PLoS One* 2014; **9**: e92739.

23 Sattar N, Nelson SM. Adiponectin, diabetes, and coronary heart disease in older persons: unraveling the paradox. *J Clin Endocrinol Metab* 2008; **93**: 3299–3301.

J D E	13094	WILEY	Dispatch: 28.8.15	CE: Arockia Raj
Journal Code	Manuscript No.		No. of pages: 6	PE: Thangaraj

doi: 10.1111/1346-8138.13094 *Journal of Dermatology* 2015; **42**: 1–6

ORIGINAL ARTICLE

Asymmetric dimethylarginine but not osteoprotegerin correlates with disease severity in patients with moderate-to-severe psoriasis undergoing anti-tumor necrosis factor-α therapy

Trinitario PINA,[1] Fernanda GENRE,[1] Raquel LOPEZ-MEJIAS,[1] Susana ARMESTO,[2] Begoña UBILLA,[1] Veronica MIJARES,[1] Trinidad DIERSSEN-SOTOS,[3] Alfonso CORRALES,[1] Marcos GONZALEZ-LOPEZ,[2] Maria C. GONZALEZ-VELA,[4] Ricardo BLANCO,[1] Jose L. ERNÁNDEZ,[5] Javier LLORCA,[3,*] Miguel A. GONZALEZ-GAY[1,*]

[1]*Epidemiology, Genetics and Atherosclerosis Research Group on Systemic Inflammatory Diseases, Rheumatology Division, Hospital Universitario Marqués de Valdecilla, IDIVAL,* [2]*Dermatology Division, Hospital Universitario Marqués de Valdecilla, IDIVAL,* [3]*Department of Epidemiology and Computational Biology, School of Medicine, University of Cantabria, and CIBER Epidemiología y Salud Pública (CIBERESP), IDIVAL,* [4]*Pathology Division, Hospital Universitario Marqués de Valdecilla, University of Cantabria,* [5]*Department of Internal Medicine, Hospital Universitario Marqués de Valdecilla, IDIVAL, Santander, Spain*

ABSTRACT

Patients with psoriasis, in particular those with severe disease, have an increased risk of cardiovascular (CV) events compared with the general population. The aim of the present study is to determine whether correlation between asymmetric dimethylarginine (ADMA) and osteoprotegerin (OPG), two biomarkers associated with CV disease, and disease severity may exist in patients with moderate-to-severe psoriasis. We also aimed to establish if baseline serum levels of these two biomarkers could correlate with the degree of change in the clinical parameters of disease severity following the use of anti-tumor necrosis factor (TNF)-α therapy in these patients. This was a prospective study on a series of consecutive non-diabetic patients with moderate-to-severe psoriasis who completed 6 months of therapy with anti-TNF-α-adalimumab. Patients with kidney disease, hypertension or body mass index of 35 kg/m^2 or more were excluded. Metabolic and clinical evaluation was performed immediately prior to the onset of treatment and at month 6. Twenty-nine patients were assessed. Unlike OPG, a significant positive correlation between ADMA and resistin serum levels was found at the onset of adalimumab and also after 6 months of biologic therapy. We also observed a positive correlation between the percent of body surface area affected (BSA) and ADMA levels obtained before the onset of adalimumab and a negative correlation between baseline ADMA levels and a 6-month BSA change compared with baseline results. In patients with moderate-to-severe psoriasis, ADMA levels correlate with clinical markers of disease severity.

Key words: anti-tumor necrosis factor, asymmetric dimethylarginine, cardiovascular, osteoprotegerin, psoriasis.

INTRODUCTION

Patients with psoriasis, in particular those with severe disease, have an increased risk of coronary heart disease and stroke compared with the general population.[1] There are a number of factors, including an association of metabolic syndrome, that have been proposed as responsible for the increased risk of cardiovascular (CV) events in these patients.[2–6] Nevertheless, it is known that the severity of psoriasis is itself a risk factor for CV mortality that is independent of traditional CV risk factors.

Several biomarkers have been found to predict the risk of CV events in patients with chronic inflammatory diseases. In this regard, in rheumatoid arthritis (RA) high levels of osteoprotegerin (OPG) were associated with endothelial cell activation, carotid plaques and CV death.[7–9] Raised levels of another biomarker, asymmetric dimethylarginine (ADMA), were also found to be associated with adverse human health consequences for CV and inflammatory diseases.[10,11] In this regard, ADMA impairs nitric oxide bioactivity due to its inhibitory effect on endothelial nitric oxide synthase.[12]

Correspondence: Miguel A. González-Gay, M.D., Ph.D., Rheumatology Division, Hospital Universitario Marqués de Valdecilla, IDIVAL, Avenida de Valdecilla, s/n, 39008 Santander, Spain. Email: miguelaggay@hotmail.com
*These authors contributed equally to this work and share senior authorship.
Received 1 June 2015; accepted 2 August 2015.

Since psoriasis and RA share an increased risk of accelerated atherosclerosis and CV death,[13] in the present study we aimed to determine whether a correlation between ADMA and OPG and disease severity may exist in patients with moderate-to-severe psoriasis. We also aimed to establish if the baseline levels of these two biomarkers could correlate with the degree of improvement in the clinical parameters of disease severity following the use of anti-tumor necrosis factor (TNF)-α therapy in patients with moderate-to-severe psoriasis.

METHODS

Patients and treatment

We consecutively enrolled patients with moderate-to-severe psoriasis over an 18-month period from the dermatology outpatient clinics of the University Hospital Marques de Valdecilla (Santander, Spain). Arthralgia was often described by the patients but none of them had a clinical pattern of psoriatic arthritis. The recruitment protocol has been previously described.[14–16] Briefly, psoriatic patients with diabetes, kidney disease, hypertension or body mass index of 35 kg/m^2 or more were excluded. Patients received s.c. injections of adalimumab (Humira; Abbott Laboratories, Madrid, Spain) 80 mg at week 0 followed by 40 mg every other week, starting 1 week after the initial dose. The study protocol was approved by the local institutional ethics committee of Cantabria (Spain), and it was in accordance with the ethical standards outlined in the Declaration of Helsinki. Patients gave informed consent to participate in this study.

Evaluation of disease severity

At the time of enrolment, all patients underwent evaluation of their demographic and clinical characteristics. At baseline (before adalimumab) and after 6 months of therapy all patients were assessed for disease activity, including the percent of body surface area (BSA) affected, Psoriasis Area and Severity Index (PASI), Psoriatic Arthritis Screening and Evaluation questionnaire (PASE), Nail Psoriasis Severity Index (NAPSI) and Physician Global Assessment (PGA) of disease severity. Moderate-to-severe psoriasis was defined if BSA affected was 10% or more and/or PASI of 10 or more.

Metabolic and serological assessments

Blood samples, for routine biochemical parameters and specific determinations, were taken after a 12-h overnight fast between 08.00 and 10.00 hours for two separate visits: prior to starting adalimumab (at time 0) and 6 months after initiation of treatment. Glucose, creatinine, total cholesterol, high-density lipoprotein cholesterol and triglycerides were measured by standard automated methods on an ADVIA 2400 Chemistry System from Siemens (Siemens Medical Solutions Diagnostics, Los Angeles, CA, USA), using the reagents supplied by Siemens. Low-density lipoprotein cholesterol was calculated by the Friedewald equation. Apolipoprotein (Apo)-A, Apo-B, lipoprotein a (Lp[a]), homocysteine and ultrasensitive C-reactive protein (usCRP) were analyzed by immunonephelometry (Behring Nephelometer Analyzer II; Behring Diagnostics, Marburg, Germany). Glycated hemoglobin (HbA1c) was measured by high-performance liquid chromatography (DiamatTM; Bio-Rad, München, Germany). Insulin was quantified by specific automated immunoassay (Liaison; DiaSorin, Stillwater, MN, USA). Erythrocyte sedimentation rate (ESR) was determined using the Westergren method. The Homeostasis Model of Assessment (HOMA) for insulin resistance and the Quantitative Insulin Sensitivity Check Index (QUICKI) were used as non-invasive surrogate markers of insulin resistance and insulin sensitivity, respectively.

Enzyme-linked immunoassays (ELISA) using commercially available kits were used to determine serum levels of retinol binding protein 4 (RBP-4, EK-028-28; Phoenix Pharmaceuticals, Burlingame, CA, USA), leptin (EZHL-80SK; Linco Research, St Charles, MO, USA), resistin (EZHR-95K; Linco Research), visfatin (EK-003-80; Phoenix Pharmaceuticals), adiponectin (EZHADP-61K; Linco Research) and ADMA (K7860; Immundiagnostik, Bensheim, Germany).

Osteoprotegerin serum levels were also determined by ELISA. Briefly, 96-well microplates were precoated with antihuman OPG antibody (Peprotech, Rocky Hill, NJ, USA). Recombinant human OPG (Peprotech) was used to prepare the standard curve. The standard dilution series ranged 0.313–20 ng/mL. First, 50 μL of each standard or sample was added to the appropriate wells and incubated for 3 h at room temperature. After discarding the solution and washing four times, 50 μL of prepared biotinylated antihuman OPG antibody (Peprotech) was added to each well and incubated for 1 h. After washing away unbound biotinylated antibody, 50 μL of horseradish peroxidase (HRP)-conjugated avidin (eBioscience, San Diego, CA, USA) was pipetted into the wells and incubated for 30 min. Finally, plates were developed with ABTS Liquid Substrate (Peprotech) and read at 405 and 600 nm (as reference wavelength).

Statistical analysis

Statistical analysis was performed using STATA version 12/SE (StataCorp, College Station, TX, USA). Results were reported as mean $\pm$ standard deviation (SD), median (interquartile range [IQR]) or percentages. ADMA and OPG serum levels before and after treatment were compared using paired Student's *t*-test. Correlation of OPG and ADMA levels prior to adalimumab (at time 0) and after 6 months of treatment with selected continuous variables was performed adjusting by age, sex and disease duration via estimation of the Pearson partial correlation coefficient (*r*). Differences were considered statistically significant at $P < 0.05$.

RESULTS

Twenty-nine patients completed 6 months of therapy with adalimumab and were suitable for the comparative analyses. Table 1 summarizes the epidemiological and clinical features of these 29 patients immediately prior to the onset of adalimumab therapy. As previously reported, at 6 months after the onset of adalimumab a significant reduction ($P < 0.05$ for each comparison) in all of the markers of disease activity and severity including ESR, usCRP, BSA, PASI, NAPSI, PGA and PASE was observed.[14] In this regard, BSA and PASI experienced a significant reduction (BAS from 37.9 $\pm$ 16.3% to 3.1 $\pm$ 5.5; PASI from 18.9 $\pm$ 7.8 to 1.3 $\pm$ 2.1).

Table 1. Epidemiological features (baseline results) in 29 patients with psoriasis who completed 6 months of therapy with adalimumab

Variable	
Men/women, *n* (%)	14 (48)/15 (52)
Age at the time of the study (years), mean ± SD	38.6 ± 10.7
Disease duration (years), mean ± SD	18.2 ± 12.1
Classic cardiovascular risk factors, *n* (%)	
Current smokers	10 (34)
Ever smoked	14 (48)
Obese (BMI >30 and <35 kg/m^2)	7 (24)
Dyslipidemia	13 (44)
BMI (kg/m^2), mean ± SD	27.5 ± 3.7
Waist circumference (cm), mean ± SD	96.1 ± 10.8
BSA	37.9 ± 16.3%
PASI	18.9 ± 7.8
ESR (mm/1st hour)	13.4 ± 12.8
usCRP (mg/dL)	0.36 ± 0.33

BMI, body mass index; BSA, percent of body surface area affected; ESR, erythrocyte sedimentation rate; PASI, Psoriasis Area and Severity Index; SD, standard deviation; usCRP, ultrasensitive C-reactive protein.

Relationship between inflammation, adiposity and adipokines and circulating levels of ADMA and OPG

Osteoprotegerin levels did not show a significant correlation with laboratory markers of inflammation (ESR and usCRP) or body mass index either before or after 6 months of therapy with adalimumab. It was also the case when potential correlations between OPG and adipokines (RBP-4, adiponectin, leptin, resistin and visfatin) were assessed (Table 2).

Unlike OPG, a significant positive correlation between ADMA and resistin serum levels was found prior to the onset of adalimumab ($r = 0.49$, $P = 0.011$) and also after 6 months of treatment with this biologic therapy ($r = 0.44$, $P = 0.023$) (Table 2). However, no significant correlation of ADMA with routine laboratory markers of inflammation or with adipokines was observed (Table 2).

Relationship between metabolic syndrome features other than adiposity and circulating levels of ADMA and OPG

Before adalimumab therapy, we did not observe any statistically significant correlation between OPG and ADMA levels with blood pressure, lipids, insulin sensitivity (QUICKI) or insulin resistance (HOMA) (Table 2). Interestingly, a positive correlation between Lp(a) and ADMA ($r = 0.42$, $P = 0.037$) was observed after 6 months of therapy with adalimumab.

Relationship between disease severity and circulating levels of ADMA and OPG

Circulating OPG concentrations did not correlate with disease severity parameters (Table 2). In contrast, a statistically significant positive correlation between BSA and ADMA serum levels obtained immediately before the onset of adalimumab therapy ($r = 0.47$, $P = 0.016$) was found (Table 2). In addition, a borderline significant correlation ($P > 0.05$ and <0.10) was observed between ADMA serum levels and other clinical markers of disease severity (PASI, PGA psoriasis and PASE) before the onset of adalimumab therapy (Table 2). The correlation between ADMA serum levels and disease severity was not found after 6 months of therapy with adalimumab (Table 2).

Influence of adalimumab therapy on serum biomarker levels

No significant differences between baseline serum concentrations of ADMA and OPG (time 0) and those obtained after 6 months of treatment with adalimumab were seen (ADMA, median [IQR] before adalimumab, 0.47 [0.37–0.55] vs 0.46 μmol/L [0.38–0.54] after 6 months of therapy, $P = 0.95$; OPG, median [IQR], 3.21 [2.60–3.63] vs 2.95 ng/mL [2.33–3.64] after 6 months of therapy, $P = 0.31$). Nevertheless, the correlation between parameters of disease severity and ADMA before the onset of the biologic therapy prompted us to establish if the baseline levels of these two biomarkers could correlate with the degree of improvement in the clinical parameters of disease severity following the use of anti-TNF-α therapy in these patients with moderate-to-severe psoriasis.

For this purpose, we assessed a partial correlation of ADMA and OPG serum levels prior to adalimumab (time 0) and a 6-month change in selected continuous variables compared with baseline results in our series of 29 adalimumab-treated patients with moderate-to-severe psoriasis. Following this procedure, we found a statistically significant negative correlation between baseline levels of ADMA and change in the results of BSA after 6 months of adalimumab therapy compared with BSA baseline results (Table 3).

Figure 1 displays this relationship: X axis, basal ADMA; Y axis, BSA at 0 − BSA at 6 months. Dots represent each patient and the line represents the linear regression. All patients had BSA at 6 months lower than BSA at 0. The linear trend disclosed that the decrease of BSA was stronger in patients with higher basal ADMA. After adjusting for age at the time of the study, sex and disease duration, the decreasing trend was even stronger (unadjusted $r = -0.24$; adjusted $r = -0.47$; $P = 0.017$).

In addition, a borderline significant negative correlation between baseline levels of ADMA and change in PASI at 6 months compared with PASI baseline results ($r = -0.36$, $P = 0.075$). Taking into account the positive correlation between baseline levels of ADMA and BSA previously shown (Table 2), these findings indicate that the higher the baseline ADMA levels the greater the decrease of disease severity parameters following 6 months of therapy with adalimumab.

With regard to OPG, we only observed a negative correlation between baseline levels of OPG and changes in triglycerides after the 6-month period of therapy with adalimumab (Table 3).

DISCUSSION

The present study shows that in patients with moderate-to-severe psoriasis ADMA serum levels correlate with severity

Table 2. Partial correlation of ADMA and OPG serum levels prior to adalimumab (time 0) and after 6 months of therapy with this biologic agent with selected continuous variables adjusted for age at the time of the study, sex and disease duration in 29 patients with moderate-to-severe psoriasis

	ADMA				OPG			
	Time 0		6 months		Time 0		6 months	
Variables	*r*	*P*	*r*	*P*	*r*	*P*	*r*	*P*
HOMA	0.06	0.767	−0.15	0.477	0.06	0.767	0.11	0.612
QUICKI	−0.07	0.737	0.31	0.122	−0.07	0.737	−0.07	0.750
Systolic BP	0.14	0.486	0.07	0.740	0.14	0.486	0.00	0.995
Diastolic BP	0.10	0.636	0.15	0.492	0.10	0.636	0.22	0.306
Total cholesterol	−0.26	0.198	−0.03	0.875	−0.26	0.198	0.15	0.468
HDL-C	0.02	0.941	−0.02	0.910	0.02	0.941	−0.14	0.509
LDL-C	−0.30	0.140	−0.10	0.632	−0.30	0.140	0.23	0.276
Triglycerides	−0.20	0.334	0.19	0.356	−0.20	0.334	0.07	0.736
Apo-A1	−0.15	0.475	0.19	0.352	−0.15	0.475	−0.13	0.529
Apo-B	−0.15	0.460	−0.04	0.862	−0.15	0.460	0.23	0.270
Lp(a)	0.38	0.062	**0.42**	**0.037**	0.38	0.062	−0.09	0.687
Total cholesterol/HDL-C	−0.27	0.175	−0.11	0.577	−0.27	0.175	0.27	0.193
Apo-B/Apo-A1	−0.07	0.723	−0.22	0.291	−0.33	0.121	0.33	0.110
Homocysteine	−0.10	0.650	−0.18	0.373	0.15	0.522	−0.07	0.744
ESR	0.08	0.710	−0.12	0.557	−0.15	0.487	0.25	0.225
Ultrasensitive CRP	0.27	0.187	0.02	0.920	−0.07	0.732	−0.02	0.919
Body mass index	−0.09	0.667	−0.27	0.177	0.22	0.305	0.27	0.196
Waist circumference	−0.07	0.750	−0.37	0.060	0.20	0.345	0.15	0.468
BSA	**0.47**	**0.016**	0.13	0.532	−0.16	0.463	0.21	0.336
PASI	0.33	0.098	0.26	0.205	−0.16	0.457	0.28	0.186
NAPSI hands	0.22	0.275	0.07	0.755	0.17	0.417	−0.03	0.910
PGA psoriasis	0.33	0.099	0.03	0.880	0.26	0.220	0.22	0.302
PASE total score	0.35	0.077	0.06	0.765	0.13	0.551	−0.11	0.586
PASE functional	0.36	0.072	0.07	0.751	0.13	0.544	−0.09	0.668
PASE symptoms	0.34	0.091	0.06	0.787	0.12	0.571	−0.13	0.528
RBP4 (time 0)	−0.28	0.169	0.18	0.387	−0.29	0.172	0.15	0.474
Adiponectin (time 0)	−0.15	0.477	0.04	0.836	0.35	0.092	−0.14	0.500
Leptin (time 0)	−0.15	0.461	−0.06	0.783	0.04	0.868	0.25	0.238
Resistin (time 0)	**0.49**	**0.011**	**0.44**	**0.023**	−0.09	0.679	−0.23	0.259
Visfatin (time 0)	0.30	0.141	0.19	0.360	0.18	0.402	−0.12	0.557
ADMA (time 0)	–	–	–	–	0.12	0.579	−0.10	0.626
OPG (time 0)	0.12	0.579	−0.10	0.626	–	–	–	–

Significant results are highlighted in bold. ADMA, asymmetric dimethylarginine; Apo, apolipoprotein; BP, blood pressure; BSA, body surface area; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; HDL-C, high-density lipoprotein cholesterol; HOMA, Homeostasis Model of Assessment; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein a; NAPSI, Nail Psoriasis Severity Index; OPG, osteoprotegerin; PASE, Psoriatic Arthritis Screening and Evaluation; PGA, Physician Global Assessment; QUICKI, Quantitative Insulin Sensitivity Check Index; RBP4, retinol binding protein 4.

of cutaneous psoriasis in terms of extension and these values may somehow predict better response to anti-TNF-α. There was a dramatic decrease in BSA following 6-month adalimumab therapy, and this decrease was higher in those patients in whom baseline levels of ADMA prior to the onset of adalimumab therapy were higher.

Interestingly, in patients with inflammatory arthropathies including psoriatic arthritis, anti-TNF-α therapy improved the L-arginine/ADMA ratio. Both ADMA and the L-arginine/ADMA ratio were associated with aortic pulse wave velocity and may have a mechanistic role in the aortic stiffening observed in these patients.[17]

Our findings are in keeping with a recent study on 42 patients with chronic plaque psoriasis in which PASI score strongly correlated with the ADMA level.[18] This study along with our present data highlight the potential role of ADMA in the pathogenesis of psoriasis.

Besides the potential relevance of serum ADMA level as a marker of disease severity in patients with psoriasis, it is possible that high ADMA levels may predict a greater clinical response to anti-TNF-α therapy in individuals with moderate-to-severe psoriasis. However, this observation needs to be replicated in an independent cohort with a larger number of patients with moderate-to-severe psoriasis.

Nitric oxide acts as an anti-atherosclerotic molecule through a complex combination of effects. ADMA is an endogenous molecule that inhibits nitric oxide synthesis, leading to endothelial dysfunction that is an early step in the atherogenesis process.[19,20] On the other hand, it is well known that elevated levels of Lp(a) are often associated with endothelial

Table 3. Partial correlation of ADMA and OPG serum levels prior to adalimumab (time 0) and the change at 6 months in the selected continuous variables compared with baseline results, adjusted for age at the time of the study, sex and disease duration, in 29 patients with moderate-to-severe psoriasis treated with adalimumab

	ADMA		OPG	
Variables	*r*	*P*	*r*	*P*
HOMA	0.21	0.300	0.06	0.769
QUICKI	−0.20	0.328	−0.09	0.668
Systolic BP	−0.05	0.811	0.11	0.615
Diastolic BP	−0.27	0.203	0.13	0.569
Total cholesterol	0.18	0.373	−0.10	0.633
HDL-C	0.20	0.335	0.00	0.986
LDL-C	0.20	0.329	−0.01	0.968
Triglycerides	−0.28	0.173	**−0.43**	**0.038**
Apo-A1	0.32	0.125	0.01	0.969
Apo-B	−0.14	0.493	−0.08	0.724
Lp(a)	−0.16	0.448	0.26	0.238
Total cholesterol/HDL-C	−0.09	0.656	−0.13	0.550
Apo-B/Apo-A1	−0.29	0.159	−0.08	0.716
Homocysteine	−0.23	0.296	0.15	0.528
ESR	−0.09	0.655	0.09	0.661
Ultra-sensitive CRP	−0.19	0.354	0.07	0.752
Body mass index	−0.07	0.740	−0.16	0.448
Waist circumference	−0.36	0.073	−0.16	0.452
BSA	**−0.47**	**0.017**	0.19	0.376
PASI	−0.36	0.075	0.22	0.323
NAPSI hands	−0.19	0.372	−0.12	0.596
PGA psoriasis	−0.34	0.100	−0.14	0.516
PASE total score	−0.25	0.227	−0.02	0.920
PASE functional	−0.22	0.289	−0.03	0.875
PASE symptoms	−0.27	0.190	−0.01	0.974
RBP4	0.28	0.173	−0.05	0.817
Adiponectin	0.09	0.653	−0.41	0.050
Leptin	0.18	0.393	0.32	0.127
Resistin	−0.35	0.082	−0.14	0.500
Visfatin	−0.42	0.033	−0.14	0.525
ADMA	**−0.51**	**0.008**	−0.08	0.715
OPG	−0.01	0.955	0.15	0.470

Significant results are highlighted in bold. ADMA, asymmetric dimethylarginine; Apo, apolipoprotein; BP, blood pressure; BSA, body surface area; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; HDL-C, high-density lipoprotein cholesterol; HOMA, Homeostasis Model of Assessment; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein a; NAPSI, Nail Psoriasis Severity Index; OPG, osteoprotegerin; PASE, Psoriatic Arthritis Screening and Evaluation; PGA, Physician Global Assessment; QUICKI, Quantitative Insulin Sensitivity Check Index; RBP4, retinol binding protein 4.

dysfunction and enhanced atherosclerosis.[21] However, the biologic implication of the correlation between ADMA levels and Lp(a) after 6 months of biologic therapy requires further investigation.

In our study we also disclosed a significant positive correlation of ADMA with resistin. This is in accordance with recent results from our group that confirmed an association of this adipokine with inflammation and disease severity in patients with moderate-to-severe psoriasis.[16]

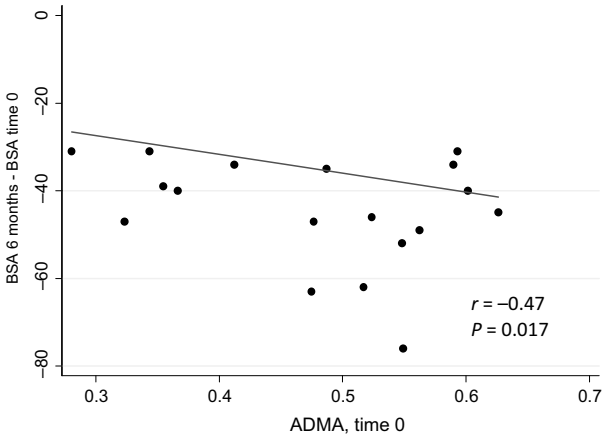

Figure 1. Scatter plot and linear trend on the relationship between basal asymmetric dimethylarginine (ADMA) levels (X axis) and changes in body surface area (BSA) score after 6 months of treatment with anti-tumor necrosis factor-α therapy.

In patients with chronic inflammatory diseases, OPG was associated with endothelial cell activation, subclinical atherosclerosis and increased risk of CV events.[7–9] Increased levels of OPG have been found in patients with psoriatic arthritis when compared with individuals who had psoriasis alone.[22] However, our results do not support a role of this molecule in the mechanisms associated with disease severity of psoriasis and the results from our study do not confer a pivotal role for OPG in the complex mechanisms leading to metabolic syndrome in patients with moderate-to-severe psoriasis without arthritis.

A potential limitation of our study is the relatively small sample size. Nevertheless, data on ADMA and OPG in patients with moderate-to-severe psoriasis undergoing adalimumab therapy are scarce.[18]

In conclusion, our results highlight the potential value of ADMA as a marker of disease severity in patients with psoriasis.

ACKNOWLEDGMENT: The study was supported by a research grant from Abbvie (to M. A. G.-G.).

CONFLICT OF INTEREST: The authors had sole responsibility for data analysis and manuscript preparation. The opinions expressed in this paper are those of the authors and do not necessarily represent those of Abbvie.

REFERENCES

1 Kimball AB, Guerin A, Latremouille-Viau D *et al.* Coronary heart disease and stroke risk in patients with psoriasis: retrospective analysis. *Am J Med* 2010; **123**: 350–357.
2 Prodanovich S, Kirsner RS, Kravetz JD, Ma F, Martinez L, Federman DG. Association of psoriasis with coronary artery, cerebrovascular, and peripheral vascular diseases and mortality. *Arch Dermatol* 2009; **145**: 700–703.

3 Balci DD, Balci A, Karazincir S *et al.* Increased carotid intima-media thickness and impaired endothelial function in psoriasis. *J Eur Acad Dermatol Venerol* 2009; **23**: 1–6.
4 Love TJ, Qureshi AA, Karlson EW, Gelfand JM, Choi HK. Prevalence of the metabolic syndrome in psoriasis: results from the National Health and Nutrition Examination Survey, 2003–2006. *Arch Dermatol* 2011; **147**: 419–424.
5 Langan SM, Seminara NM, Shin DB *et al.* Prevalence of metabolic syndrome in patients with psoriasis: a population-based study in the United Kingdom. *J Invest Dermatol* 2012; **132**: 556–562.
6 Mehta NN, Azfar RS, Shin DB, Neimann AL, Troxel AB, Gelfand JM. Patients with severe psoriasis are at increased risk of cardiovascular mortality: cohort study using the General Practice Research Database. *Eur Heart J* 2010; **31**: 1000–1006.
7 Genre F, López-Mejías R, Miranda-Filloy JA *et al.* Osteoprotegerin correlates with disease activity and endothelial activation in non-diabetic ankylosing spondylitis patients undergoing TNF-α antagonist therapy. *Clin Exp Rheumatol* 2014; **32**: 640–646.
8 Dessein PH, López-Mejias R, González-Juanatey C *et al.* Independent relationship of osteoprotegerin concentrations with endothelial activation and carotid atherosclerosis in patients with severe rheumatoid arthritis. *J Rheumatol* 2014; **41**: 429–436.
9 López-Mejias R, Ubilla B, Genre F *et al.* Osteoprotegerin concentrations relate independently to established cardiovascular disease in rheumatoid arthritis. *J Rheumatol* 2015; **42**: 39–45.
10 Di Franco M, Spinelli FR, Metere A *et al.* Serum levels of asymmetric dimethylarginine and apelin as potential markers of vascular endothelial dysfunction in early rheumatoid arthritis. *Mediators Inflamm* 2012; **2012**: 347268.
11 Genre F, López-Mejías R, Miranda-Filloy JA *et al.* Asymmetric dimethylarginine serum levels in non-diabetic ankylosing spondylitis patients undergoing TNF-α antagonist therapy. *Clin Exp Rheumatol* 2013; **31**: 749–755.
12 Sibal L, Agarwal SC, Home PD, Boger RH. The role of asymmetric dimethylarginine (ADMA) in endothelial dysfunction and cardiovascular disease. *Curr Cardiol Rev* 2010; **6**: 82–90.
13 Ogdie A, Yu Y, Haynes K *et al.* Risk of major cardiovascular events in patients with psoriatic arthritis, psoriasis and rheumatoid arthritis: a population-based cohort study. *Ann Rheum Dis* 2015; **74**: 326–332.
14 Pina T, Armesto S, Lopez-Mejias R *et al.* Anti-TNF-α therapy improves insulin sensitivity in non-diabetic patients with psoriasis: a 6-month prospective study. *J Eur Acad Dermatol Venereol* 2015; **29**: 1325–1330.
15 Pina T, Genre F, Lopez-Mejias R *et al.* Anti-TNF-α therapy reduces retinol-binding protein 4 serum levels in non-diabetic patients with psoriasis: a 6-month prospective study. *J Eur Acad Dermatol Venereol* 2015; doi: 10.1111/jdv.13005. [Epub ahead of print]
16 Pina T, Genre F, Lopez-Mejias R *et al.* Relationship of Leptin with adiposity and inflammation and resistin with disease severity in psoriatic patients undergoing anti-TNF-alpha therapy. *J Eur Acad Dermatol Venereol* 2015; doi:10.1111/jdv.13131. [Epub ahead of print]
17 Angel K, Provan SA, Mowinckel P, Seljeflot I, Kvien TK, Atar D. The L-arginine/asymmetric dimethylarginine ratio is improved by anti-tumor necrosis factor-α therapy in inflammatory arthropathies. Associations with aortic stiffness. *Atherosclerosis* 2012; **225**: 160–165.
18 Bilgiç Ö, Altınyazar HC, Baran H, Ünlü A. Serum homocysteine, asymmetric dimethyl arginine (ADMA) and other arginine-NO pathway metabolite levels in patients with psoriasis. *Arch Dermatol Res* 2015; **307**: 439–444.
19 Surdacki A, Nowicki M, Sandmann J *et al.* Reduced urinary excretion of nitric oxide metabolites and increased plasma levels of asymmetric dimethylarginine in men with essential hypertension. *J Cardiovasc Pharmacol* 1999; **33**: 652–658.
20 Böger RH, Bode-Böger SM, Szuba A *et al.* Asymmetric dimethylarginine (ADMA): a novel risk factor for endothelial dysfunction: its role in hypercholesterolemia. *Circulation* 1998; **98**: 1842–1847.
21 Koschinsky ML. Novel insights into Lp(a) physiology and pathogenicity: more questions than answers? *Cardiovasc Hematol Disord Drug Targets* 2006; **6**: 267–278.
22 Chandran V, Cook RJ, Edwin J *et al.* Soluble biomarkers differentiate patients with psoriatic arthritis from those with psoriasis without arthritis. *Rheumatology (Oxford)* 2010; **49**: 1399–1405.

RESULTADOS

De los 33 pacientes con psorasis moderada-grave (BSA 37.9±16.3%, PASI 18.9±7.8) inicialmente reclutados, 29 (52% mujeres; edad media ± SD, 38.6 ± 10.7) completaron los 6 meses de tratamiento y fueron susceptibles de evaluación. La duración media de la enfermedad fue de 18.2±12.1 años. En la tabla 1 se resumen los principales datos epidemiológicos de estos 29 pacientes en la visita basal.

Tabla 1. Datos epidemiológicos de 29 pacientes que completaron 6 meses de tratamiento con adalimumab.

Variable	n (%) o media±de
Hombre/Mujer, n (%)	14 (48)/15 (52)
Edad en años en la visita basal; media±DE	38.6±10.7
Duración de la enfermedad (años); media±DE	18.2±12.1
Factores de riesgo cardiovascular clásicos, n (%)	
Fumador activo	10 (34)
Con historia de tabaquismo	14 (48)
Obesidad (IMC > 30 Kg/m^2)	7 (24)
Dislipemia	13 (44)
IMC (kg/m^2); media±DE	27.5±3.7
Perímetro abdominal (cm); media±DE	96.1±10.8
BSA; media±DE	37.9±16.3%
PASI; media±DE	18.9±7.8
VSG; media±DE	13.4±12.8
PCRus; media±DE	0.36±0.33

EFECTO DEL TRATAMIENTO SOBRE LA SENSIBILIDAD INSULÍNICA

La tabla 2 muestra las diferencias observadas en los parámetros clínicos y serológicos entre la visita basal (inmediatamente antes del inicio de la terapia con adalimumab) y tras 6 meses de tratamiento.

La terapia con el fármaco anti-TNFα provocó una mejora significativa de la sensibilidad a la insulina (SI) (QUICKI basal 0.35±0.04, QUICKI 6 meses 0.37±0.04, expresado como media ± DE, p=0.008). Acorde con ello, también se apreció una

tendencia a la mejora del índice insulina/glucosa de 0.12± 0.07 a 0.10±0.06, sin llegar a alcanzar significación estadística (p=0.07).

En base a este hallazgo se analizó la existencia de correlaciones entre la SI antes y después de tratamiento con variables continuas ajustando por edad, sexo y duración de la enfermedad. Los resultados se muestran en la tabla 3.

Se observó una correlación negativa estadísticamente significativa entre los niveles basales de PCRus y la SI basal. Esta correlación perdió su significación estadística tras 6 meses de tratamiento. También se apreció una correlación negativa estadísticamente significativa entre el IMC basal y la SI basal, y entre el perímetro abdominal basal y la SI basal. Estas correlaciones se mantuvieron estadísticamente significativas tras 6 meses de tratamiento. Finalmente, también se apreció una correlación negativa marginalmente significativa (p=0.05) tras 6 meses de tratamiento entre la SI y la extensión cutánea de la psoriasis (BSA).

EFECTO DEL TRATAMIENTO SOBRE EL PERFIL LIPÍDICO

Tras 6 meses de tratamiento con adalimumab se apreció un incremento no significativo del colesterol total y del LDL-colesterol. No se apreciaron cambios en los niveles de HDL-colesterol, por lo que el índice aterogénico (colesterol total/HDL-colesterol) mostró un incremento no significativo. En contraste con estos hallazgos, se apreció un descenso no significativo en los niveles de Lp(a) (de 20.0 mg/dl a 15.4 mg/dl; p= 0.21) y homocisteína (de 15.9±7.5 µmol/L a 14.4±9.8; p= 0.11). (Tabla 2).

EFECTO DEL TRATAMIENTO SOBRE LA ACTIVIDAD DE LA ENFERMEDAD

La terapia con adalimumab provocó una mejora significativa de todos los parámetros de actividad de la enfermedad analizados, incluyendo PCRus, VSG, BSA, PASI, NAPSI y PGA. (Tabla 2).

Tabla 2. Hallazgos clínicos y de laboratorio. Diferencias entre los datos antes del inicio del tratamiento y tras 6 meses de terapia con adalimumab.

	Basal	**6 meses**	
Variable	**Media ±DE**	**Media ±DE**	**p**
HOMA	2.2±1.5	1.7±1.3	0.13
QUICKI	**0.35±0.04**	**0.37±0.04**	**0.008**
Glucosa en ayunas (mg/dl)	84.3±8.9	82.5±7.8	0.33
Hemoglobina glicosilada (%)	5.3±0.3	5.4±1.7	0.62
Insulina (μU/ml)	10.2±6.3	8.3±5.5	0.10
Ratio insulina/glucosa	0.12±0.07	0.10±0.06	0.07
Creatinina sérica (mg/dl)	0.77±0.12	0.77±0.13	0.97
Colesterol total (mg/dl)	196.9±38.5	202.9±36.6	0.19
HDL-colesterol (mg/dl)	53.2±14.9	52.9±14.3	0.89
LDL-colesterol (mg/dl)	120.7±28.4	127.0±27.9	0.13
Triglicéridos (mg/dl)	118.2±56.3	115.2±53.3	0.71
Apo-A1 (mg/dl)	161.6±28.4	160.7±29.4	0.85
Apo-B (mg/dl)	100.0±26.8	100.0±23.4	0.99
Lp(a) (mg/dl)	20.0±23.3	15.4±14.8	0.21
Colesterol total/HDL-colesterol	3.87±0.95	4.01±0.98	0.25
Apo-B/Apo-A1	0.63±0.16	0.64±0.18	0.73
Homocisteína (μmol/L)	15.9±7.5	14.4±9.8	0.11
VSG (mm/1ª hora)	**13.4±12.8**	**8.3±7.7**	**0.01**
PCRus (mg/dl)	**0.36±0.33**	**0.19±0.17**	**0.008**
IMC (Kg/m^2)	27.5±3.7	27.6±3.7	0.59
TA Sistólica (mm Hg)	120.7±12.5	118.4±12.4	0.19
TA diastólica (mm Hg)	74.4±6.8	74.2±6.4	0.86
BSA (%)	**37.9±16.3**	**3.1±5.5**	**<0.001**
PASI (0-72)	**18.9±7.8**	**1.3±2.1**	**<0.001**
NAPSI manos (0-80)	**5.4±10.5**	**1.5±3.9**	**0.04**
PGA psoriasis (0-6)	**3.9±0.6**	**0.7±0.6**	**<0.001**

Los resultados significativos están resaltados en negrita.

Tabla 3. Correlaciones parciales entre la SI (QUICKI) antes y después de tratamiento con variables continuas seleccionadas ajustando por edad, sexo y duración de la enfermedad.

	Basal		**6 meses**	
Variable	**r**	**p**	**r**	**p**
TA Sistólica	-0.11	0.55	-0.34	0.09
TA Diastólica	0.0005	0.99	-0.17	0.40
Colesterol total (mg/dl)	0.13	0.48	-0.19	0.33
HDL-colesterol (mg/dl)	0.22	0.23	-0.06	0.74
LDL-colesterol (mg/dl)	0.14	0.44	-0.21	0.29
Triglicéridos (mg/dl)	-0.28	0.12	-0.02	0.91
Apo-A1 (mg/dl)	0.10	0.57	-0.07	0.70
Apo-B (mg/dl)	0.12	0.53	-0.18	0.36
Lp(a) (mg/dl)	0.02	0.89	-0.28	0.17
Colesterol total/HDL-colesterol	-0.19	0.29	-0.14	0.49
Apo-B/Apo-A1	0.02	0.91	-0.17	0.39
Homocisteína (µmol/L)	0.20	0.32	-0.04	0.84
VSG (mm/1ª hora)	0.27	0.14	0.09	0.63
PCRus (mg/dl)	**-0.39**	**0.02**	-0.35	0.07
IMC (Kg/m2)	**-0.49**	**0.01**	**-0.69**	**<0.001**
Perímetro abdominal	**-0.45**	**0.01**	**-0.59**	**0.001**
BSA	-0.25	0.18	**-0.38**	**0.05**
PASI	-0.21	0.26	-0.26	0.20
NAPSI manos	-0.009	0.95	-0.18	0.39
PGA psoriasis	-0.24	0.19	-0.21	0.30

Los resultados significativos están resaltados en negrita.

EFECTO DEL TRATAMIENTO SOBRE LAS ADIPOCINAS

EFECTO SOBRE LEPTINA

No se apreciaron diferencias significativas entre los niveles basales de leptina y los niveles medidos tras 6 meses de tratamiento con adalimumab (Tabla 4).

Los niveles de leptina fueron más altos en mujeres que en hombres tanto antes como después del tratamiento (niveles basales hombres 4.7 ± 4.7 ng/ml; niveles basales mujeres 11.6 ± 4.4 ng/ml) (Tabla 5).

En cuanto a la relación de la leptina con los factores del síndrome metabólico, cuando se estratificó por sexos la leptina se asoció con obesidad en hombres pero no en mujeres (datos no mostrados).

La tabla 6 muestra las correlaciones parciales de los niveles séricos de leptina con variables seleccionadas tras ajustar por edad, sexo y duración de la enfermedad. Los niveles séricos de leptina se correlacionaron positivamente con el perímetro abdominal tanto antes como después del tratamiento, además tras 6 meses de tratamiento surgió una correlación positiva significativa con el IMC.

A pesar de haber excluido a pacientes hipertensos, los niveles séricos de leptina se correlacionaron positivamente con los niveles de presión arterial sistólica y diastólica antes del tratamiento. No se apreció correlación de los niveles séricos de leptina con el perfil lipídico de los pacientes. En cuanto a la IS (QUICKI), se halló una correlación negativa marginalmente significativa tanto antes ($r = -0.38$; $p = 0.058$) como después del tratamiento ($r = -0.39$; $p = 0.052$).

En cuanto a los parámetros de actividad de la enfermedad, antes del tratamiento con adalimumab la leptina presentó una correlación positiva estadísticamente significativa con los niveles de PCRus. Esta correlación desapareció tras tratamiento.

EFECTO SOBRE RESISTINA

No se apreciaron diferencias significativas entre los niveles basales de resistina y los niveles medidos tras 6 meses de tratamiento con adalimumab (Tabla 4).

No se encontró asociación entre los niveles séricos de resistina y los parámetros del síndrome metabólico (Tabla 6).

En cuanto a los parámetros de actividad de la enfermedad, tanto antes como después del tratamiento con adalimumab, la resistina mostró una correlación positiva estadísticamente significativa con los niveles de PCRus (Tabla 6). Antes del tratamiento los niveles séricos de resistina también presentaron una correlación positiva significativa con BSA ($r = 0.60$; $p = 0.001$), PASI ($r = 0.63$; $p = 0.001$) y PGA ($r = 0.45$; $p = 0.021$) (Tabla 6).

Además se analizó la correlación de los niveles basales de resistina con el cambio (valor a 6 meses menos valor basal) experimentado por las variables continuas seleccionadas

tras 6 meses de tratamiento (Tabla 7). Los niveles séricos basales de resistina presentaron una correlación negativa con el cambio en los parámetros de actividad de la enfermedad (BSA: r = -0.65; p < 0.001, PASI: r = -0.69; p < 0.001, PGA: r = -0.45; p = 0.03).

EFECTO SOBRE RBP4

La terapia con adalimumab redujo de forma significativa los niveles séricos de RBP4 (Figura 1). Los valores medios±DE de RBP4 se redujeron de 55.7±21.4 µg/ml a 35.6±29.9 µ/ml (p=0.0001).

No se halló correlación de los niveles séricos basales de RBP4 con los parámetros del síndrome metabólico ni con los de actividad de la enfermedad (Tabla 8).

Tras 6 meses de tratamiento con adalimumab RBP4 presentó una correlación negativa estadísticamente significativa con el IMC (r = -0.49; p=0.012), el perímetro abdominal (r = -0.40; p=0.046), PCRus (r = -0.41; p=0.036), BSA (r = -0.51; p=0.009) y PASI (r = -0.49; p=0.013) (Tabla 8).

Tabla 4. Diferencias entre el momento basal y tras 6 meses de terapia con adalimumab en los niveles séricos de leptina y resistina.

		Basal	**6 meses**	**p**
Leptina	**Media±DE (ng/ml)**	8.28 ± 5.66	8.75 ± 5.49	0.458
	Mediana (rango IQ)	7.65 (3.50 - 9.91)	7.69 (4.69 - 13.24)	
Resistina	**Media±DE (ng/ml)**	7.56 ± 3.26	7.13 ± 4.19	0.597
	Mediana (rango IQ)	7.06 (4.79 - 9.46)	6.48 (4.64 - 7.64)	

Tabla 5. Diferencias entre los niveles séricos basales y tras 6 meses de tratamiento de leptina y resistina según variables categóricas.

		Leptina (ng/ml)				Resistina (ng/ml)			
		Basal		6 meses		Basal		6 meses	
Variable	**Categoría**	**Media±DE**	**p**	**Media±DE**	**p**	**Media±DE**	**p**	**Media±DE**	**p**
Sexo	**Mujer**	11.6 ± 4.4	<0.001	12.3 ± 4.7	<0.001	7.3 ± 3.9	0.680	7.2 ± 3.6	0.931
	Hombre	4.7 ± 4.7		5.0 ± 3.4		7.8 ± 2.5		7.1 ± 4.9	
Dislipemia	**Si**	8.7 ± 5.3	0.722	10.1 ± 6.2	0.237	8.4 ± 4.1	0.200	8.5 ± 5.4	0.112
	No	7.9 ± 6.1		7.6 ± 4.8		6.9 ± 2.3		6.0 ± 2.5	
Obesidad	**Si**	10.6 ± 6.9	0.226	11.2 ± 6.1	0.184	9.0 ± 4.8	0.190	6.8 ± 1.8	0.844
	No	7.6 ± 5.2		8.0 ± 5.2		7.1 ± 2.6		7.2 ± 4.7	
Tabaquismo	**Si**	8.9 ± 7.0	0.671	8.9 ± 6.1	0.942	7.0 ± 2.2	0.512	8.3 ± 5.9	0.287
	No	7.9 ± 5.0		8.7 ± 5.3		7.9 ± 3.7		6.5 ± 2.9	

Tabla 6. Correlaciones parciales de los niveles séricos de leptina y resistina antes y después de tratamiento con variables continuas seleccionadas ajustando por edad, sexo y duración de la enfermedad.

	Leptina				**Resistina**			
Variable	**Basal**		**6 meses**		**Basal**		**6 meses**	
	r	**p**	**r**	**p**	**r**	**p**	**r**	**p**
HOMA	0.30	0.132	0.37	0.061	0.15	0.452	0.01	0.967
QUICKI	-0.38	0.058	-0.39	0.052	-0.17	0.395	0.21	0.309
TA Sistólica	**0.48**	**0.013**	0.33	0.112	0.34	0.087	0.27	0.200
TA Diastólica	**0.50**	**0.010**	0.29	0.176	0.08	0.681	0.13	0.544
Colesterol total	0.02	0.939	-0.05	0.792	-0.04	0.842	0.00	0.999
HDL-colesterol	0.03	0.894	-0.01	0.969	-0.31	0.119	0.07	0.731
LDL-colesterol	0.06	0.770	-0.05	0.795	0.03	0.890	-0.05	0.814
Triglicéridos	-0.16	0.424	-0.04	0.833	0.10	0.634	0.06	0.789
Apo-A1	0.10	0.649	0.05	0.807	-0.19	0.365	0.21	0.296
Apo-B	0.05	0.809	-0.05	0.801	0.14	0.491	-0.01	0.959
Lpa	-0.02	0.915	-0.11	0.612	0.38	0.058	0.11	0.602
Colesterol total/HDL-colesterol	0.07	0.739	-0.05	0.814	0.24	0.244	-0.11	0.610
Apo-B/Apo-A1	0.12	0.583	-0.11	0.601	0.28	0.181	-0.17	0.400
Homocisteína	0.02	0.938	0.17	0.393	-0.03	0.909	-0.11	0.608
VSG	0.03	0.867	-0.28	0.170	0.28	0.171	0.08	0.695
PCRus	**0.45**	**0.020**	0.15	0.456	**0.45**	**0.020**	**0.55**	**0.004**
IMC	0.35	0.084	**0.55**	**0.003**	0.19	0.344	-0.09	0.654
Perímetro abdominal	**0.43**	**0.029**	**0.43**	**0.030**	0.14	0.482	-0.16	0.425
BSA	-0.31	0.126	0.39	0.056	**0.60**	**0.001**	-0.17	0.430
PASI	-0.01	0.953	0.34	0.100	**0.63**	**0.001**	0.01	0.945
NAPSI manos	-0.19	0.358	0.38	0.069	0.35	0.079	0.03	0.905
PGA	-0.34	0.085	0.29	0.166	**0.45**	**0.021**	-0.36	0.073
Leptina (basal)	-	-	-	-	-0.08	0.694	0.02	0.930
Resistina (basal)	-0.08	0.694	0.02	0.930	-	-	-	-

Los resultados significativos están resaltados en negrita.

Tabla 7. Correlación de los niveles basales de resistina con el cambio (valor a 6 meses menos valor basal) experimentado por las variables continuas seleccionadas tras 6 meses de tratamiento.

Cambio en	Leptina		Resistina	
	r	p	r	p
HOMA	-0.06	0.76	0.22	0.28
QUICKI	-0.04	0.84	-0.14	0.48
TA sistólica	-0.07	0.75	-0.06	0.79
TA diastólica	-0.32	0.13	-0.18	0.40
Colesterol total	-0.33	0.11	0.33	0.10
HDL-colesterol	-0.19	0.36	0.33	0.10
LDL-colesterol	-0.23	0.26	0.30	0.14
Triglicéridos	-0.02	0.93	-0.29	0.15
Apo-A1	-0.18	0.39	0.15	0.47
Apo-B	-0.28	0.17	-0.12	0.58
Lpa	-0.04	0.84	-0.37	0.07
Colesterol total/HDL-colesterol	-0.08	0.69	-0.16	0.43
Apo-B/Apo-A1	-0.24	0.25	-0.18	0.40
Homocisteína	-0.15	0.50	-0.30	0.18
VSG	-0.07	0.75	-0.17	0.39
PCRus	-0.29	0.15	-0.31	0.12
IMC	0.19	0.36	-0.31	0.12
Perímetro abdominal	0.28	0.17	-0.16	0.43
BSA	**0.40**	**0.05**	**-0.65**	**<0.001**
PASI	0.07	0.73	**-0.69**	**<0.001**
NAPSI manos	0.28	0.18	-0.30	0.16
PGA psoriasis	0.35	0.09	**-0.45**	**0.03**

o Los resultados significativos están resaltados en negrita.

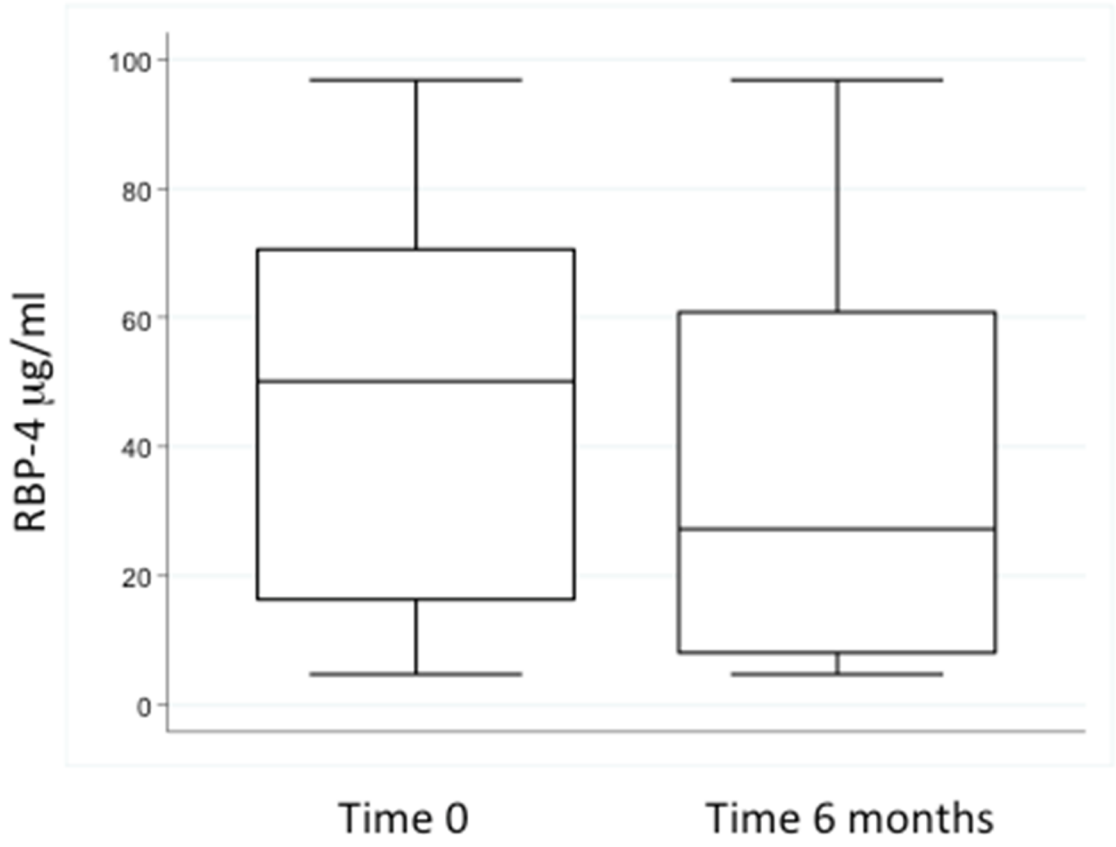

Figura 1. Box Plot. Diferencias en las concentraciones séricas de RBP-4 entre el momento basal y tras 6 meses de tratamiento con adalimumab.

Tabla 8. Correlaciones parciales de los niveles séricos de RBP4 antes y después de tratamiento con variables continuas seleccionadas ajustando por edad, sexo y duración de la enfermedad.

	Basal		**6 meses**	
Variable	r	p	r	p
HOMA	-0.07	0.751	-0.24	0.240
QUICKI	0.25	0.217	0.38	0.054
TA Sistólica	-0.09	0.661	-0.23	0.283
TA Diastólica	-0.004	0.983	-0.13	0.533
Colesterol Total	0.07	0.741	-0.04	0.854
HDL-colesterol	-0.19	0.359	0.01	0.981
LDL-colesterol	0.14	0.487	-0.01	0.965
Triglicéridos	0.07	0.717	-0.10	0.632
Apo-A1	-0.06	0.789	-0.07	0.742
Apo-B	0.16	0.455	-0.10	0.613
Lpa	0.03	0.887	0.25	0.231
Colesterol total/HDL-colesterol	0.19	0.352	-0.10	0.644
Apo-B/Apo-A1	0.19	0.361	-0.06	0.764
Homocisteína	0.40	0.064	-0.22	0.291
VSG	0.36	0.072	0.21	0.296
PCRus	0.27	0.188	**-0.41**	**0.036**
IMC	-0.02	0.918	**-0.49**	**0.012**
Perímetro abdominal	-0.10	0.626	**-0.40**	**0.046**
BSA	-0.10	0.629	**-0.51**	**0.009**
PASI	-0.09	0.670	**-0.49**	**0.013**
NAPSI manos	0.27	0.188	-0.08	0.723
PGA psoriasis	-0.39	0.050	-0.26	0.212

Los resultados significativos están resaltados en negrita.

EFECTO DEL TRATAMIENTO SOBRE ADMA

No se apreciaron diferencias significativas entre los niveles basales de ADMA y los niveles medidos tras 6 meses de tratamiento con adalimumab (mediana [rango IQ] antes de adalimumab 0.47 [0.37-0.55], frente a 0.46 [0.38-0.54] µmol/l tras 6 meses de tratamiento, p= 0.95).

La tabla 9 muestra las correlaciones parciales de los niveles séricos de ADMA con variables seleccionadas tras ajustar por edad, sexo y duración de la enfermedad.

No se observó ninguna correlación entre los niveles séricos basales de ADMA y los parámetros del síndrome metabólico. Sin embargo, tras 6 meses de tratamiento con adalimumab surgió una correlación positiva con los niveles séricos de Lp(a) ($r = 0.42$; $p = 0.037$).

Tampoco se apreció ninguna correlación de ADMA con marcadores de inflamación (VSG y PCR) o de adiposidad (IMC), ni antes de después de tratamiento.

En cuanto a la gravedad de la enfermedad, antes de iniciar tratamiento con adalimumab los niveles de ADMA se correlacionaron significativamente y de forma positiva con BSA ($r = 0.47$; $p = 0.016$). Antes de tratamiento también se apreció una correlación marginalmente significativa con el resto de parámetros de actividad de la enfermedad (PASI y PGA, $p > 0.05$ y < 0.1)). Tras tratamiento no se apreció correlación alguna con parámetros de actividad de la enfermedad.

Además se analizó la correlación de los niveles basales de ADMA con el cambio (valor a 6 meses menos valor basal) experimentado por las variables continuas seleccionadas tras 6 meses de tratamiento (Tabla 10). Como resultado de este análisis se obtuvo que los niveles séricos basales de ADMA se correlacionaban negativamente con el cambio en el parámetro de actividad de la enfermedad BSA ($r = -0.47$; $p = 0.017$).

Los niveles séricos de ADMA se correlacionaron positivamente con los niveles séricos de resistina, tanto antes como después del tratamiento con adalimumab (basal: $r = 0.49$; $p = 0.011$, 6 meses: $r = 0.44$; $p = 0.023$). Estos resultados indican que un mayor nivel sérico basal de ADMA predice una mejor respuesta al tratamiento en términos de actividad de la enfermedad.

EFECTO DEL TRATAMIENTO SOBRE OPG

No se apreciaron diferencias significativas entre los niveles basales de OPG y los niveles medidos tras 6 meses de tratamiento con adalimumab (mediana [rango IQ] antes de adalimumab 3.21 [2.60-3.63], frente a 2.95 [2.33-3.64] ng/ml tras 6 meses de tratamiento, p= 0.31).

La **tabla 9** muestra las correlaciones parciales de los niveles séricos de OPG con variables seleccionadas tras ajustar por edad, sexo y duración de la enfermedad.

No se observó ninguna correlación de OPG con los parámetros del síndrome metabólico ni con parámetros de actividad de la enfermedad. Tampoco se apreció correlación con los niveles de otras adipocinas. Se analizó la correlación de los niveles basales de OPG con el cambio (valor a 6 meses menos valor basal) experimentado por las variables continuas seleccionadas tras 6 meses de tratamiento (**Tabla 10**). Los niveles séricos basales de OPG presentaron una correlación negativa con el cambio en los niveles séricos de triglicéridos tras tratamiento con adalimumab (r = -0.43; p = 0.038).

Tabla 9. Correlaciones parciales de los niveles séricos de ADMA y OPG antes y después de tratamiento con variables continuas seleccionadas ajustando por edad, sexo y duración de la enfermedad.

	ADMA				**OPG**			
	Basal		**6 meses**		**Basal**		**6 meses**	
Variables	**r**	**p**	**r**	**p**	**r**	**p**	**R**	**p**
HOMA	0.06	0.767	-0.15	0.477	0.06	0.767	0.11	0.612
QUICKI	-0.07	0.737	0.31	0.122	-0.07	0.737	-0.07	0.750
TA sistólica	0.14	0.486	0.07	0.740	0.14	0.486	0.00	0.995
TA diastólica	0.10	0.636	0.15	0.492	0.10	0.636	0.22	0.306
Colesterol total	-0.26	0.198	-0.03	0.875	-0.26	0.198	0.15	0.468
HDL-colesterol	0.02	0.941	-0.02	0.910	0.02	0.941	-0.14	0.509
LDL-colesterol	-0.30	0.140	-0.10	0.632	-0.30	0.140	0.23	0.276
Triglicéridos	-0.20	0.334	0.19	0.356	-0.20	0.334	0.07	0.736
Apo-A1	-0.15	0.475	0.19	0.352	-0.15	0.475	-0.13	0.529
Apo-B	-0.15	0.460	-0.04	0.862	-0.15	0.460	0.23	0.270
Lp(a)	0.38	0.062	**0.42**	**0.037**	0.38	0.062	-0.09	0.687
Colesterol total/HDL-colesterol	-0.27	0.175	-0.11	0.577	-0.27	0.175	0.27	0.193
Apo-B/Apo-A1	-0.07	0.723	-0.22	0.291	-0.33	0.121	0.33	0.110
Homocisteína	-0.10	0.650	-0.18	0.373	0.15	0.522	-0.07	0.744
VSG	0.08	0.710	-0.12	0.557	-0.15	0.487	0.25	0.225
PCRus	0.27	0.187	0.02	0.920	-0.07	0.732	-0.02	0.919
IMC	-0.09	0.667	-0.27	0.177	0.22	0.305	0.27	0.196
Perímetro abdominal	-0.07	0.750	-0.37	0.060	0.20	0.345	0.15	0.468
BSA	**0.47**	**0.016**	0.13	0.532	-0.16	0.463	0.21	0.336
PASI	0.33	0.098	0.26	0.205	-0.16	0.457	0.28	0.186
NAPSI manos	0.22	0.275	0.07	0.755	0.17	0.417	-0.03	0.910
PGA psoriasis	0.33	0.099	0.03	0.880	0.26	0.220	0.22	0.302
RBP4 (time 0)	-0.28	0.169	0.18	0.387	-0.29	0.172	0.15	0.474
Adiponectina (time 0)	-0.15	0.477	0.04	0.836	0.35	0.092	-0.14	0.500
Leptina (time 0)	-0.15	0.461	-0.06	0.783	0.04	0.868	0.25	0.238
Resistina (time 0)	**0.49**	**0.011**	**0.44**	**0.023**	-0.09	0.679	-0.23	0.259
Visfatina (time 0)	0.30	0.141	0.19	0.360	0.18	0.402	-0.12	0.557
ADMA (time 0)	-	-	-	-	0.12	0.579	-0.10	0.626
OPG (time 0)	0.12	0.579	-0.10	0.626	-	-	-	-

Los resultados significativos están resaltados en negrita.

Tabla 10. Correlación parcial de los niveles basales de ADMA y OPG con el cambio (valor a 6 meses menos valor basal) experimentado por las variables continuas seleccionadas tras 6 meses de tratamiento.

Variable	**ADMA**		**OPG**	
	r	**p**	**r**	**p**
HOMA	0.21	0.300	0.06	0.769
QUICKI	-0.20	0.328	-0.09	0.668
TA sistólica	-0.05	0.811	0.11	0.615
TA diastólica	-0.27	0.203	0.13	0.569
Colesterol total	0.18	0.373	-0.10	0.633
HDL-colesterol	0.20	0.335	0.00	0.986
LDL-colesterol	0.20	0.329	-0.01	0.968
Triglicéridos	-0.28	0.173	**-0.43**	**0.038**
Apo-A1	0.32	0.125	0.01	0.969
Apo-B	-0.14	0.493	-0.08	0.724
Lp(a)	-0.16	0.448	0.26	0.238
Colesterol total/HDL-colesterol	-0.09	0.656	-0.13	0.550
Apo-B/Apo-A1	-0.29	0.159	-0.08	0.716
Homocisteína	-0.23	0.296	0.15	0.528
VSG	-0.09	0.655	0.09	0.661
PCRus	-0.19	0.354	0.07	0.752
IMC	-0.07	0.740	-0.16	0.448
Perímetro abdominal	-0.36	0.073	-0.16	0.452
BSA	**-0.47**	**0.017**	0.19	0.376
PASI	-0.36	0.075	0.22	0.323
NAPSI manos	-0.19	0.372	-0.12	0.596
PGA psoriasis	-0.34	0.100	-0.14	0.516
RBP4	0.28	0.173	-0.05	0.817
Adiponectina	0.09	0.653	-0.41	0.050
Leptina	0.18	0.393	0.32	0.127
Resistina	-0.35	0.082	-0.14	0.500
Visfatina	-0.42	0.033	-0.14	0.525
ADMA	**-0.51**	**0.008**	-0.08	0.715
OPG	-0.01	0.955	0.15	0.470

Los resultados significativos están resaltados en negrita.

DISCUSIÓN

TRATAMIENTO CON ANTITNF-α Y SENSIBILIDAD INSULÍNICA

Los pacientes con psorasis moderada-grave experimentaron una mejoría mantenida de la sensibilidad insulínica tras tratamiento con el fármaco antiTNF-α adalimumab.

Estos resultados están en línea con los datos publicados por Marra el al en los que se mostró una mejora de la sensibilidad insulínica en 9 pacientes tratados con el fármaco antiTNF-α etanercept durante 24 semanas.[127]

Hace más de 20 años, investigadores escandinavos pusieron de manifiesto la existencia de intolerancia a la glucosa en pacientes con AR y otras enfermedades inflamatorias crónicas. En estos pacientes el grado de alteración en el manejo de la glucosa por el organismo se relacionó con el grado de actividad inflamatoria definido por los reactantes de fase aguda.[128] Además, en pacientes con AR activa el deterioro en el manejo de la glucosa por el organismo se relacionó directamente con la RI.[129] Más tarde Paolisso et al confirmaron la presencia de RI en diferentes enfermedades inflamatorias crónicas y encontraron que la RI estaba principalmente asociada a la musculatura estriada más que al hígado.[130] Por otro lado Dessein et al hallaron que el grado de inflamación predice la RI en AR.[131]

La producción del TNF-α está aumentada en situaciones de hiperglucemia y tiene un efecto ominoso sobre la sensibilidad insulínica.[132] El TNF-α es también un importante mediador de la RI en la obesidad y la DM a través de su capacidad para disminuir la actividad tirosin-kinasa del receptor insulínico y de su efecto directo de bloqueo de absorción glucosa-insulina en el músculo esquelético.[133]

Adalimumab ha demostrado un efecto beneficioso persistente sobre la función endotelial de pacientes con AR.[134] Es más, el tratamiento con fármacos antiTNF-α se ha asociado a una reducción de mortalidad en pacientes con AR, principalmente asociada a una reducción de eventos cardiovasculares.[135]

La psoriasis presenta ciertas similitudes con la AR. Ambas enfermedades asocian un aumento de la frecuencia del síndrome metabólico, una alteración de la elasticidad aórtica, anomalías ecocardiográficas y un GIMc aumentado.[6,9,32,33,136-8] Además, y de acuerdo con las observaciones en AR, Wu et al encontraron una reducción significativa del riesgo de IAM en pacientes con psoriasis tratados con fármacos antiTNF-α.[139,140]

Nuestros resultados sugieren un efecto beneficioso del bloqueo del TNF-α sobre la RI que es uno de los mecanismos implicados en el desarrollo del síndrome metabólico y la aterosclerosis en pacientes con psoriasis. No obstante, son precisos estudios adicionales y datos a más largo plazo para confirmar la mejoría de la sensibilidad insulínica encontrada en nuestro estudio, así como para detectar y confirmar la reducción de riesgo cardiovascular asociada a la toma de fármacos antiTNF-α.

TRATAMIENTO CON ANTITNF-α Y PERFIL LIPÍDICO.

En nuestro estudio no encontramos una reducción significativa de los niveles de lípidos tras 6 meses de tratamiento con adalimumab. Tan solo hallamos una reducción no significativa de los niveles de Lp(a).

Estos resultados están en línea con los resultados publicados por Bacchetti et al, que solo encontraron una reducción en los niveles de Lp(a) en pacientes con psoriasis tras 24 semanas de tratamiento con el fármaco antiTNF-α etanercept.[141]

La Lp(a) es un reconocido factor de riesgo independiente para enfermedad aterosclerótica, por lo que su reducción puede tener un efecto beneficioso sobre el riesgo cardiovascular.[142]

TRATAMIENTO CON ANTITNF-α Y ADIPOCINAS.

Las citocinas derivadas del tejido adiposo blanco median entre los factores exógenos relacionados con la obesidad, tales como la nutrición y el estilo de vida, y los eventos moleculares que influyen en el desarrollo del síndrome metabólico, la inflamación y la enfermedad cardiovascular.[143] En otras enfermedades inflamatorias crónicas, como la AR, se ha descrito una compleja interacción mediada por adipocinas entre el tejido adiposo blanco y la enfermedad cardiovascular.[144]

La leptina es una adipocina implicada en la regulación del peso corporal a través de la inhibición del apetito y estimulando el gasto energético.[36] Es también un factor proinflamatorio que actúa en la red de citocinas interconectando el sistema inmune y los procesos inflamatorios del sistema neuroendocrino.[36,145] Es una adipocina que participa en la regulación y homeostasis tanto del sistema inmune como de los procesos inflamatorios. Los niveles de leptina dependen fundamentalmente de la cantidad de grasa corporal y su síntesis está influenciada por mediadores inflamatorios como el

TNF-α y la IL-1.[146] Los niveles elevados de leptina pueden jugar un papel relevante en la enfermedad cardiovascular asociada a la obesidad, incluida la aterosclerosis. Se han encontrado niveles elevados de leptina en pacientes con IAM y ACV, independientemente de la presencia de FRCV clásicos y de la presencia de obesidad.[39] Además, se ha sugerido que la leptina puede jugar un papel en el mecanismo patogénico de la placa de ateroma debido a su asociación positiva con la PCR y el receptor soluble de IL-6.[40]

En nuestra población de estudio (pacientes no diabéticos con psoriasis moderada-grave) los niveles séricos de leptina se correlacionaron con los factores del síndrome metabólico y la inflamación.

Encontramos una correlación positiva entre los niveles basales de leptina y los niveles de PCR. Esta correlación desaparecía tras 6 meses de tratamiento con adalimumab. Es posible que la correlación inicial antes de tratamiento fuese resultado del estado proinflamatorio asociado a la psoriasis moderada-grave. De hecho se produjo una mejoría significativa de los niveles de PCR tras tratamiento con adalimumab. Esta reducción asociada a la disminución de la actividad inflamatoria podría justificar la pérdida de correlación con leptina.

Los niveles séricos de leptina se han relacionado con el grado de obesidad, y a igualdad de IMC son mayores en mujeres que en hombres.[147] De acuerdo con esto, y al igual que se ha observado en espondilitis anquilosante,[148] en nuestro estudio también hemos encontrado unos niveles de leptina mas elevados en mujeres que en hombres.

De acuerdo también con lo observado en población general, el IMC y especialmente la adiposidad central se correlacionaron con los niveles séricos de leptina en los pacientes de nuestro estudio. En este sentido, detectamos una correlación positiva del perímetro abdominal con los niveles de leptina, tanto antes como después del tratamiento. De igual manera, tras 6 meses de tratamiento el IMC mostró una correlación significativamente positiva con los niveles de leptina, cuando esta correlación era marginalmente significativa antes de tratamiento. Estos resultados son acordes con los obtenidos en una serie de 58 pacientes con AR tratados con antiTNF-α durante 6 meses, en la que los niveles de leptina se correlacionaron positivamente con el IMC.[149] Además, y también en línea con nuestras observaciones en pacientes con psoriasis, en este estudio tampoco encontraron correlación de los niveles de leptina con la actividad

de la AR.[149] En un estudio previo de nuestro grupo en pacientes con AR tampoco se detectó correlación de los niveles de leptina con la actividad de la enfermedad.[150]

Los niveles séricos de leptina en nuestra serie de pacientes con psoriasis también se correlacionaron con otros factores del síndrome metabólico, como la tensión arterial. Además, se detectó una correlación marginalmente significativa con la RI.

En pacientes con artritis reumatoide se ha postulado que el potencial efecto de la leptina sobre la aterosclerosis coronaria podría estar mediado a través de interacciones con los FRCV clásicos.[151] De acuerdo con estas observaciones, Dessein et al encontraron que el efecto de la leptina sobre la placa aterosclerótica carotidea depende del número de FRCV clásicos presentes.[152]

Con todo ello, nuestros resultados en pacientes con psoriasis moderada-grave refuerzan la potencial implicación de la leptina en los complejos mecanismos asociados con la aterosclerosis acelerada en psoriasis.

En nuestra población de estudio (pacientes no diabéticos con psoriasis moderada-grave) los niveles séricos de resistina se correlacionaron con la actividad de la enfermedad y la inflamación.

Los resultados obtenidos en nuestra serie de pacientes con psoriasis están en concordancia con los obtenidos en un estudio previo de nuestro grupo llevado a cabo en pacientes con AR grave en tratamiento con el fármaco antiTNF-α infliximab.[153] En este estudio se puso de manifiesto una correlación de los niveles de resistina con los marcadores de inflamación, especialmente con PCR.

En enfermedades inflamatorias crónicas como la AR se ha apreciado una fuerte correlación entre inflamación y enfermedad cardiovascular. Sin embargo, y tal y como indicaba Dessein et al, el papel que juega la resistina en el incremento de la morbimortalidad cardiovascular de las enfermedades inflamatorias es a día de hoy incierto.[154] En este sentido, las concentraciones séricas de resistina no se correlacionaron con el depósito de calcio en arterias coronarias ni con el GIMc en pacientes con AR.[151,155] Tal y como hemos comentado anteriormente, en un estudio previo de nuestro grupo en pacientes con AR grave pusimos en evidencia una reducción de los niveles de resistina tras tratamiento con infliximab.[153] Sin embargo estos resultados no se replicaron en una serie de pacientes con espondilitis anquilosante con

una carga inflamatoria menor.[156] En este sentido, los resultados obtenidos en nuestros pacientes con psoriasis moderada-grave son equiparables a los obtenidos en pacientes con AR grave con elevada carga inflamatoria. En ambos casos apreciamos una correlación positiva entre los niveles de resistina y los niveles de PCR.[153] En base a estos resultados, se podría especular que los niveles de resistina tras tratamiento antiTNF-α podrían estar influenciados por la carga inflamatoria inicial. En este sentido, los pacientes de nuestra serie no presentaban una elevada carga inflamatoria reflejada en unos niveles moderados de PCR. Ello explicaría por qué se produjo una reducción significativa de los niveles de PCR, pero no así de los niveles de resistina (resistina basal 7.56 ± 3.26 ng/ml versus 7.13 ± 4.19 en mes 6).

Los datos de leptina y resistina son escasos en pacientes con psoriasis en tratamiento con antiTNF-α. Un estudio que incluyó a 10 pacientes japoneses con psoriasis puso de manifiesto una mejoría significativa del PASI tras 12 semanas de tratamiento con adalimumab. Curiosamente, los niveles séricos de leptina y resistina no se modificaron tras 12 semanas de tratamiento, pero sí se apreció una reducción significativa en los niveles de las 2 adipocinas tras 6 meses de tratamiento.[157] En nuestra serie de pacientes caucásicos se produjo una reducción del PASI, pero no en los niveles de leptina y resistina tras 6 meses de tratamiento con adalimumab. Estas diferencias entre los hallazgos de los dos estudios podrían explicarse por el diferente sustrato genético de los sujetos (asiáticos Vs caucásicos) , así como por el reducido número de pacientes del estudio japonés.

En nuestra población de estudio (pacientes no diabéticos con psoriasis moderada-grave) se produjo una reducción significativa de los niveles séricos de RBP4 tras 6 meses de tratamiento con el fármaco antiTNF-α adalimumab.

Los niveles séricos de RBP4 se han correlacionado positivamente con los niveles séricos de TNF-α en pacientes diabéticos con enfermedad arterial coronaria.[158] En línea con estos resultados, Erikstrup et al encontraron una correlación positiva entre los niveles de mRNA de RBP-4 en tejido adiposo y los niveles de mRNA de TNF-α con origen en plasma y músculo esquelético.[159] Nuestros hallazgos están en concordancia con estos resultados. Sin embargo, Sell y Eckel encontraron que el TNF-α reduce de forma muy potente la producción de RBP4 por los adipocitos, un resultado totalmente inesperado ya que los adipocitos tratados con TNF-α desarrollan IR.[160] El TNF-α es un

importante mediador de RI en obesidad y DM a través de su capacidad para disminuir la actividad tirosin-kinasa del receptor de la insulina, así como por su capacidad para inhibir la captación glucosa mediada por la interacción insulina-glucosa en el músculo esquelético.[133] De forma sorprendente, en nuestra serie de pacientes con psoriasis la reducción de los niveles séricos de RBP4 tras tratamiento con antiTNF-α no se correlacionó con la RI. Una posible explicación para este resultado puede ser que en nuestra cohorte se excluyeron pacientes con DM u obesidad grave. Además, también resultó muy llamativo el hallazgo de ausencia de correlaciones de RBP4 con la actividad de la enfermedad y los FRCV antes de tratamiento, mientras que tras tratamiento surgió una correlación negativa con la PCR, las medidas de obesidad, el BSA y el PASI. En este sentido, recientemente se ha descrito una relación paradójica en los niveles de adiponectina y RBP4 en cuanto a la relación de estas adipocinas con el riesgo de enfermedad cardiovascular en pacientes tratados con AR.[161,162] Esta asociación paradójica también ha sido descrita en pacientes sin AR, y se interpreta como un cambio compensatorio en la producción de adipocinas en presencia de enfermedad vascular crónica con el objeto de reducir el riesgo metabólico.[163]

En base a nuestros resultados, tampoco podemos excluir que la reducción de los niveles de RBP4 mediada por el tratamiento con el fármaco antiTNF-α adalimumab sea independiente del efecto de este fármaco sobre la actividad inflamatoria. En este sentido, nuestros resultados son concordantes con los hallazgos publicados en AR, en la que no se encontró correlación de los niveles de RBP4 con la RI.[164]

TRATAMIENTO CON ANTITNF-α Y OPG

En pacientes con enfermedades inflamatorias crónicas, OPG se ha asociado con activación endotelial, aterosclerosis subclínica y aumento del riesgo de eventos cardiovasculares.[165-7] En pacientes con psoriasis los niveles de OPG son más elevados en aquellos que asocian artritis.[168] Sin embargo, nuestros resultados no apoyan la relación de esta molécula con la gravedad de la psoriasis ni tampoco sugieren un papel de OPG en los complejos mecanismos implicados en el desarrollo de síndrome metabólico en los pacientes con psoriasis moderada-grave sin artritis.

TRATAMIENTO CON ANTITNF-α Y DISFUNCIÓN ENDOTELIAL (ADMA).

Los resultados de nuestro estudio sugieren que en pacientes con psoriasis moderada-grave los niveles séricos de ADMA se correlacionan con la gravedad de la psoriasis en términos de extensión, y que estos valores pueden de alguna forma predecir una mejor respuesta a la terapia antiTNF-α. Así, hallamos una dramática reducción del BSA tras tratamiento, y esta reducción fue mayor en aquellos pacientes en los que los niveles basales de ADMA eran mayores. Por tanto, más allá de la potencial relevancia de los niveles de ADMA como marcador de la gravedad de la psoriasis, es posible que unos niveles elevados de ADMA puedan ser predictores de una mayor respuesta clínica al tratamiento con antiTNF-α en pacientes con psoriasis moderada-grave.

Hay que destacar que en pacientes con artropatías inflamatorias, incluida la artritis psoriásica, la terapia con antiTNF-α mejoró el ratio L-arginina/ADMA. Además, tanto ADMA como el ratio L-arginina/ADMA se asociaron con la VOP aórtica y pueden jugar un papel en la rigidez aórtica observada en estos pacientes.[169]

Nuestros resultados son congruentes con un estudio reciente de 42 pacientes con psoriasis en el que el PASI se correlacionó con los niveles de ADMA.[14] Este estudio, junto con nuestros resultados apoyan un papel potencial de ADMA en la patogénesis de la psoriasis.

El oxido nítrico actúa como una molécula anti-aterosclerótica a través de una compleja combinación de efectos. ADMA es una molécula endógena que inhibe la síntesis del óxido nítrico, provocando disfunción endotelial que es una etapa precoz del proceso aterogénico.[170,171] Por otro lado, es bien sabido que los niveles elevados de Lp(a) se asocian con disfunción endotelial y aterosclerosis.[172] Sin embargo, la implicación biológica de la correlación entre los niveles de ADMA y Lp(a) que surge en nuestro estudio tras 6 meses de terapia con antiTNF-α requiere estudios adicionales.

LIMITACIONES DEL ESTUDIO.

Una potencial limitación del estudio es el pequeño tamaño muestral.

Aunque es la serie prospectiva más grande que analiza el efecto de un fármaco antiTNF-α sobre los marcadores indirectos de aterosclerosis en pacientes con psoriasis moderada-severa, es preciso un seguimiento a más largo plazo para poder establecer el efecto del tratamiento sobre los mecanismos implicados en el desarrollo de

aterosclerosis en este gurpo de pacientes, así como para establecer su relación con eventos cardiovasculares.

Son por ello precisos estudios a más largo plazo para poder establecer la implicación biológica de los hallazgos de nuestro estudio a nivel de riesgo cardiovascular.

CONCLUSIONES

1. En pacientes no diabéticos con psoriasis moderada-grave, el tratamiento con el fármaco antiTNF-α adalimumab mejora la actividad de la enfermedad medida a través del BSA, PASI, NAPSI y PGA, mejora la actividad inflamatoria medida por PCR, la sensibilidad insulínica expresada a través del índice QUICKI, y los niveles séricos de la adipocina RBP-4.

2. El tratamiento antiTNF-α también podría tener un efecto beneficioso sobre el perfil lipídico de estos pacientes a través de un descenso en los niveles de Lp(a).

3. En pacientes no diabéticos con psoriasis moderada-grave, el tratamiento con el fármaco antiTNF-α adalimumab no modifica los niveles séricos de las adipocinas leptina y resistina. Tampoco modifica los niveles séricos del marcador de disfunción endotelial ADMA ni de OPG.

4. En pacientes no diabéticos con psoriasis moderada-grave los niveles séricos de ADMA actuan como un marcador de gravedad de la enfermedad y son además predictores de respuesta a tratamiento con antiTNF-α.

5. En pacientes no diabéticos con psoriasis moderada-grave los niveles séricos de leptina se correlacionan con los factores del síndrome metabólico y la inflamación, mientras que los niveles séricos de resistina se correlacionan con la actividad de la enfermedad y la inflamación.

6. En pacientes no diabéticos con psoriasis moderada-grave los niveles séricos de OPG no se relacionan con la actividad de la enfermedad ni con los parámetros del síndrome metabólico.

7. Son necesarios estudios adicionales que permitan validar nuestros resultados y confirmar una reducción del riesgo cardiovascular asociado al uso de terapia antiTNF-α.

8. En definitiva, el tratamiento con fármacos antiTNF-α en pacientes con psoriasis moderada-grave ejerce un efecto beneficioso sobre los mecanismos implicados en el desarrollo del síndrome metabólico y la aterosclerosis.

BIBLIOGRAFÍA

1. Troitzsch P, Paulista Markus MR, Dörr M, Felix SB, Jünger M, Schminke U, et al. Psoriasis is associated with increased intima-media thickness--the Study of Health in Pomerania (SHIP). Atherosclerosis. 2012 Dec;225(2):486-90.

2. Yiu KH, Yeung CK, Zhao CT, Chan JC, Siu CW, Tam S, et al. Prevalence and extent of subclinical atherosclerosis in patients with psoriasis. J Intern Med. 2013 Mar;273(3):273-82.

3. Kim SY, Yang HS, Lee YW, Choe YB, Ahn KJ. Evaluation of the Beta Stiffness Index and Carotid Intima-Media Thickness in Asian Patients With Psoriasis. Angiology. 2015 Jan 29. pii: 0003319714568790. [Epub ahead of print] PMID: 25635116.

4. Robati RM, Partovi-Kia M, Haghighatkhah HR, Younespour S, Abdollahimajd F. Increased serum leptin and resistin levels and increased carotid intima-media wall thickness in patients with psoriasis: is psoriasis associated with atherosclerosis? J Am Acad Dermatol. 2014 Oct;71(4):642-8.

5. Vlachopoulos C, Aznaouridis K, Stefanadis C. Prediction of cardiovascular events and all-cause mortality with arterial stiffness: a systematic review and meta-analysis. J Am Coll Cardiol. 2010 Mar 30;55(13):1318-27.

6. Bicer A, Acikel S, Kilic H, Ulukaradag Z, Karasu BB, Cemil BC, et al. Impaired aortic elasticity in patients with psoriasis. Acta Cardiol. 2009 Oct;64(5):597-602.

7. Torres T, Bettencourt N, Mendonça D, Vasconcelos C, Gama V, Silva BM, et al. Epicardial adipose tissue and coronary artery calcification in psoriasis patients. J Eur Acad Dermatol Venereol. 2015 Feb;29(2):270-7.

8. Staniak HL, Bittencourt MS, de Souza Santos I, Sharovsky R, Sabbag C, Goulart AC, et al. Association between psoriasis and coronary calcium score. Atherosclerosis. 2014 Dec;237(2):847-52.

9. Balci DD, Balci A, Karazincir S, Ucar E, Iyigun U, Yalcin F, et al. Increased carotid artery intima-media thickness and impaired endothelial function in psoriasis. J Eur Acad Dermatol Venereol. 2009 Jan;23(1):1-6.

10. De Simone C, Di Giorgio A, Sisto T, Carbone A, Ghitti F, Tondi P, et al. Endothelial dysfunction in psoriasis patients: cross-sectional case-control study. Eur J Dermatol. 2011 Jul-Aug;21(4):510-4

11. Karoli R, Fatima J, Shukla V, Dhillon KS, Khanduri S, Maini S, et al. A study of cardio-metabolic risk profile in patients with psoriasis. J Assoc Physicians India. 2013 Nov;61(11):798-803.

12. Erturan I, Köroğlu BK, Adiloğlu A, Ceyhan AM, Akkaya VB, Tamer N, et al. Evaluation of serum sCD40L and homocysteine levels with subclinical atherosclerosis indicators in patients with psoriasis: a pilot study. Int J Dermatol. 2014 Apr;53(4):503-9.

13. Ulusoy RE, Karabudak O, Yokusoglu M, Kilicaslan F, Kirilmaz A, Cebeci BS. Noninvasive assessment of impaired endothelial function in psoriasis. Rheumatol Int. 2010 Feb;30(4):479-83.

14. Bilgiç Ö, Altınyazar HC, Baran H, Ünlü A. Serum homocysteine, asymmetric dimethyl arginine (ADMA) and other arginine-NO pathway metabolite levels in patients with psoriasis. Arch Dermatol Res. 2015 Jul;307(5):439-44.

15. Neimann AL, Shin DB, Wang X, Margolis DJ, Troxel AB, Gelfand JM. Prevalence of cardiovascular risk factors in patients with psoriasis. J Am Acad Dermatol. 2006 Nov;55(5):829-35.

16. Armstrong AW, Harskamp CT, Armstrong EJ. The association between psoriasis and obesity: a systematic review and meta-analysis of observational studies. Nutr Diabetes. 2012 Dec 3;2:e54.

17. Armstrong AW, Harskamp CT, Armstrong EJ. The association between psoriasis and hypertension: a systematic review and meta-analysis of observational studies. J Hypertens. 2013 Mar;31(3):433-42.

18. Khalid U, Hansen PR, Gislason GH, Lindhardsen J, Kristensen SL, Winther SA, et al. Psoriasis and new-onset diabetes: a Danish nationwide cohort study. Diabetes Care. 2013 Aug;36(8):2402-7.

19. Ma C, Harskamp CT, Armstrong EJ, Armstrong AW. The association between psoriasis and dyslipidaemia: a systematic review. Br J Dermatol. 2013 Mar;168(3):486-95.

20. Pietrzak A, Michalak-Stoma A, Chodorowska G, Szepietowski JC. Lipid disturbances in psoriasis: an update. Mediators Inflamm. 2010;2010. pii: 535612.

21. Akhyani M, Ehsani AH, Robati RM, Robati AM. The lipid profile in psoriasis: a controlled study. J Eur Acad Dermatol Venereol 2007; 21:1330-2.

22. Chi CC, Wang J, Chen YF, Wang SH, Chen FL, Tung TH. Risk of incident chronic kidney disease and end-stage renal disease in patients with psoriasis: A nationwide population-based cohort study. J Dermatol Sci. 2015 Jun;78(3):232-8.

23. Wan J, Wang S, Haynes K, Denburg MR, Shin DB, Gelfand JM. Risk of moderate to advanced kidney disease in patients with psoriasis: population based cohort study. BMJ. 2013 Oct 15;347:f5961.

24. Wilcox G. Insulin and insulin resistance. Clin Biochem Rev. 2005 May;26(2):19-39.

25. Hotamisligil GS, Spiegelman BM. Tumor necrosis factor alpha: a key component of the obesity-diabetes link. Diabetes. 1994 Nov;43(11):1271-8.

26. Wasko MC, Kay J, Hsia EC, Rahman MU. Diabetes mellitus and insulin resistance in patients with rheumatoid arthritis: risk reduction in a chronic inflammatory disease. Arthritis Care Res (Hoboken). 2011 Apr;63(4):512-21.

27. Bonora E, Kiechl S, Willeit J, Oberhollenzer F, Egger G, Targher G, et al. Prevalence of insulin resistance in metabolic disorders: the Bruneck Study. Diabetes. 1998 Oct;47(10):1643-9.

28. Jucci A, Vignini M, Pelfini C, Criffõ A, Fratino P. Psoriasis and insulin secretion. Preliminary results. Arch Dermatol Res. 1977 Jan 31;257(3):239-46.

29. Ucak S, Ekmekci TR, Basat O, Koslu A, Altuntas Y. Comparison of various insulin sensitivity indices in psoriatic patients and their relationship with type of psoriasis. J Eur Acad Dermatol Venereol. 2006 May;20(5):517-22.

30. Boehncke S, Thaci D, Beschmann H, Ludwig RJ, Ackermann H, Badenhoop K, et al. Psoriasis patients show signs of insulin resistance. Br J Dermatol. 2007 Dec;157(6):1249-51.

31. Kaur J. A comprehensive review on metabolic syndrome. Cardiol Res Pract. 2014;2014:943162.

32. Sommer DM, Jenisch S, Suchan M, Christophers E, Weichenthal M. Increased prevalence of the metabolic syndrome in patients with moderate to severe psoriasis. Arch Dermatol Res. 2006 Dec;298(7):321-8.

33. Langan SM, Seminara NM, Shin DB, Troxel AB, Kimmel SE, Mehta NN, et al. Prevalence of metabolic syndrome in patients with psoriasis: a population-based study in the United Kingdom. J Invest Dermatol. 2012 Mar;132(3 Pt 1):556-62.

34. Scotece M, Conde J, Gómez R, López V, Pino J, González A, et al. Role of adipokines in atherosclerosis: interferences with cardiovascular complications in rheumatic diseases. Mediators Inflamm. 2012;2012:125458.

35. Berg AH, Scherer PE. Adipose tissue, inflammation, and cardiovascular disease. Circ Res. 2005 May 13;96(9):939-49.

36. Tilg H, Moschen AR. Adipocytokines: mediators linking adipose tissue, inflammation and immunity. Nat Rev Immunol. 2006 Oct;6(10):772-83.

37. Neumann E, Frommer KW, Vasile M, Müller-Ladner U. Adipocytokines as driving forces in rheumatoid arthritis and related inflammatory diseases? Arthritis Rheum. 2011 May;63(5):1159-69.

38. Johnston A, Arnadottir S, Gudjonsson JE, Aphale A, Sigmarsdottir AA, Gunnarsson SI, et al. Obesity in psoriasis: leptin and resistin as mediators of cutaneous inflammation. Br J Dermatol. 2008 Aug;159(2):342-50.

39. Sierra-Johnson J, Romero-Corral A, Lopez-Jimenez F, Gami AS, Sert Kuniyoshi FH, Wolk R, et al. Relation of increased leptin concentrations to history of myocardial infarction and stroke in the United States population. Am J Cardiol. 2007 Jul 15;100(2):234-9.

40. Karaduman M, Oktenli C, Musabak U, Sengul A, Yesilova Z, Cingoz F, et al. Leptin, soluble interleukin-6 receptor, C-reactive protein and soluble vascular cell adhesion molecule-1 levels in human coronary atherosclerotic plaque. Clin Exp Immunol. 2006 Mar;143(3):452-7.

41. Blüher M. Clinical relevance of adipokines. Diabetes Metab J. 2012 Oct;36(5):317-27.

42. Zhu KJ, Zhang C, Li M, Zhu CY, Shi G, Fan YM. Leptin levels in patients with psoriasis: a meta-analysis. Clin Exp Dermatol. 2013 Jul;38(5):478-83.

43. Wang Y, Chen J, Zhao Y, Geng L, Song F, Chen HD. Psoriasis is associated with increased levels of serum leptin. Br J Dermatol. 2008 May;158(5):1134-5.

44. Cerman AA, Bozkurt S, Sav A, Tulunay A, Elbaşi MO, Ergun T. Serum leptin levels, skin leptin and leptin receptor expression in psoriasis. Br J Dermatol. 2008 Sep;159(4):820-6.

45. Chen YJ, Wu CY, Shen JL, Chu SY, Chen CK, Chang YT, et al. Psoriasis independently associated with hyperleptinemia contributing to metabolic syndrome. Arch Dermatol. 2008 Dec;144(12):1571-5.

46. Coimbra S, Oliveira H, Reis F, Belo L, Rocha S, Quintanilha A, et al. Circulating adipokine levels in Portuguese patients with psoriasis vulgaris according to body mass index, severity and therapy. J Eur Acad Dermatol Venereol. 2010 Dec;24(12):1386-94.

47. Kaur S, Zilmer K, Leping V, Zilmer M. The levels of adiponectin and leptin and their relation to other markers of cardiovascular risk in patients with psoriasis. J Eur Acad Dermatol Venereol. 2011 Nov;25(11):1328-33.

48. Nakajima H, Nakajima K, Tarutani M, Sano S. Clear association between serum levels of adipokines and T-helper 17-related cytokines in patients with psoriasis. Clin Exp Dermatol. 2013 Jan;38(1):66-70.

49. Gerdes S, Osadtschy S, Rostami-Yazdi M, Buhles N, Weichenthal M, Mrowietz U. Leptin, adiponectin, visfatin and retinol-binding protein-4 - mediators of comorbidities in patients with psoriasis? Exp Dermatol. 2012 Jan;21(1):43-7.

50. Baran A, Flisiak I, Jaroszewicz J, Świderska M. Effect of psoriasis activity on serum adiponectin and leptin levels. Postepy Dermatol Alergol. 2015 Apr;32(2):101-6.

51. Xue K, Liu H, Jian Q, Liu B, Zhu D, Zhang M, et al. Leptin induces secretion of pro-inflammatory cytokines by human keratinocytes in vitro--a possible reason for increased severity of psoriasis in patients with a high body mass index. Exp Dermatol. 2013 Jun;22(6):406-10.

52. Steppan CM, Bailey ST, Bhat S, Brown EJ, Banerjee RR, Wright CM, et al. The hormone resistin links obesity to diabetes. Nature (2001) 409:307–12.

53. Fain JN, Cheema PS, Bahouth SW, Lloyd HM. Resistin release by human adipose tissue explants in primary culture. Biochem Biophys Res Commun (2003) 300:674–8.

54. Patel L, Buckels AC, Kinghorn IJ, Murdock PR, Holbrook JD, Plumpton C, et al. Resistin is expressed in human macrophages and directly regulated by PPAR gamma activators. Biochem Biophys Res Commun (2003) 300:472–6.

55. Gerber M, Boettner A, Seidel B, Lammert A, Bar J, Schuster E, et al. Serum resistin levels of obese and lean children and adolescents: biochemical analysis and clinical relevance. J Clin Endocrinol Metab (2005) 90:4503–9.

56. Savage DB, Sewter CP, Klenk ES, Segal DG, Vidal-Puig A, Considine RV, et al. Resistin/Fizz3 expression in relation to obesity and peroxisome proliferator-activated receptor-gamma action in humans. Diabetes (2001) 50:2199–202.

57. McTernan PG, Fisher FM, Valsamakis G, Chetty R, Harte A, McTernan CL, et al. Resistin and type 2 diabetes: regulation of resistin expression by insulin and rosiglitazone and the effects of recombinant resistin on lipid and glucose metabolism in human differentiated adipocytes. J Clin Endocrinol Metab (2003) 88:6098–106.

58. Reilly MP, Lehrke M, Wolfe ML, Rohatgi A, Lazar MA, Rader DJ. Resistin is an inflammatory marker of atherosclerosis in humans. Circulation (2005) 111:932–9.

59. Hivert MF, Sullivan LM, Fox CS, Nathan DM, D'Agostino RBSr., Wilson PW, et al. Associations of adiponectin, resistin, and tumor necrosis factor-alpha with insulin resistance. J Clin Endocrinol Metab (2008) 93:3165–72.

60. Norata GD, Ongari M, Garlaschelli K, Raselli S, Grigore L, Catapano AL. Plasma resistin levels correlate with determinants of the metabolic syndrome. Eur J Endocrinol (2007) 156:279–84.

61. Mojiminiyi OA, Abdella NA. Associations of resistin with inflammation and insulin resistance in patients with type 2 diabetes mellitus. Scand J Clin Lab Invest (2007) 67:215–25.

62. Lim S, Koo BK, Cho SW, Kihara S, Funahashi T, Cho YM, et al. Association of adiponectin and resistin with cardiovascular events in Korean patients with type 2 diabetes: the Korean atherosclerosis study (KAS): a 42-month prospective study. Atherosclerosis (2008) 196:398–404.

63. Pischon T, Bamberger CM, Kratzsch J, Zyriax BC, Algenstaedt P, Boeing H, et al. Association of plasma resistin levels with coronary heart disease in women. Obes Res (2005) 13:1764–71.

64. Yaturu S, Daberry RP, Rains J, Jain S. Resistin and adiponectin levels in subjects with coronary artery disease and type 2 diabetes. Cytokine (2006) 34:219–23.

65. Bokarewa M, Nagaev I, Dahlberg L, Smith U, Tarkowski A. Resistin, an adipokine with potent proinflammatory properties. J Immunol (2005) 174:5789–95.

66. Calabro P, Samudio I, Willerson JT, Yeh ET. Resistin promotes smooth muscle cell proliferation through activation of extracellular signal-regulated kinase 1/2 and phosphatidylinositol 3-kinase pathways. Circulation (2004) 110:3335–40.

67. Quadro L, Blaner WS, Salchow DJ, Vogel S, Piantedosi R, Gouras P, et al. Impaired retinal function and vitamin A availability in mice lacking retinol-binding protein. EMBO J (1999) 18:4633–44.

68. Yang Q, Graham TE, Mody N, Preitner F, Peroni OD, Zabolotny JM, et al. Serum retinol binding protein 4 contributes to insulin resistance in obesity and type 2 diabetes. Nature (2005) 436:356–62

69. Graham TE, Yang Q, Bluher M, Hammarstedt A, Ciaraldi TP, Henry RR, et al. Retinol-binding protein 4 and insulin resistance in lean, obese, and diabetic subjects. N Engl J Med (2006) 354:2552–63

70. Meisinger C, Ruckert IM, Rathmann W, Doring A, Thorand B, Huth C, et al. Retinol-binding protein 4 is associated with prediabetes in adults from the general population: the Cooperative Health Research in the Region of Augsburg (KORA) F4 Study. Diabetes Care (2011) 34:1648-50

71. Solini A, Santini E, Madec S, Rossi C, Muscelli E. Retinol-binding protein-4 in women with untreated essential hypertension. Am J Hypertens (2009) 22:1001-6.

72. Ingelsson E, Sundstrom J, Melhus H, Michaelsson K, Berne C, Vasan RS, et al. Circulating retinol-binding protein 4, cardiovascular risk factors and prevalent cardiovascular disease in elderly. Atherosclerosis (2009) 206:239-44.

73. Janke J, Engeli S, Boschmann M, Adams F, Bohnke J, Luft FC, et al. Retinol-binding protein 4 in human obesity. Diabetes (2006) 55:2805-10.

74. Promintzer M, Krebs M, Todoric J, Luger A, Bischof MG, Nowotny P, et al. Insulin resistance is unrelated to circulating retinol binding protein and protein C inhibitor. J Clin Endocrinol Metab (2007) 92:4306-12.

75. Romaní J, Caixàs A, Ceperuelo-Mallafré V, Carrascosa JM, Ribera M, Rigla M, et al. Circulating levels of lipocalin-2 and retinol-binding protein-4 are increased in psoriatic patients and correlated with baseline PASI. Arch Dermatol Res. 2013 Mar;305(2):105-12.

76. Venuraju SM, Yerramasu A, Corder R, Lahiri A. Osteoprotegerin as a predictor of coronary artery disease and cardiovascular mortality and morbidity. J Am Coll Cardiol. 2010 May 11;55(19):2049-61.

77. Bucay N, Sarosi I, Dunstan CR, Morony S, Tarpley J, Capparelli C, et al. Osteoprotegerin-deficient mice develop early onset osteoporosis and arterial calcification. Genes Dev. 1998 May 1;12(9):1260-8.

78. Min H, Morony S, Sarosi I, Dunstan CR, Capparelli C, Scully S, et al. Osteoprotegerin reverses osteoporosis by inhibiting endosteal osteoclasts and prevents vascular calcification by blocking a process resembling osteoclastogenesis. J Exp Med. 2000 Aug 21;192(4):463-74.

79. Abedin M, Omland T, Ueland T, Khera A, Aukrust P, Murphy SA, et al. Relation of osteoprotegerin to coronary calcium and aortic plaque (from the Dallas Heart Study). Am J Cardiol. 2007 Feb 15;99(4):513-8.

80. Omland T, Drazner MH, Ueland T, Abedin M, Murphy SA, Aukrust P, et al. Plasma osteoprotegerin levels in the general population: relation to indices of left ventricular structure and function. Hypertension. 2007 Jun;49(6):1392-8.

81. Kiechl S, Schett G, Wenning G, Redlich K, Oberhollenzer M, Mayr A, et al. Osteoprotegerin is a risk factor for progressive atherosclerosis and cardiovascular disease. Circulation. 2004 May 11;109(18):2175-80.

82. Semb AG, Ueland T, Aukrust P, Wareham NJ, Luben R, Gullestad L, et al. Osteoprotegerin and soluble receptor activator of nuclear factor-kappaB ligand and risk for coronary events: a nested case-control approach in the prospective EPIC-Norfolk population study 1993-2003. Arterioscler Thromb Vasc Biol. 2009 Jun;29(6):975-80.

83. Bartosińska J, Michalak-Stoma A, Juszkiewicz-Borowiec M, Kowal M, Chodorowska G. The Assessment of Selected Bone and Cartilage Biomarkers in Psoriatic Patients from Poland. Mediators Inflamm. 2015;2015:194535.

84. McDonald CJ, Calabresi P. Psoriasis and occlusive vascular disease. Br J Dermatol. 1978 Nov;99(5):469-75.

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

86. Gelfand JM, Troxel AB, Lewis JD, Kurd SK, Shin DB, Wang X, et al. The risk of mortality in patients with psoriasis: results from a population-based study. Arch Dermatol. 2007 Dec;143(12):1493-9.

87. Mehta NN, Azfar RS, Shin DB, Neimann AL, Troxel AB, Gelfand JM. Patients with severe psoriasis are at increased risk of cardiovascular mortality: cohort study using the General Practice Research Database. Eur Heart J. 2010 Apr;31(8):1000-6.

88. Gelfand JM, Dommasch ED, Shin DB, Azfar RS, Kurd SK, Wang X, et al. Troxel AB. The risk of stroke in patients with psoriasis. J Invest Dermatol. 2009 Oct;129(10):2411-8.

89. Mehta NN, Yu Y, Pinnelas R, Krishnamoorthy P, Shin DB, Troxel AB, et al. Attributable risk estimate of severe psoriasis on major cardiovascular events. Am J Med. 2011 Aug;124(8):775.e1-6.

90. Prodanovich S, Kirsner RS, Kravetz JD, Ma F, Martinez L, Federman DG. Association of psoriasis with coronary artery, cerebrovascular, and peripheral vascular diseases and mortality. Arch Dermatol. 2009 Jun;145(6):700-3.

91. Kimball AB, Guerin A, Latremouille-Viau D, Yu AP, Gupta S, Bao Y, et al. Coronary heart disease and stroke risk in patients with psoriasis: retrospective analysis. Am J Med. 2010 Apr;123(4):350-7.

92. Ahlehoff O, Gislason GH, Charlot M, Jørgensen CH, Lindhardsen J, Olesen JB, et al. Psoriasis is associated with clinically significant cardiovascular risk: a Danish nationwide cohort study. J Intern Med. 2011 Aug;270(2):147-57.

93. Ahlehoff O, Gislason GH, Jørgensen CH, Lindhardsen J, Charlot M, Olesen JB, et al. Abildstrøm SZ, Skov L, Torp-Pedersen C, Hansen PR. Psoriasis and risk of atrial fibrillation and ischaemic stroke: a Danish Nationwide Cohort Study. Eur Heart J. 2012 Aug;33(16):2054-64.

94. Armstrong AW, Harskamp CT, Ledo L, Rogers JH, Armstrong EJ. Coronary artery disease in patients with psoriasis referred for coronary angiography. Am J Cardiol. 2012 Apr 1;109(7):976-80.

95. Armstrong EJ, Harskamp CT, Armstrong AW. Psoriasis and major adverse cardiovascular events: a systematic review and meta-analysis of observational studies. J Am Heart Assoc. 2013 Apr 4;2(2):e000062.

96. Prodanovich S, Ma F, Taylor JR, Pezon C, Fasihi T, Kirsner RS. Methotrexate reduces incidence of vascular diseases in veterans with psoriasis or rheumatoid arthritis. J Am Acad Dermatol. 2005 Feb;52(2):262-7.

97. Ahlehoff O, Skov L, Gislason G, Gniadecki R, Iversen L, Bryld LE, et al. Cardiovascular outcomes and systemic anti-inflammatory drugs in patients with severe psoriasis: 5-year follow-up of a Danish nationwide cohort. J Eur Acad Dermatol Venereol. 2015 Jun;29(6):1128-34.

98. Ridker PM, Danielson E, Fonseca FA, Genest J, Gotto AM Jr, Kastelein JJ, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. N Engl J Med. 2008 Nov 20;359(21):2195-207.

99. Strober B, Teller C, Yamauchi P, Miller JL, Hooper M, Yang YC, et al. Dann F. Effects of etanercept on C-reactive protein levels in psoriasis and psoriatic arthritis. Br J Dermatol. 2008 Aug;159(2):322-30.

100. Ahlehoff O, Hansen PR, Gislason GH, Frydland M, Bryld LE, Elming H, et al. Myocardial function and effects of biologic therapy in patients with severe psoriasis: a prospective echocardiographic study. J Eur Acad Dermatol Venereol. 2015 Apr 6.

101. Ahlehoff O, Skov L, Gislason G, Lindhardsen J, Kristensen SL, Iversen L, et al. Lasthein S, Gniadecki R, Dam TN, Torp-Pedersen C, Hansen PR. Cardiovascular disease event rates in patients with severe psoriasis treated with systemic anti-inflammatory drugs: a Danish real-world cohort study. J Intern Med. 2013 Feb;273(2):197-204.

102. Hansson GK. Inflammation, atherosclerosis, and coronary artery disease. N Engl J Med. 2005 Apr 21;352(16):1685-95.

103. W Casas JP, Shah T, Hingorani AD, Danesh J, Pepys MB. C-reactive protein and coronary heart disease: a critical review. J Intern Med. 2008 Oct;264(4):295-314.

104. Gonzalez-Gay MA, Gonzalez-Juanatey C, Martin J. Rheumatoid arthritis: a disease associated with accelerated atherogenesis. Semin Arthritis Rheum. 2005 Aug;35(1):8-17.

105. Nossent J, Cikes N, Kiss E, Marchesoni A, Nassonova V, Mosca M, et al. Current causes of death in systemic lupus erythematosus in Europe, 2000--2004: relation to disease activity and damage accrual. Lupus. 2007;16(5):309-17.

106. Van Leuven SI, Franssen R, Kastelein JJ, Levi M, Stroes ES, Tak PP. Systemic inflammation as a risk factor for atherothrombosis. Rheumatology (Oxford). 2008 Jan;47(1):3-7.

107. Giles JT, Szklo M, Post W, Petri M, Blumenthal RS, Lam G, et al. Coronary arterial calcification in rheumatoid arthritis: comparison with the Multi-Ethnic Study of Atherosclerosis. Arthritis Res Ther. 2009;11(2):R36.

108. Gabriel SE. Heart disease and rheumatoid arthritis: understanding the risks. Ann Rheum Dis. 2010 Jan;69 Suppl 1:i61-64.

109. Gladman DD. Mortality in psoriatic arthritis. Clin Exp Rheumatol 2008; 26(5 Suppl 51):S62-5.

110. *Miguel A González-Gay, Carlos González-Juanatey. Inflammation, endothelial function and atherosclerosis in rheumatoid arthritis. Arthritis Res Ther. 2012; 14(4): 122.

111. **Iván Ferraz-Amaro, Carlos González-Juanatey, Raquel López-Mejias, Leyre Riancho-Zarrabeitia, Miguel A. González-Gay. Metabolic Syndrome in Rheumatoid Arthritis. Mediators Inflamm. 2013; 2013: 710928.

112. Jacobsson LT, Turesson C, Gülfe A, Kapetanovic MC, Petersson IF, Saxne T, et al. Treatment with tumor necrosis factor blockers is associated with a lower incidence of first cardiovascular event in patients with rheumatoid arthritis. J Rheumatol 2005; 32:1213-8.

113. Gonzalez-Gay MA, De Matias JM, Gonzalez-Juanatey C, Garcia-Porrua C, Sanchez-Andrade A, Martin J, et al. Anti-tumor necrosis factor-α blockade improves insulin resistance in patients with rheumatoid arthritis. Clin Exp Rheumatol 2006; 24:83-86.

114. Gonzalez-Gay MA, Garcia- Unzueta MT, De Matias JM, Gonzalez-Juanatey C, Garcia-Porrua C, Sanchez-Andrade A, et al. Influence of anti-TNF-α-infliximab therapy on adhesion molecules associated with atherogenesis in patients with rheumatoid arthritis. Clin Exp Rheumatol 2006; 24:373-9.

115. Gonzalez-Gay MA, Llorca J, Garcia-Unzueta MT, Gonzalez-Juanatey C, De Matias JM, Martin J, et al. High-grade inflammation, circulating adiponectin concentrations and cardiovascular risk factors in severe rheumatoid arthritis. Clin Exp Rheumatol. 2008; 26:596-603.

116. Gonzalez-Gay MA, Garcia-Unzueta MT, Berja A, Gonzalez-Juanatey C, Miranda-Filloy JA, et al. Anti-TNF-alpha therapy does not modulate leptin in patients with severe rheumatoid arthritis. Clin Exp Rheumatol. 2009;27:222-8.

117. Miguel A Gonzalez-Gay, Carlos Gonzalez-Juanatey, Jose A Miranda-Filloy, Javier Martin, Maria T Garcia-Unzueta, Javier Llorca. Response to 'Infliximab therapy increases body fat mass in early rheumatoid arthritis independently of changes in disease activity and levels of leptin and adiponectin: a randomized study over 21 months. Arthritis Res Ther. 2011; 13(2): 404.

118. Gonzalez-Gay MA, Garcia-Unzueta MT, Gonzalez-Juanatey C, Miranda-Filloy JA, Vazquez-Rodriguez TR, De Matias JM, et al. Anti-TNF-alpha therapy modulates resistin in patients with rheumatoid arthritis. Clin Exp Rheumatol 2008; 26:311-6.

119. Mease PJ, Signorovitch J, Yu AP, Wu EQ, Gupta SR, Bao Y, et al. Impact of Adalimumab on Symptoms of Psoriatic Arthritis in Patients with Moderate to Severe Psoriasis: A Pooled Analysis of Randomized Clinical Trials. Dermatology 2010;220:1-7.

120. Puig L, Bordas X, Carrascosa JM, Daudén E, Ferrándiz C, Hernanz JM, et al. Documento de consenso sobre la evaluación y el tratamiento de la psoriasis moderada/grave del Grupo Español de Psoriasis de la Academia Española de Dermatología y Venereología. Actas Dermosifiliogr. 2009; 100:277-86.

121. Definition and diagnosis of diabetes mellitus and intermediate hyperglycaemia. Report of a WHO/IDF consultation. 2006. ISBN:9789241594936.

122. Feldman SR, Krueger GG. Psoriasis assessment tools in clinical trials. Ann Rheum Dis 2005; 64(suppl 2): 65-8, discussion 69-73.

123. Rich P, Scher RK. Nail Psoriasis Severity Index: a useful tool for evaluation of nail psoriasis. J Am Acad Dermatol 2003; 49:206-12.

124. Guidelines Committee. 2003 European Society of Hypertension–European Society of Cardiology guidelines for the management of arterial hypertension. J Hypertens 2003; 21:1011-53.

125. Gordillo-Moscoso A, Valadéz-Castillo JF, Mandeville PB, Hernández-Sierra JF. Comparison of equivalence and determination of diagnostic utility of min-mod and clamp methods for insulin resistance in diabetes free subjects: a meta-analysis. Endocrine. 2004 Dec;25(3):259-63.

126. Katz A, Nambi SS, Mather K, Baron AD, Follmann DA, Sullivan G, et al. Quantitative insulin sensitivity check index: a simple, accurate method for assessing insulin sensitivity in humans. J Clin Endocrinol Metab. 2000 Jul;85(7):2402-10.

127. Marra M, Campanati A, Testa R, Sirolla C, Bonfigli AR, Franceschi C et al. Effect of etanercept on insulin sensitivity in nine patients with psoriasis. Int J Immunopathol Pharmacol. 2007; 20:731-6.

128. Hallgren R, Berne C. Glucose intolerance in patients with chronic inflammatory diseases is normalized by glucocorticoids. Acta Med Scand 1983; 213:351-5.

129. Svenson KL, Pollare T, Lithell H, Hällgren R. Impaired glucose handling in active rheumatoid arthritis: relationships to peripheral insulin resistance. Metabolism 1988; 37:125-30.

130. Paolisso G, Valentini G, Giugliano D, Marrazzo G, Tirri R, Gallo M, et al. Evidence of peripheral impaired glucose handling in patients with connective tissue diseases. Metabolism 1991; 40:902-7.

131. Dessein PH, Joffe BI, Stanwix A, Botha AS, Moomal Z. The acute phase response does not fully predict the presence of insulin resistance and dyslipidemia in inflammatory arthritis. J Rheumatol 2002; 29:462-6.

132. Fukuzawa M, Satoh J, Qiang X, Miyaguchi S, Sakata Y, Nakazawa T, et al. Inhibition of tumor necrosis factor-alpha with anti-diabetic agents. Diabetes Res Clin Pract. 1999; 43:147-54.

133. Hotamisligil GS, Peraldi P, Budavari A, Ellis R, White MF, Spiegelman BM. IRS-1-mediated inhibition of insulin receptor tyrosine kinase activity in TNF-alpha- and obesity-induced insulin resistance. Science. 1996; 271:665-8.

134. Gonzalez-Juanatey C, Llorca J, Sanchez-Andrade A, Garcia-Porrua C, Martin J, Gonzalez-Gay MA. Short-term adalimumab therapy improves endo-thelial function in patients with rheumatoid arthritis refractory to infliximab. Clin Exp Rheumatol. 2006; 24:309-12.

135. Barnabe C, Martin BJ, Ghali WA. Systematic review and meta-analysis: anti-tumor necrosis factor α therapy and cardiovascular events in rheumatoid arthritis. Arthritis Care Res (Hoboken). 2011; 63:522-9.

136. Mäki-Petäjä KM, Hall FC, Booth AD, Wallace SM, Yasmin, Bearcroft PW, et al. Rheumatoid arthritis is associated with increased aortic pulse-wave velocity, which is reduced by anti-tumor necrosis factor-alpha therapy. Circulation. 2006; 114:1185-92.

137. Biyik I, Narin A, Bozok MA, Ergene O. Echocardiographic and clinical abnormalities in patients with psoriasis. J Int Med Res. 2006; 34:632-9.

138. Gonzalez-Juanatey C, Testa A, Garcia-Castelo A, Garcia-Porrua C, Llorca J, Ollier WE, et al. Echocardiographic and Doppler findings in long-term treated rheumatoid arthritis patients without clinically evident cardiovascular disease. Semin Arthritis Rheum. 2004; 33:231-8.

139. Dixon WG, Watson KD, Lunt M, Hyrich KL. Reduction in the incidence of myocardial infarction in patients with rheumatoid arthritis who respond to anti-tumor necrosis factor alpha therapy: results from the British Society for Rheumatology Biologics Register. Arthritis Rheum. 2007; 56:2905-12.

140. Wu JJ, Poon KY, Channual JC, Shen AY. Association between tumor necrosis factor inhibitor therapy and myocardial infarction risk in patients with psoriasis. Arch Dermatol. 2012; 148:1244-50.

141. Bacchetti T, Campanati A, Ferretti G, Simonetti O, Liberati G, Offidani AM. Oxidative stress and psoriasis: the effect of antitumour necrosis factor-α inhibitor treatment. Br J Dermatol. 2013; 168:984-9.

142. Nordestgaard BG, Chapman MJ, Ray K, Borén J, Andreotti F, Watts GF, et al. Lipoprotein(a) as a cardiovascular risk factor: current status. Eur Heart J. 2010; 31:2844-53.

143. Gualillo O, González-Juanatey JR, Lago F. The emerging role of adipokines as mediators of cardiovascular function: physiologic and clinical perspectives. Trends Cardiovasc Med 2007; 17(8): 275-83.

144. Gómez R, Conde J, Scotece M, Gómez-Reino JJ, Lago F, Gualillo O. What's new in our understanding of the role of adipokines in rheumatic diseases? Nat Rev Rheumatol 2011; 7(9): 528-36.

145. Otero M, Lago R, Gómez R, Lago F, Gómez-Reino JJ, Gualillo O. Leptin: a metabolic hormone that functions like a proinflammatory adipokine. Drug News Perspect 2006; 19(1): 21-6.

146. Beltowski J. Leptin and atherosclerosis. Atherosclerosis. 2006 Nov; 189(1): 47-60.

147. Nicklas BJ, Katzel LI, Ryan AS, Dennis KE, Goldberg AP. Gender differences in the response of plasma leptin concentrations to weight loss in obese older individuals. Obes Res 1997; 5(1): 62-8.

148. Miranda-Filloy JA, López-Mejias R, Genre F, Carnero-López B, Ochoa R, Diaz de Terán T, et al. Leptin and visfatin serum levels in non-diabetic ankylosing spondylitis patients undergoing TNF-α antagonist therapy. Clin Exp Rheumatol 2013; 31(4): 538-45.

149. Popa C, Netea MG, de Graaf J, van den Hoogen FH, Radstake TR, Toenhake-Dijkstra H, et al. Circulating leptin and adiponectin concentrations during tumor necrosis factor blockade in patients with active rheumatoid arthritis. J Rheumatol 2009; 36(4): 724-30.

150. Gonzalez-Gay MA, Garcia-Unzueta MT, Berja A, Gonzalez-Juanatey C, Miranda-Filloy JA, Vazquez-Rodriguez TR, et al. Anti-TNF-alpha therapy does not modulate leptin in patients with severe rheumatoid arthritis. Clin Exp Rheumatol 2009; 27(2): 222-8. (116)

151. Rho YH, Chung CP, Solus JF, Raggi P, Oeser A, Gebretsadik T, et al. Adipocytokines, insulin resistance, and coronary atherosclerosis in rheumatoid arthritis. Arthritis Rheum 2010; 62(5): 1259-64.

152. Dessein PH, Tsang L, Woodiwiss AJ, Solomon A. Effect of traditional cardiovascular risk factors on the independent relationship of leptin with atherosclerosis in rheumatoid arthritis. J Rheumatol 2014; 41(10): 2087-9.

153. Gonzalez-Gay MA, Garcia-Unzueta MT, Gonzalez-Juanatey C, Miranda-Filloy JA, Vazquez-Rodriguez TR, De Matias JM, et al. Anti-TNF-alpha therapy modulates resistin in patients with rheumatoid arthritis. Clin Exp Rheumatol 2008; 26(2): 311-6. (118)

154. Dessein PH, Tsang L, Woodiwiss AJ, Hsu HC, Norton GR, Solomon A. Leukocyte count influences the relationship of circulating resistin concentrations with advanced atherosclerosis in rheumatoid arthritis. Clin Exp Rheumatol 2014; 32(6): 989-990.

155. Gonzalez-Gay MA, Gonzalez-Juanatey C, Rodriguez-Rodriguez L, Miranda-Filloy JA, Martin J, Llorca J. Lack of association between adipokines and ghrelin and carotid intima-media thickness in patients with severe rheumatoid arthritis. Clin Exp Rheumatol 2011; 29(2): 358-9.

156. Miranda-Filloy JA, López-Mejias R, Genre F, Carnero-López B, Ochoa R, Diaz de Terán T, et al. Adiponectin and resistin serum levels in non-diabetic ankylosing spondylitis patients undergoing TNF-α antagonist therapy. Clin Exp Rheumatol 2013; 31(3): 365-71.

157. Takahashi H, Tsuji H, Ishida-Yamamoto A, Iizuka H. Serum level of adiponectin increases and those of leptin and resistin decrease following the treatment of psoriasis. J Dermatol. 2013; 40(6): 475-6.

158. Al-Daghri NM, Al-Attas OS, Alokail M, Draz HM, Bamakhramah A, Sabico S. Retinol binding protein-4 is associated with TNF-alpha and not insulin resistance in subjects with type 2 diabetes mellitus and coronary heart disease. Dis Markers. 2009; 26(3): 135-40.

159. Erikstrup C, Mortensen OH, Nielsen AR, Fischer CP, Plomgaard P, Petersen AM, et al. RBP-to-retinol ratio, but not total RBP, is elevated in patients with type 2 diabetes. Diabetes Obes Metab. 2009 Mar; 11(3): 204-12.

160. Sell H, Eckel J. Regulation of retinol binding protein 4 production in primary human adipocytes by adiponectin, troglitazone and TNF-alpha. Diabetologia. 2007 Oct; 50(10): 2221-3.

161. Dessein PH, Woodiwiss AJ, Norton GR, Tsang L, Solomon A. Independent associations of total and high molecular weight adiponectin with cardiometabolic risk and surrogate markers of enhanced early atherogenesis in black and White patients with rheumatoid arthritis: a cross-sectional study. Arthritis Res Ther 2013; 15: R128.

162. Dessein PH, Tsang L, Norton GR, Woodiwiss AJ, Solomon A. Retinol Binding protein 4 concentrations relate to enhanced aterosclerosis in obese patients with rheumatoid arthritis. PLoS One 2014; 9: e92739.

163. Sattar N, Nelson SM. Adiponectin, diabetes, and coronary heart disease in older persons: unraveling the paradox. J Cñin Endocrinol Metab 2008; 93: 3299-3301.

164. Ferraz-Amaro I, González-Gay MA, Diaz-González F. Retinol-binding protein 4 in rheumatoid arthritis-related insulin resistance and β-cell function. J Rheumatol. 2014 Apr; 41(4): 658-65.

165. Genre F, López-Mejías R, Miranda-Filloy JA, Ubilla B, Carnero-López B, Palmou-Fontana N, et al. Osteoprotegerin correlates with disease activity and endothelial activation in non-diabetic ankylosing spondylitis patients undergoing TNF-α antagonist therapy. Clin Exp Rheumatol 2014; 32: 640-646.

166. Dessein PH, López-Mejias R, González-Juanatey C, Genre F, Miranda-Filloy JA, Llorca J, et al. Independent relationship of osteoprotegerin concentrations with endothelial activation and carotid atherosclerosis in patients with severe rheumatoid arthritis. J Rheumatol 2014; 41: 429-436.

167. López-Mejias R, Ubilla B, Genre F, Corrales A, Hernández JL, Ferraz-Amaro I, et al. Osteoprotegerin concentrations relate independently to established cardiovascular disease in rheumatoid arthritis. J Rheumatol 2015; 42: 39-45.

168. Chandran V, Cook RJ, Edwin J, Shen H, Pellett FJ, Shanmugarajah S, et al. Soluble biomarkers differentiate patients with psoriatic arthritis from those with psoriasis without arthritis. Rheumatology (Oxford) 2010; 49: 1399-1405.

169. Angel K, Provan SA, Mowinckel P, Seljeflot I, Kvien TK, Atar D. The L-arginine/asymmetric dimethylarginine ratio is improved by anti-tumor necrosis factor-α therapy in inflammatory arthropathies. Associations with aortic stiffness. Atherosclerosis 2012; 225: 160-165.

170. Surdacki A, Nowicki M, Sandmann J, Tsikas D, Boeger RH, Bode-Boeger SM, *et al*. Reduced urinary excretion of nitric oxide metabolites and increased plasma levels of asymmetric dimethylarginine in men with essential hypertension. *J Cardiovasc Pharmacol* 1999; **33**: 652-658.

171. Böger RH, Bode-Böger SM, Szuba A, Tsao PS, Chan JR, Tangphao O, et al. Asymmetric dimethylarginine (ADMA): a novel risk factor for endothelial dysfunction: its role in hypercholesterolemia. *Circulation* 1998; **98**: 1842-1847.

172. Koschinsky ML. Novel insights into Lp(a) physiology and pathogenicity: more questions than answers? *Cardiovasc Hematol Disord Drug Targets* 2006; **6**: 267-278.