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PREVALENCIA DE LA ENFERMEDAD ARTERIAL PERIFÉRICA EN PACIENTES CON LUPUS ERITEMATOSO SISTÉMICO Y FACTORES DE RIESGO ASOCIADOS

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Sección 1

INTRODUCCION:

ESTADO ACTUAL DEL CONOCIMIENTO

1.1.-ATEROSCLEROSIS Y ENFERMEDAD ARTERIAL PERIFÉRICA

1.1.1.-Aterosclerosis: Patogenia y manifestaciones clínicas

La aterosclerosis es una enfermedad inflamatoria que afecta a las arterias de mediano y gran calibre, caracterizada por la presencia de placas de ateroma originadas en la íntima arterial. La aterosclerosis no es un proceso pasivo de depósito de lípidos en las paredes vasculares, sino que tiene una base inflamatoria subyacente en la que la interacción de múltiples mediadores inflamatorios causa cambios en el endotelio vascular, acelerando la formación de placas de ateroma [1-6].

De forma sucinta, los procesos que llevan a la formación de la placa de ateroma se inician con la disfunción endotelial, que puede producirse como consecuencia de diferentes agentes (pe. en respuesta al estrés hemodinámico producido por la hipertensión arterial). La disfunción endotelial se caracteriza por: 1) inhibición de la producción de óxido nitroso, lo que causa una disminución de la vasodilatación dependiente del endotelio; 2) incremento en la permeabilidad de la barrera endotelial; 3) activación de las células del endotelio. Esta activación endotelial es un estado proinflamatorio y procoagulante, en el que se facilita el paso de LDL al espacio subendotelial (en donde se acumulan y se modifican mediante oxidación formando las LDL oxidadas) y en el que se producen una variedad de moléculas quimiotácticas y de adhesión leucocitarias (VCAM-1, ICAM-1, selectina-E, IL-8, MCP-1 y M-CSF, entre otras). La expresión de estas moléculas puede ser inducida también por citoquinas proinflamatorias (como el TNFα o la IL-1) en el contexto de procesos inflamatorios o infecciosos. Las moléculas quimiotácticas y de adhesión leucocitarias inducen el reclutamiento de monocitos y linfocitos T, que se desplazan al espacio subendotelial; los monocitos se diferencian en macrófagos y fagocitan

mediante receptores *scavenger* las LDL oxidadas, transformándose en células espumosas. Este fenómeno marca el primer estadio de la lesión ateromatosa, la estría grasa, que puede observarse ya en la infancia (hacia los 10-12 años de edad). La activación endotelial facilita asimismo la migración de células musculares lisas desde la capa media hacia la íntima, en donde expresan un fenotipo caracterizado por una alta replicación y por la producción de proteínas de la matriz extracelular (pe. colágeno). Todos estos mecanismos se traducen en la formación de una placa fibrosa (observable hacia los 15-30 años de edad) y finalmente en una placa ateromatosa madura caracterizada por un núcleo central graso necrótico con un margen externo inflamatorio infiltrado por monocitos y linfocitos T y rodeado por una capa fibrosa formada por una matriz de proteínas extracelulares y por células musculares lisas.

Desde un punto de vista clínico, la aparición de ateromatosis se ve facilitada por una serie de factores de riesgo, entre los que destacan la edad, hipertensión arterial (HTA), diabetes mellitus (DM), dislipemia, obesidad, tabaquismo, estilo de vida sedentario y la existencia de antecedentes familiares de eventos cardiovasculares precoces. Las manifestaciones clínicas de la aterosclerosis aparecen cuando la placa ateromatosa crece causando estenosis arterial o cuando se produce la rotura de la capa fibrosa con formación de un trombo que causa estenosis u oclusión de la arteria o embolismo en territorio más distal. Dependiendo del territorio vascular afectado, las manifestaciones clínicas de la aterosclerosis son variadas y abarcan desde una enfermedad silente hasta la aparición de eventos vasculares agudos (infarto agudo de miocardio, accidente cerebrovascular isquémico, isquemia aguda intestinal…) o sintomatología isquémica crónica/recurrente (claudicación intermitente, ángor de esfuerzo, ángor intestinal…).

1.1.2.-Enfermedad arterial periférica: Definición, prevalencia y manifestaciones clínicas

En sentido amplio, la enfermedad arterial periférica (EAP) incluye toda afectación vascular que conduce a la estenosis, oclusión o dilatación aneurismática de las arterias con exclusión del territorio coronario (aorta, arterias cerebrales, arterias viscerales incluyendo las arterias renales y arterias de los miembros superiores e inferiores). Sin embargo, en la práctica clínica habitual el territorio cerebrovascular suele recibir una atención específica y no se incluye dentro del concepto EAP, de manera que habitualmente la expresión EAP se restringe a la afectación arterial de las extremidades, la aorta y las arterias viscerales, específicamente las renales [7]. A efectos del presente trabajo nos referiremos en exclusiva a la afectación arterial aterosclerótica en los miembros; dado que la arteriosclerosis apenas tiene repercusión clínica en los miembros superiores, a efectos prácticos EAP es sinónimo de arteriosclerosis de los miembros inferiores [8].

La prevalencia de EAP en la población general no se conoce con exactitud [9-13]. En estudios poblacionales en Estados Unidos la prevalencia de EAP es variable, según los grupos de edad y los diferentes estudios publicados. En la Encuesta de Salud y Nutrición Nacional Norteamericana (NHANES) se detecta una prevalencia de EAP del 2.5% en la sexta edad de la vida, y ésta asciende al 14.5% a partir de los 70 años [10]. En el caso del estudio PARTNERS, también en Estados Unidos y en una población de mayores de 70 años, la prevalencia de EAP es del 29% [11]. En nuestro entorno, diferentes estudios realizados en España muestran que la prevalencia de EAP en la población general oscila entre en el 4.5-8.5% [12]. La prevalencia de EAP se incrementa claramente con la edad: en personas de 50-59 años se sitúa en torno al 12%, mientras que en mayores de 80 puede alcanzar casi el 60% en la década de los 80 [13]. La prevalencia de

EAP en población joven parece ser algo mayor en varones respecto a las mujeres, si bien esta diferencia se va reduciendo hasta igualarse en edades avanzadas, aunque esto podría cambiar en los próximos años debido a la tendencia a la baja en el consumo de tabaco en hombres y al aumento de dicho consumo en mujeres [11]. En EEUU, la población afroamericana presenta una prevalencia de EAP mayor que la caucásica, prevalencia que es mayor en la población caucásica europea respecto a la población caucásica de EEUU [10,12].

La epidemiología de la EAP es la propia de la aterosclerosis, con una mayor prevalencia en personas con factores de riesgo vascular clásicos [9], tales como DM, HTA, tabaquismo, dislipemia y obesidad (definida como un índice de masa corporal igual o mayor de 30 o por un perímetro abdominal ≥102 cm en hombres y ≥88 cm en mujeres [14,15]); por ejemplo, aproximadamente un 25-30% de pacientes diabéticos tipo 2 y un 20-40% de pacientes con HTA presentan EAP [16]. El riesgo de aterosclerosis se incrementa con la edad y es mayor en personas con historia familiar de eventos vasculares precoces (en varones con edad <55 años y en mujeres con edad <65 años) [16]. Estos factores de riesgo con frecuencia aparecen de forma combinada en un mismo individuo, por lo que resulta de utilidad estratificar el riesgo de cada paciente mediante escalas adaptadas a la población en estudio (en nuestro entorno, la escala SCORE -*European Vascular Risk Systematic Coronary Risk Evaluation*- para población mediterránea [17]); analizar la prevalencia de EAP asociada a cada uno de los factores de riesgo puede ser importante para reclasificar el riesgo cardiovascular de un paciente concreto [12]. La prevalencia de EAP es asimismo muy alta en sujetos con enfermedad cardiovascular establecida en otros territorios, aunque frecuentemente curse de forma asintomática: uno de cada 2-3 pacientes con cardiopatía isquémica o ictus isquémico tienen EAP [12].

La expresión clínica de la EAP es muy variable y no existe una buena correlación entre la presencia de sintomatología y la gravedad [8,9]. En un cierto número de pacientes (hasta un 25% de los casos, según las series) puede cursar de forma silente (por ejemplo, personas con EAP grave pueden no referir dolor si llevan un estilo de vida sedentario o presentan otra comorbilidad que limite su capacidad de realizar ejercicio físico), mientras que en otros casos se manifiesta como claudicación intermitente (el síntoma más característico de la EAP, pero sólo presente en su forma típica en el 6-30% de los pacientes) o con síntomas atípicos o solapados con manifestaciones clínicas de otros procesos muy prevalentes (por ejemplo, estenosis de canal lumbar o coxartrosis). La presencia de claudicación intermitente no es siempre indicativa de EAP grave, ya que puede aparecer sintomatología en sujetos con vida muy activa y EAP de grado leve-moderado. Es frecuente además que muchos pacientes que presentan claudicación intermitente (entre el 10 y 50%) nunca hayan consultado a un médico acerca de este problema. Todas estas circunstancias hacen que la prevalencia de EAP detectada con estudios de valoración vascular "objetivos" (por ejemplo, índice tobillo-brazo o ecografía Doppler arterial de extremidades inferiores) sea muy superior a la prevalencia estimada por valoraciones clínicas, basadas en los síntomas referidos por el paciente, en el empleo de cuestionarios dirigidos a su detección o en los hallazgos de la exploración física [11].

1.1.3.- Índice Tobillo-Brazo: Valor diagnóstico y pronóstico en la EAP

El método objetivo más utilizado en la práctica clínica y en los estudios epidemiológicos para el diagnóstico de EAP es la medición del Índice Tobillo-Brazo (ITB). Esta técnica consiste en la toma de la presión arterial en ambos brazos y piernas con un esfigmomanómetro

calibrado mientras se localizan las arterias humeral y pedia en ambos lados con una sonda Doppler de 8 MHz de frecuencia. Se obtienen unos valores de presión arterial con los que se calcula el ITB, escogiéndose el valor más elevado de los brazos como denominador y los obtenidos en los pies como numerador [18]. La mayoría de los estudios definen la EAP como la presencia de un ITB ≤ 0.9. Con este criterio, en muchos de los estudios poblacionales se identifica una prevalencia de EAP (sintomática o asintomática) que triplica o cuadriplica la EAP detectada mediante cuestionarios clínicos o por la presencia de síntomas o hallazgos en de la exploración física [18]. Comparando los resultados del ITB con la angiografía, técnica considerada como el *gold standard* para el diagnóstico de EAP, se observa que el ITB tiene una sensibilidad del 95% y una especificidad cercana al 100% para detectar una estenosis de al menos el 50% de la luz arterial [19-21]. Esta gran precisión diagnóstica, unida a su fácil disponibilidad, la convierte en el método de elección para estudio de la EAP en la práctica clínica diaria.

Además de su utilidad diagnóstica, el ITB ha mostrado utilidad pronóstica, ya que la presencia de EAP con ITB patológico se ha relacionado en la población general (incluso en paciente con EAP asintomática) con la presencia de aterosclerosis extensa (con afectación de varios territorios vasculares), con un mayor riesgo de eventos cardiovasculares graves (infarto agudo de miocardio, accidente isquémico cerebro-vascular) y con una mayor mortalidad por causas tanto vasculares como no vasculares [22-25]. El estudio clásico de Jelnes *et al* [23] sobre la mortalidad a 10 años en pacientes con EAP detectada mediante ITB mostró un riesgo aumentado de mortalidad total respecto a pacientes sin EAP, con un RR 5.9 (IC95% 3.0-11.4, $p<0.005$), debido fundamentalmente a enfermedad cardiovascular en los territorios coronario y cerebro-vascular; aunque el aumento de mortalidad era mayor en los pacientes sintomáticos (fallecían el 60% a los 10 años, RR 11.2, IC 95% 4.5-27.9) también se observó un

aumento de mortalidad en pacientes con EAP asintomática (fallecían el 40% a los 10 años, RR 4.7, IC 95% 2.3-9.8). Por otra parte, el meta-análisis realizado por Fowkes *et al* [25], que incluía 16 estudios con 24.955 varones y 23.339 mujeres, mostró una mortalidad cardiovascular a los 10 años en hombres con ITB ≤ 0.9 del 18.7% (IC 95%, 13.3%-24.1%) frente al 4.4% en hombres con ITB normal (1.11-1.4) (IC 95%, 3.2%-5.7%), con una *Hazard Ratio* (HR) de 4, (IC 95%, 3.3-5.4); en mujeres con ITB ≤ 0.9 la mortalidad a 10 años era del 12.6% (IC 95%, 6.2%-19%) frente al 4,1% (IC 95%, 2.2%-6.1) en mujeres con ITB normal, lo que suponía una HR del 3,5% (IC 95%, 2.4-5.1); tanto en hombres como en mujeres las HR permanecían elevados incluso después del ajuste con el score de Framingham (2.9 y 3 respectivamente).

Por todo lo expuesto previamente podemos decir que el ITB nos sirve como herramienta de diagnóstico de la EAP en la población general y además nos puede identificar pacientes con un mayor riesgo de sufrir enfermedad vascular, tanto en el territorio periférico como en el coronario o cerebro-vascular.

1.2.-LUPUS ERITEMATOSO SISTÉMICO Y ATEROSCLEROSIS

1.2.1.-Lupus Eritematoso Sistémico

El lupus eritematoso sistémico (LES) es una enfermedad autoinmune crónica que típicamente cursa en brotes y que puede afectar simultánea o sucesivamente a diversos sistemas orgánicos, adoptando diferentes expresiones clínico-inmunológicas [26-28]. Aunque puede aparecer en cualquier momento de la vida, la edad de inicio suele ser entre los 15 y los 40 años, con una prevalencia más

alta en mujeres (relación mujeres/hombres de 9:1) y en personas con ancestros de origen africano o, en menor medida, hispano o asiático. Las manifestaciones clínicas del LES son muy variadas; entre las más frecuentes destacan la afectación renal (nefritis lúpica), hematológica (anemia hemolítica autoinmune, trombocitopenia autoinmune, linfopenia), mucocutánea (fotosensibilidad, lupus discoide, aftosis oral, *rash* malar), serosa (pericarditis, pleuritis), neurológica (psicosis, convulsiones, mielitis) o musculoesquelética (artritis, miositis), aunque puede afectarse prácticamente cualquier órgano o sistema. Desde el punto de vista inmunológico, la presencia de autoanticuerpos es característica de LES; los anticuerpos antinucleares (ANA) son positivos en prácticamente todos los pacientes (pero poco específicos), mientras que los anticuerpos anti-DNA (anti-DNA) son más específicos y su titulación se relaciona con la actividad de la enfermedad. Un cierto número de pacientes presenta asimismo anticuerpos frente a antígenos extraíbles del núcleo (ENA), entre los que cabe destacar los anticuerpos anti-Sm (muy específicos del LES), anti-RNP, anti-Ro, anti-La, anti-Jo 1, anti–ScL 70 y anti-centrómero; la presencia de ciertos anticuerpos se relaciona con un mayor riesgo de ciertas manifestaciones clínicas o asociación con otras enfermedades sistémicas autoinmunes (síndromes de solapamiento).

Al considerar las manifestaciones clínicas del LES hay que diferenciar claramente entre aquellas derivadas de la actividad inflamatoria de la enfermedad (y por lo tanto potencialmente reversibles) de las secuelas establecidas como consecuencia del propio LES o de sus complicaciones (daño irreversible); los eventos vasculares y sus secuelas entrarían dentro de la categoría de daño. Para evaluar la actividad de la enfermedad se utiliza el índice SLEDAI (*Systemic Lupus Erythematosus Disease Activity Index*) mientras que para estimar el daño acumulado se emplea el índice SLICC (*Systemic Lupus*

Erythematosus International Collaborating Clinics Damage Index) [29,30].

El diagnóstico de LES se basa en criterios clínicos e inmunológicos, que pueden ser muy diferentes entre distintos pacientes dado el amplio espectro clínico de la enfermedad. La introducción a partir de los años 70 de criterios de clasificación (con frecuencia utilizados incorrectamente como criterios diagnósticos) que recogen el amplio espectro de manifestaciones clínicas e inmunológicas del LES ha permitido efectuar estudios epidemiológicos y clínicos que han contribuido a conocer mejor la incidencia y prevalencia de la enfermedad, así como de sus principales manifestaciones clínicas; los últimos criterios clasificatorios del LES propuestos por EULAR/ACR son de 2019, con una elevada sensibilidad y especificidad [31-34].

Otra característica importante del LES es su asociación con el síndrome antifosfolípido (SAF) [35-38]. Aproximadamente un 40% de los pacientes con LES son portadores de anticuerpos antifosfolípido (anticoagulante lúpico y/o anticuerpos anticardiolipina y/o anticuerpos anti-β2 glicoproteína I), de los cuales a su vez un 40% van a presentar en algún momento manifestaciones clínicas de SAF. El SAF produce un estado de hipercoagulabilidad que se manifiesta en forma de trombosis arteriales, venosas o de pequeño vaso. Las manifestaciones clínicas más frecuentes del SAF son las trombosis (tromboembolismo venoso, en menor medida trombosis arteriales) y la morbilidad gestacional secundaria a insuficiencia placentaria por trombosis de pequeño vaso (pérdidas gestacionales precoces o tardías, gestación pretérmino, pre-eclampsia); sin embargo, el espectro clínico del SAF es muy amplio y se solapa en parte con las manifestaciones clínicas del LES: trombocitopenia, anemia hemolítica, microangiopatía trombótica renal, glomerulonefritis, enfermedad valvular cardiaca, manifestaciones neurológicas (convulsiones, deterioro cognitivo, mielitis transversa), *livedo reticularis*… [35]. El diagnóstico se establece en base a una

combinación de criterios clínicos e inmunológicos. Respecto al tratamiento, se recomienda realizar tromboprofilaxis primaria en todos los pacientes con LES portadores de anticuerpos antifosfolípido; el tratamiento en aquellos pacientes que han presentado manifestaciones trombóticas es la anticoagulación a largo plazo [37]. La presencia de SAF con manifestaciones trombóticas es un factor asociado con peor pronóstico en pacientes con LES, ya que se asocia con un mayor daño acumulado y una menor supervivencia [38].

Antes de la incorporación de los corticoides al tratamiento, el LES era frecuentemente una enfermedad rápidamente fatal, con una supervivencia a los cinco años inferior al 50%; la introducción de los corticoides al tratamiento del LES supuso un primer paso en la reducción de la mortalidad [39,40]. En los últimos 30 años, la investigación clínica centrada en el tratamiento de las manifestaciones inflamatorias de la enfermedad ha permitido que el arsenal terapéutico frente al LES se haya incrementado considerablemente [27,28,41], con un uso más ajustado de los corticoides (uso de bolos intravenosos en brotes agudos, dosis de mantenimiento menores por vía oral) [42-45], con la incorporación de los antipalúdicos como tratamiento de base en los pacientes con LES [46-49] y con el empleo de inmunosupresores [50-54] y terapias biológicas (rituximab, belimumab) [55-59] tanto en el tratamiento de los brotes agudos de la enfermedad como en el mantenimiento de la respuesta. Todo ello, unido a la mejora y desarrollo de otros tratamientos generales (antihipertensivos, antibióticos, trasplante renal) ha permitido una gran mejoría en el pronóstico y supervivencia a largo plazo de los pacientes con LES. Sin embargo, la mortalidad continúa siendo superior en pacientes con LES respecto a la de la población general (incluso ajustada respecto a otros factores como género, edad u origen étnico), en especial en personas jóvenes [60-62].

La mortalidad en pacientes con LES se produce como consecuencia de una amplia variedad de causas, que pueden agruparse en cuatro grandes grupos: la propia actividad de la enfermedad, las infecciones, las neoplasias y las complicaciones cardiovasculares [26-28, 60-63]. La importancia relativa de cada uno de estos grupos es diferente según el momento de la enfermedad (mortalidad precoz asociada principalmente a la actividad de la enfermedad e infecciones, mortalidad tardía causada por enfermedad cardiovascular y neoplasias) y ha ido cambiando en el transcurso de los años. Ya en 1976 Urowitz y Gladman [64] describieron un patrón bimodal de mortalidad en la cohorte de pacientes con LES de Toronto, con un pico de mortalidad precoz durante el primer año de enfermedad (debido a la actividad de la enfermedad y a las infecciones) y un pico de mortalidad tardío (una media de 8.6 años desde el diagnóstico de LES) asociado a la exposición prolongada a los corticoides y a una elevada incidencia de infarto de miocardio. En las últimas décadas se ha producido una disminución progresiva de la mortalidad precoz, gracias a los avances de los tratamientos del LES y sus complicaciones (por ejemplo, nefritis lúpica e infecciones), de forma que la enfermedad cardiovascular se ha convertido en la causa principal de mortalidad en pacientes con LES desde finales del pasado siglo [39,40,65], llegando a suponer la causa de muerte en el 50% de los pacientes en algunas series [60].

1.2.2.-La enfermedad vascular en los pacientes con LES

Los pacientes con LES tienen una prevalencia de enfermedad cardiovascular que se ha estimado es el doble que la de la población general y que aparece a edades más precoces [65]. Ya en el último cuarto del pasado siglo se reconoció que la prevalencia de IAM y angina de pecho era mayor en pacientes con LES, mientras que en estudios

necrópsicos se observó la presencia frecuente de aterosclerosis moderada o severa de grandes arterias independientemente de la causa del fallecimiento [66,67]. La prevalencia de aterosclerosis en pacientes con LES es mayor que en controles sanos independientemente del método diagnóstico utilizado (ecografía Doppler de carótidas para detectar la presencia de placas de ateroma o medir el engrosamiento de la íntima media, TAC de coronarias para medir la calcificación de las arterias coronarias mediante el score de Agatston) [68-70]. En muchos casos la aterosclerosis aparece de forma precoz, a edades más tempranas en comparación con la población general, con una prevalencia de aproximadamente el 13% en menores de 35 años y del 20% en menores de 45 años [40,68-71]. Como se ha indicado en el apartado anterior, las enfermedades cardiovasculares son una de las causas de muerte más comunes en pacientes con LES; este aumento de la mortalidad cardiovascular está en estrecha relación con el desarrollo de enfermedad coronaria y cerebrovascular [39,40,60,63,65,68-72]. Los datos publicados recientemente por Urowitz *et al* [73], correspondientes a una corte de seguimiento 1.848 pacientes (13.666 pacientes/año), sugieren que la incidencia de eventos vasculares debidos a aterosclerosis en pacientes con LES parece haber disminuido en los últimos años en comparación con los datos publicados previamente, lo que probablemente sea debido a un mejor control tanto de la actividad de la enfermedad como de los factores de riesgo clásicos para el desarrollo de aterosclerosis.

Los mecanismos implicados en la aparición de aterosclerosis precoz en pacientes con LES son múltiples, complejos y en muchos casos no bien conocidos a día de hoy. Desde un punto de vista patogénico, es probable que la interacción entre los mecanismos patogénicos inflamatorios de la aterosclerosis y los subyacentes en el propio LES expliquen en parte el elevado riesgo de aterosclerosis acelerada de estos pacientes, al igual que ocurre en otras enfermedades como la

artritis reumatoide [4,74,75]. La aterosclerosis es una enfermedad inflamatoria crónica que podría expresar ciertos fenómenos de autoinmunidad, como la presencia de autoanticuerpos (pe. dirigidos contra las LDL oxidadas o la β-2-glicoproteína I); la activación del sistema del complemento por parte de los inmunocomplejos formados por estos autoanticuerpos podría ser uno de los mecanismos inflamatorios de la aterosclerosis y podría estar incrementado en pacientes con LES. La unión de los anticuerpos anti-β-2-glicoproteína I con la β-2-glicoproteína I que se encuentra en la región subendotelial y en el límite entre íntima y media de las placas de ateroma podría jugar un papel en la aceleración de las lesiones ateroscleróticas que se observan en pacientes con LES, ya que puede inducir la expresión de moléculas de adhesión que facilitan el reclutamiento de monocitos. Ciertos autoanticuerpos que podrían estar relacionados patogénicamente con la aterosclerosis (IgG anti-apolipoproteína A-I, IgG anti-HDL) se encuentran significativamente elevados en pacientes con actividad inflamatoria de la enfermedad; la disfunción endotelial, que es un punto clave en el inicio de la lesión aterosclerosa, podría estar favorecida en pacientes con LES por la presencia de autoanticuerpos (anti-célula endotelial). Se ha sugerido asimismo el riesgo de aterosclerosis en el LES podría estar asociado a una alteración de la regulación de la apoptosis, que causaría un aumento de la muerte celular por apoptosis y degradación tisular: los pacientes con LES tienen niveles plasmáticos elevados de las formas solubles de receptores relacionados con la apoptosis celular y estos niveles elevados se asocian con la presencia de enfermedad cardiovascular (por ejemplo, aterosclerosis carotidea) y con un daño orgánico mayor [4,74-81].

Desde un punto de vista clínico, parece claro que una parte del riesgo cardiovascular en paciente con LES depende como es lógico de la presencia de factores de riesgo clásicos, cuya prevalencia es más

alta en estos pacientes que en la población general: edad, HTA, hipercolesterolemia, diabetes mellitus, tabaquismo obesidad y estado postmenopáusico se han asociado con un mayor riesgo de aterosclerosis en pacientes con LES [64,67,74,82-86]. Al igual que en la población general, el tratamiento de la HTA, la hipercolesterolemia y otros factores de riesgo vascular corregibles dentro de estrategias de prevención primaria o secundaria está recomendado en pacientes con LES [87,88]. Sin embargo, los factores de riesgo clásicos no parecen explicar completamente el incremento de riesgo de enfermedad cardiovascular que se observa en paciente con LES, de forma que las escalas utilizadas ordinariamente para el cálculo del riesgo vascular (por ejemplo, la escala Framingham) tienden a infravalorar el riesgo en estos pacientes [67,75,89,90].

Además de los factores de riesgo clásicos, existen factores relacionados con la propia enfermedad o con su tratamiento que explican en parte el mayor riesgo de aterosclerosis en el LES, entre los que destacan tres: la presencia de anticuerpos antifosfolípido (que como se indicó en el apartado anterior incrementan *per se* el riesgo de trombosis arteriales y venosas [35-38]), la actividad / tiempo de evolución de la enfermedad y el tratamiento con corticoides [82-85,91,92]. La asociación entre aterosclerosis y actividad de la enfermedad ha sido variable. Algunos estudios han encontrado una relación directa entre actividad (medida mediante la escala SLEDAI) y riesgo de IAM y/o accidente cerebrovascular mientras que otros no [72,74,93,94]; Manzi et al [83] encontraron una relación inversa entre actividad y aterosclerosis carotidea, mientras que en otros estudios no se ha encontrado ninguna relación entre actividad y progresión de la aterosclerosis [95,96]. La asociación entre tiempo de evolución de la enfermedad y aterosclerosis ha sido sin embargo más consistente: diferentes estudios han descrito una asociación significativa entre una mayor duración de la enfermedad y la presencia de placas carotideas

o calcificación coronaria; un mayor daño acumulado (medido con la escala SLICC) se ha relacionado asimismo con la enfermedad coronaria o la presencia de ateromatosis carotidea en pacientes con LES [74,83,91-93,95,98]. En lo referente al tratamiento corticoideo, inicialmente los corticosteroides se emplearon a dosis altas (por ejemplo, 1 mg/Kg/día de prednisona); posteriormente, se ha reconocido que el tratamiento prolongado con corticoides a dosis altas (lo que se traduce en una mayor dosis acumulada) es un factor claramente relacionado con un mayor daño acumulado y con un riesgo aumentado de aterosclerosis precoz y de eventos vasculares en pacientes con LES, por lo que en la práctica clínica actual se han incorporado diferentes estrategias para reducir la dosis acumulada de corticoides (empleo de dosis diarias de prednisona inferiores a 7.5 mg y de inmunosupresores en el tratamiento de mantenimiento, uso de bolos de corticoides intravenosos en situaciones agudas de actividad de la enfermedad) [41-45,82,83]. Por otra parte, el efecto beneficioso sobre la supervivencia de los pacientes con LES que han demostrado los antipalúdicos está relacionado en parte con un efecto antitrombótico [46,48].

1.2.3.-Enfermedad arterial periférica en los pacientes con LES

A diferencia de la enfermedad coronaria y cerebrovascular, la EAP ha sido menos estudiada en pacientes con LES. Algunos estudios transversales y de casos controles han descrito una prevalencia de EAP en pacientes con LES de aproximadamente el 10-40%, identificando una asociación entre EAP y alguno de los factores de riesgo clásicos (edad, tabaquismo, hipercolesterolemia) [99-102]; en el estudio de Tziomalos *et al* [102], en el que se comparaban 55 pacientes con LES y 61 controles, no se observó que la prevalencia de EAP (identificada

mediante ITB) fuera diferente de los controles una vez ajustados los factores de riesgo vascular. En otros dos trabajos se ha mencionado la realización de un ITB en pacientes con LES [103-104], pero dentro de estudios de rigidez arterial y sin apenas aportar información clínica, salvo que un 4% de los pacientes tenían un ITB patológico en el trabajo de Tso *et al* [104]. Más recientemente (2019 y 2020) se han publicado dos meta-análisis sobre la enfermedad arterial periférica en los pacientes con LES y en ambos identifican una mayor prevalencia de EAP en los pacientes con LES respecto a los controles, aunque con una gran heterogeneidad en ambos trabajos [105,106].

En resumen, se trata de estudios no prospectivos con un número reducido de pacientes, o meta-análisis con una gran heterogeneidad, por lo que es difícil establecer grandes conclusiones.

Sección 2

HIPÓTESIS Y OBJETIVOS

2.1.-HIPÓTESIS

Como hemos visto en el apartado anterior, los pacientes con LES presentan una prevalencia de aterosclerosis mayor que la población general y a edades más tempranas. Esta prevalencia aumentada explica el mayor riesgo de sufrir eventos vasculares arteriales observado en estos pacientes en comparación con la población general, sobre todo en el subgrupo de pacientes más jóvenes. Los factores de riesgo relacionados con esta mayor prevalencia de aterosclerosis son tanto los factores de riesgo vascular clásicos como factores de riesgo específicos del LES, entre los que destacan la propia actividad inflamatoria de la enfermedad LES o los fármacos utilizados en el tratamiento, en especial los corticoides. La aterosclerosis y los eventos vasculares arteriales en pacientes con LES han sido estudiados especialmente en los territorios coronario y cerebral; por el contrario, la EAP en pacientes con LES ha recibido poca atención.

En base a estas consideraciones, las hipótesis que planteo en esta tesis son las siguientes:

HIPÓTESIS 1: La prevalencia de EAP en los pacientes con LES podría ser superior a la de la población general, al igual que otras manifestaciones ateroscleróticas.

HIPÓTESIS 2: La presencia de EAP en pacientes con LES se asocia probablemente con una serie de factores de riesgo cardiovascular, tanto tradicionales (por ejemplo, tabaquismo, HTA, dislipemia, diabetes mellitus, síndrome metabólico) como específicos del LES (por ejemplo, actividad inflamatoria de la enfermedad o tratamiento con corticoides).

HIPÓTESIS 3: La influencia de los factores de riesgo vascular asociados a EAP en pacientes con LES podría variar dependiendo de la edad, siendo más importantes los específicos del LES en los pacientes más jóvenes y los factores de riesgo tradicionales en los pacientes de mayor edad.

HIPÓTESIS 4: La presencia de un ITB patológico podría permitir la identificación de un subgrupo de pacientes con LES con un mayor riesgo de eventos vasculares arteriales a largo plazo.

2.2.-OBJETIVOS

Teniendo en cuenta las hipótesis anteriormente expuestas, se plantean en esta tesis cuatro objetivos:

OBJETIVO 1: Analizar la prevalencia de EAP en pacientes con LES.

OBJETIVO 2: Analizar los factores de riesgo potencialmente asociadas a la EAP en pacientes con LES.

OBJETIVO 3: Analizar la influencia de los factores de riesgo para la EAP en diferentes grupos de edad de pacientes con LES.

OBJETIVO 4: Determinar el potencial valor predictivo del ITB para la aparición de eventos vasculares arteriales en pacientes con LES.

Sección 3

METODOLOGÍA

3.1.-DISEÑO DE LOS ESTUDIOS

Se han diseñado y realizado tres estudios con la finalidad de conseguir los objetivos planteados en el apartado anterior, además de un cuarto trabajo de revisión del síndrome metabólico en los pacientes con LES.

- ESTUDIO 1: Estudio transversal para determinar la prevalencia de EAP en pacientes LES e identificar los factores de riesgo potencialmente asociados con la EAP.
- ESTUDIO 2: Editorial sobre el síndrome metabólico en pacientes con LES.
- ESTUDIO 3: Estudio transversal para analizar la influencia de los factores de riesgo para la EAP en función de la edad.
- ESTUDIO 4: Estudio prospectivo de seguimiento a 5 años para determinar el valor predictivo del ITB para la aparición de eventos vasculares arteriales.

3.2.-POBLACIÓN A ESTUDIO

Se incluyeron los estudios 216 pacientes pertenecientes a la cohorte prospectiva observacional Lupus-Cruces, atendidos en la Unidad de Enfermedades Autoinmunes del Servicio de Medicina Interna del Hospital Universitario Cruces (OSI Ezkerraldea-Enkarterri-Cruces) de Barakaldo, hospital terciario asociado a la Universidad del País Vasco / Euskal Herriko Unibertsitatea. Los 216 pacientes fueron atendidos de forma consecutiva desde enero de 2010 hasta junio de 2011. En el momento de su inclusión en el estudio todos los pacientes cumplían 4 o más los criterios de clasificación de 1997 del *American College of Rheumatology* (ACR), que se indican en la tabla 3.1 [32].

Tabla 3.1: Criterios revisados en 1997 del ACR para la clasificación del LES
Eritema malar.
Lupus discoide.
Fotosensibilidad.
Úlceras (aftas) orales.
Artritis (no erosiva).
Serositis (pleuritis o pericarditis).
Nefritis (proteinuria superior a 0,5 gr/día o cilindruria).
Afectación del SNC (convulsiones o psicosis).
Afectación hematológica (anemia hemolítica, leucopenia, linfopenia o trombopenia).
Alteración inmunológica: Anticuerpos anti-DNA, anticuerpos anti-Sm, serología luética falsamente positiva o anticuerpos antifosfolípido positivos.
Anticuerpos antinucleares.

3.3.-<u>PROTOCOLO DE SEGUIMIENTO</u>

En el momento de entrada al estudio se realizó a cada paciente:

1.-Entrevista clínica, que incluía una anamnesis dirigida para sintomatología sugerente de claudicación intermitente.

2.-Exploración física, con medida de peso, talla, altura, perímetro abdominal y cálculo del índice de masa corporal.

3.- ITB. El ITB se realizó por dos médicos del Servicio de Medicina Interna del Hospital Universitario Cruces (Dr. Jose Gabriel Erdozain y Dr. Javier Nieto) entrenados en la realización de esta prueba. Se utilizó

una sonda Doppler de 8MHz (MD2/SD2 *Dopplex High Sensitivity Pocket Doppler*) y un esfigmomanómetro calibrado. Se realizó toma de presión arterial en ambos brazos (arteria humeral), tomando como referencia el valor más elevado (denominador); y se tomó la presión arterial en ambas arterias pedias o tibiales posteriores (numerador). Se obtuvieron dos medidas de ITB por paciente, escogiéndose la medida más baja de ambas [18]. Se consideró patológico cuando el ITB ≤0,9.

Los pacientes fueron valorados durante el seguimiento en consultas de forma rutinaria cada 3-6 meses (2-4 visitas anuales), salvo que existieran circunstancias clínicas que obligaran a visitas más frecuentes. Se realizó un seguimiento de 5 años, hasta junio de 2016 (momento en el que cumplió 5 años de seguimiento el último paciente incluido).

Las variables incluidas en los estudios, recogidas el momento de la entrada en el estudio y durante el seguimiento, se detallan en el siguiente apartado.

3.4.-VARIABLES RECOGIDAS PARA LOS ESTUDIOS

En el momento de inclusión de los pacientes en el estudio y durante el seguimiento se recogieron las siguientes variables (entre paréntesis cómo se codificaron en la base de datos):

- Variables demográficas: edad (años), edad al diagnóstico de LES (años), edad a la realización de ITB (años), sexo (mujer/hombre) y raza (caucásica, afro-americana, asiática, árabe).

- Variables antropométricas: talla (cm), peso (Kg), perímetro abdominal (cm; codificado como perímetro abdominal aumentado si ≥102 cm en hombres y ≥88 cm en mujeres).
- Manifestaciones clínicas del LES: duración del LES (años), nefritis lúpica (si/no), síndrome antifosfolípido (si/no), lupus neuropsiquiátrico (si/no).
- Perfil de autoanticuerpos: anti-DNA (si/no), anti-Ro/SSA (si/no), anti-La/SSB (si/no), anti-RNP (si/no), anti-Sm (si/no), anticuerpos antifosfolípido (si/no).
- Tratamientos del LES: corticoides (si/no), inmunosupresores (azatioprina, micofenolato de mofetilo, ciclofosfamida) (si/no), antipalúdicos (si/no).
- Índices de actividad y daño: SLICC *damage index* (SDI) y SLEDAI.
- Factores de riesgo vascular: historia familiar de eventos vasculares precoces (varones con edad<55 años, mujeres con edad <65 años, si/no), HTA (definida como dos determinaciones consecutivas de al menos 140/90 mmHg o tratamiento antihipertensivo, si/no), diabetes mellitus (definida como dos determinaciones de glucosa basal ≥126 mg/dl o tratamiento antidiabético, si/no), hipercolesterolemia (definida como dos determinaciones consecutivas de colesterol total >200 mg/dl o tratamiento hipolipemiante, si/no), síndrome metabólico (según la definición del *Adult Treatment Panel* III [15], si/no), tabaquismo previo o actual (si/no), actividad física (definida como ejercicio aeróbico 1 hora al día al menos 3 días por semana, si/no), y menopausia en mujeres (si/no).
- Tratamientos relacionados con enfermedad cardiovascular (con una duración de al menos 6 meses): Antiagregación (si/no), anticoagulación (si/no), estatinas y/o fibratos (si/no).

- Estratificación del riesgo cardiovascular, según la escala SCORE para población mediterránea [17], considerándose bajo riesgo (<1%), riesgo moderado (1-4%), riego alto (5-10%), y riesgo muy alto (>10%).
- ITB patológico (≤0,9) (si/no).

En el momento de la inclusión de los pacientes en el estudio se identificó la presencia o no de daño de órgano diana subclínico o eventos cardiovasculares previos, definidos con la presencia de signos y síntomas compatibles confirmados con las pruebas diagnósticas (analíticas, funcionales o de imagen) adecuadas según la práctica clínica habitual:

- Hipertrofia ventricular izquierda, definida según criterios en ECG o en ecocardiograma (si/no).
- Microalbuminuria, definida como 30-300 mg/día (si/no).
- Retinopatía avanzada (grado IV), definida por la presencia de hemorragias y/o exudados y/o papiledema (si/no).
- Enfermedad renal crónica, definida por un aclaramiento de creatinina calculado inferior a 60 ml/min/1,73 m2 (si/no).
- Enfermedad coronaria, ángor, infarto agudo de miocardio: definidos por la presencia de dolor torácico típico, hallazgos electrocardiográficos y elevación de marcadores de daño miocárdico, hallazgos en prueba de esfuerzo o coronariografía (si/no).
- Enfermedad cerebrovascular, definida por manifestaciones neurológicas compatibles con hallazgos en TC o RM (si/no).
- Accidente isquémico transitorio, definido como síntomas focales neurológicos compatibles de menos de 24 h de duración (si/no).
- Enfermedad arterial periférica, definida por la presencia de claudicación intermitente y/o hallazgos en ecografía Doppler, angioTC, angioRM o arteriografía (si/no).

Durante el seguimiento se registraron:

- Los brotes de lupus, definidos como cualquier manifestación clínica de lupus que implica el uso de altas dosis de corticosteroides, el uso de un nuevo inmunosupresor o el aumento de la dosis de algún inmunosupresor utilizado previamente.
- Los eventos vasculares arteriales (EVA): eventos coronarios (angina de pecho, infarto agudo de miocardio, revascularización coronaria por angioplastia o cirugía), eventos cerebro-vasculares (accidente isquémico transitorio, ictus isquémico o hemorrágico), enfermedad arterial periférica (claudicación intermitente, isquemia distal, revascularización por angioplastia o cirugía).
- Muerte relacionada con enfermedad vascular o por otras causas.

3.5.-ANÁLISIS ESTADÍSTICO

Se han empleado los programas SPSS 20.0 para Mac OS X (SPSS Inc.) y Stata 14.2 para Windows (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP).

Los análisis estadísticos detallados se describen en la 'Sección 4 – Resultados', en el apartado correspondiente de cada uno de los tres artículos publicados. A modo de resumen, los análisis estadísticos realizados han sido los siguientes:

1) Descripción de las variables. Las variables continuas con distribución normal se describen con media y desviación

estándar, las variables continuas de distribución no normal con mediana y rango y las variables categóricas con frecuencias relativas y porcentajes. La normalidad de las variables continuas ha sido confirmada con las pruebas estadísticas apropiadas.

2) Análisis univariantes: para identificar las asociaciones entre variables independientes y variable dependiente se realizaron los análisis univariantes apropiados (Chi cuadrado, T de Student). Aquellas variables con un valor p <0.1 fueron seleccionadas para su inclusión en los análisis multivariantes.
3) Análisis multivariantes: regresión logística con eliminación secuencial de variables no significativas, análisis de riesgos competitivos (*Competing Risk Regression - Sub-distribution Hazard Ratios –SHR-*).

3.6.-ASPECTOS ÉTICOS

El Comité Ético del Hospital Universitario Cruces aprobó el protocolo del estudio (CEIC E09/07), en conformidad con el acuerdo de la Declaración de Helsinki. Todos los pacientes fueron informados y firmaron un consentimiento informado a la entrada en el estudio, garantizándose la confidencialidad del manejo de los datos obtenidos.

Sección 4

DESCRIPCIÓN DE LA COHORTE

4.1.-VARIABLES DEMOGRÁFICAS Y RELACIONADAS CON EL LES

La cohorte está formada por 216 pacientes, de los cuales 200 (92%) son mujeres. Se trata de una cohorte muy homogénea desde el punto de vista étnico: 209 (96%) pacientes son de raza blanca, 3 afro-caribeños, 2 sudamericanos y 2 árabes. La edad media (DE) al diagnóstico de LES era de 36 (15) años, mientras que la edad media (DE) en el momento de la realización del ITB era de 49 (15) años, con un tiempo de seguimiento medio de 12 (9) años. El conjunto de variables demográficas y variables relacionadas con el LES se muestran en la tabla 4.1.

4.2.-VARIABLES RELACIONADAS CON EL RIESGO CARDIOVASCULAR, DAÑO EN ÓRGANO DIANA Y EVENTOS CARDIOVASCULARES PREVIOS

Los factores de riesgo vascular tradicionales son muy prevalentes en la cohorte de pacientes estudiados: 162 pacientes (74.7%) tienen al menos un factor de riesgo; 21 pacientes cumplen criterios de síndrome metabólico, de acuerdo a ATP III; 11 pacientes presentaban un índice SCORE igual o superior a 5, lo que significa un riesgo cardiovascular alto o muy alto (tabla 4.2).

Respecto al daño en órganos diana, la hipertrofia ventricular izquierda estaba presente en 15/216 (7%) pacientes, la microalbuminuria en 39/196 (20%) pacientes, mientras que la retinopatía avanzada no se encontró en ningún caso. 22/216 pacientes (22%) presentaban algún grado de insuficiencia renal, en la mayor parte de los casos como consecuencia de nefritis lúpica previa. Un total

de 26/216 pacientes (12%) tenían antecedente de al menos un evento cardiovascular: 6/216 (2,8%) cardiopatía isquémica y/o insuficiencia cardiaca, 19/216 (8,8%) ictus y 3/216 (1,4%) enfermedad arterial periférica (tabla 4.3).

Tabla 4.1. Variables demográficas y clínicas de la cohorte (N=216)

Edad al ITB, años, media (DE)	49 (15)
Edad al diagnóstico de LES, años, media (DE)	36 (15)
Sexo: mujer	200 (92%)
Duración del LES, años, mediana (rango)	11 (0-37)
Raza: Caucásica	209 (96%)
Afro-caribeño	3 (1,3%)
Hispano	2 (0,9%)
Árabe	2 (0,9%)
Autoanticuerpos: Anti-DNA	106 (48,8%)
Anti-Ro	70 (32,3%)
Anti-La	18 (8%)
Anti-RNP	30 (13,8%)
Anti-Sm	29 (13,4%)
aFL	75 (34,6%)
Nefritis lúpica	60 (27,6%)
SAF	21 (9,7%)
LES neuropsiquiátrico	5 (2,3%)
SDI al ITB	
0	98 (45,2%)
1	53 (24,4%)
2	31 (14,3%)
3	19 (8,8%)
4	11 (5,1%)
5	4 (1,8%)
8	1 (0,5%)
SLEDAI al ITB	
0	104 (48,1%)
1-5	91 (42,2%)
≥6	21 (9,7%)
Uso de prednisona: si/no	191/25
Dosis media diaria de prednisona, mg/día, media (DE)	5,6 (8,2%)
Dosis máxima de prednisona, mg/día, media (DE)	30.8 (25,9%)
Dosis acumulada de prednisona (gramos)	
Media (DE)	18.7 (57)
Mediana (RIQ)	7.32 (0-177,6)
Uso de hidroxicloroquina: si/no	193 (89,3%)
Uso de fármacos inmunosupresores	
Ciclofosfamida	52 (24%)
Micofenolato mofetilo	34 (15,7%)
Azatioprina: si/no	64 (29,6%)
Uso de estatinas: si/no	73 (33,7%)
Uso de antiagregantes: si/no	103 (47,6%)
Uso de anticoagulantes: si/no	26 (12%)

aFL: anticuerpos antifosfolípido; ITB: índice tobillo-brazo; LES: lupus eritematoso sistémico; RIQ: rango intercuartil; SAF: síndrome antifosfolipido; SDI: SLEDAI: SLE Disease Activity Index; SLICC Damage Index.

Tabla 4.2. Prevalencia de los factores de riesgo vascular (n=216)

Historia familiar de eventos vasculares precoces	25 (11,5%)
Tabaquismo activo	65 (30%)
Exposición tabaco (actual o previa)	109 (50,2%)
Consumo de alcohol	26 (12%)
Sedentarismo	97 (44,9%)
Obesidad abdominal	73 (33,6%)
Diabetes mellitus	7 (3,2%)
Hipertensión arterial	71 (32,7%)
Hipercolesterolemia	74 (34,1%)
Síndrome metabólico (ATP III)	21 (9,7%)
IMC Bajo peso Normopeso Sobrepeso Obesidad Obesidad mórbida	 20 (9,3%) 86 (39,8%) 69 (31,8%) 36 (16,6%) 5 (2,3%)
SCORE 0-4 ≥5	 205 (95%) 11 (5%)
Variable combinada de factores de riesgo vascular (Diabetes mellitus o hipertensión arterial o hipercolesterolemia o tabaquismo previo o actual)	162 (74,7%)

Tabla 4.3. Prevalencia del daño de órgano diana y de los eventos cardiovasculares (n=216)

Hipertrofia ventricular izquierda	15 (6,9%)
Microalbuminuria*	65 (30%)
Cardiopatía isquémica o insuficiencia cardiaca	6 (2,8%)
Ictus	19 (8,8%)
Enfermedad renal crónica	22 (10%)
Enfermedad arterial periférica	3 (1,4%)
Retinopatía avanzada	0 (0%)
Cualquier evento vascular (cardiopatía isquémica/insuficiencia cardiaca, ictus, enfermedad renal crónica, enfermedad arterial periférica)	26 (12%)

*196 pacientes.

Sección 5

RESULTADOS

5.1.-ESTUDIO 1

Peripheral Arterial Disease in Systemic Lupus Erythematosus: Prevalence and Risk Factors.

Jose Gabriel Erdozain, Irama Villar, Javier Nieto, Guillermo Ruiz-Irastorza.

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Peripheral Arterial Disease in Systemic Lupus Erythematosus: Prevalence and Risk Factors

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Peripheral Arterial Disease in Systemic Lupus Erythematosus: Prevalence and Risk Factors

Jose Gabriel Erdozain, Irama Villar, Javier Nieto, and Guillermo Ruiz-Irastorza

ABSTRACT. ***Objective.*** To analyze the prevalence of peripheral arterial disease (PAD) and cardiovascular (CV) risk factors in a cohort of patients with systemic lupus erythematosus (SLE) and to identify variables potentially related to PAD.

Methods. The study included 216 patients with SLE from the Lupus-Cruces prospective observational cohort. The ankle brachial index (ABI) was determined in each patient, with values < 0.9 considered diagnostic of PAD. Demographic and clinical variables, presence of traditional risk factors and CV events, cardiovascular risk calculated by Systematic Coronary Risk Evaluation (SCORE), and treatments received by each patient were analyzed.

Results. Ninety-two percent of patients were women. The mean age (SD) was 49 years (15), with a mean followup (SD) of 12 years (9). The prevalence of low ABI was 21%. CV risk factors were frequent: smoking, 30% of patients; high blood pressure, 32.7%; diabetes mellitus, 3.2%; hypercholesterolemia, 34.1%; and metabolic syndrome, 9.7%. The following variables were associated with low ABI in the univariate analysis: age ($p < 0.001$), hypertension ($p = 0.002$), diabetes ($p = 0.018$), hypercholesterolemia ($p = 0.018$), CV events ($p < 0.001$), SCORE ($p = 0.004$), cumulative dose of cyclophosphamide ($p = 0.03$), and fibrinogen levels ($p = 0.002$). In the multivariate analysis, the only independent variable in the final model was age (OR 1.04, 95% CI 1.02–1.07, $p < 0.001$), with a tendency for the presence of any vascular risk factor (diabetes, hypertension, hypercholesterolemia, or current smoking; OR 2.3, 95% CI 0.99–5.1, $p = 0.053$).

Conclusion. The prevalence of low ABI in patients with SLE is higher than expected. While the association with CV risk factors and vascular disease in other territories was strong, we could not identify SLE-specific variables independently associated with PAD. (First Release Jan 15 2014; J Rheumatol 2014;41:310–17; doi:10.3899/jrheum.130817)

Key Indexing Terms:
SYSTEMIC LUPUS ERYTHEMATOSUS VASCULAR DISEASE HYPERTENSION
CARDIOVASCULAR RISK FACTORS ATHEROSCLEROSIS HYPERCHOLESTEROLEMIA

Patients with systemic lupus erythematosus (SLE) have an increased prevalence of cardiovascular (CV) disease. The bimodal pattern of mortality proposed by Urowitz, *et al* in 1976 described a late peak of mortality mainly due to atherosclerotic heart disease[1]. In different series, the prevalence of symptomatic coronary artery disease (CAD) ranged from 6 to 10%[1,2,3,4]. Women younger than 55 years of age with SLE have a 5-fold to 8-fold higher risk of developing CAD compared to women in the general population[2]. The risk of hospitalization for stroke has been shown to be 2-fold higher in patients with SLE[3].

Premature atherosclerosis has been primarily related to traditional vascular risk factors[2,4]. However [and despite the higher prevalence of hypertension (HTN) and hypercholesterolemia in patients with SLE compared with the general population], traditional Framingham CV risk factors fail to fully explain the increased CV morbidity and mortality seen in SLE[5]. Several studies have found an association between premature atherosclerosis and some SLE-related factors, such as disease duration, steroid therapy, or irreversible organ damage[2,4,5,6].

Peripheral arterial disease (PAD) is frequently asymptomatic and can be difficult to diagnose[7]. The development of noninvasive, simple techniques with low intraobserver and interobserver variability, such as the ankle-brachial index (ABI), has facilitated the detection of subclinical PAD[8]. An ABI lower than 0.9 is diagnostic of PAD with 95–99% accuracy[9]. Moreover, a low ABI has been related to a higher incidence of myocardial infarction and stroke and higher

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mortality, both vascular and nonvascular, in studies in the general European and North American populations[10,11].

The incidence, risk factors, and consequences of PAD have not been well studied in patients with SLE. Given the high risk for atherosclerotic disease in patients with SLE, subclinical PAD is possibly frequent and underdiagnosed, with potential prognostic implications. We aimed to study the prevalence of PAD in the Lupus-Cruces cohort and to analyze the associated vascular and nonvascular risk factors.

MATERIALS AND METHODS

Study objectives. The primary objective in this cross-sectional study was to determine the prevalence of PAD in patients with SLE. The secondary objective was to identify factors potentially associated with PAD.

Study population and variables. Consecutive patients within the Lupus-Cruces longitudinal observational cohort, at the Autoimmune Diseases Unit, Hospital Universitario Cruces (a tertiary teaching center in Barakaldo, Spain, associated with the University of the Basque Country), were invited to participate in our study between January 2010 and June 2011. All patients fulfilled the 1997 classification criteria of the American College of Rheumatology[12]. The local institutional review board of the Hospital Universitario Cruces approved the study protocol in compliance with the Helsinki Declaration. All patients signed an informed consent at the time of enrollment.

Patients were routinely assessed every 3 to 6 months, unless clinical status demands more frequent visits. On the other hand, patients on longterm remission were seen on a yearly basis. At each followup visit, a number of clinical and immunological variables from every patient were routinely collected in a database: demographic characteristics (age, sex, race, year of diagnosis), SLE manifestations, autoantibody profile (anti-DNA, anti-Ro, anti-La, anti-RNP, anti-Sm, antiphospholipid), treatments received (corticosteroids, immunosuppressives, antimalarials, anticoagulants, etc.), complications of the disease and/or treatment. Date of death and cause of death were recorded when appropriate. This database was completed with CV variables: presence of CV risk factors [age, defined as more than 55 and 65 years in men and women, respectively; arterial HTN, defined as 2 consecutive measurements of at least 140/90 mmHg or antihypertensive therapy; diabetes mellitus (DM), defined as 2 consecutive fasting blood glucose determinations ≥ 126 mg/dl or treatment with antidiabetic drugs; hypercholesterolemia, defined as total blood cholesterol fasting levels > 200 mg/dl on 2 consecutive determinations or treatment with cholesterol-lowering drugs; metabolic syndrome according to the Adult Treatment Panel III definition[13]; and current or past smoking], degree of physical exercise (aerobic exercise 1 h/day, at least 3 days a week), presence of previous subclinical organ damage [left ventricular hypertrophy (LVH), presence of microalbuminuria], previous CV events (previous coronary events, heart failure, cerebrovascular disease, renal disease, PAD, or advanced retinopathy), and CV disease-related treatments (aspirin, statins). CV events were defined as the presence of compatible clinical signs and symptoms and eventually confirmed by complementary tests: myocardial infarction was defined as typical chest pain with characteristic electrocardiographic features and elevated levels of creatine kinase (MB fraction) and/or T troponine; stroke by computed tomography (CT) scanning or magnetic resonance imaging; cerebral transient ischemic attacks (TIA) were diagnosed in the setting of acute focal neurologic symptoms/signs lasting < 24 h. CV risk stratification was performed using the European Vascular Risk Systematic Coronary Risk Evaluation (SCORE) scale for the Mediterranean population[14]. The Systemic Lupus International Collaborating Clinics damage index (SDI)[15] and the SLE Disease Activity Index (SLEDAI)[16] were calculated at the time of enrollment for each patient.

The size, weight, and waist and hip circumference were determined in each patient at the time of performing the ABI, along with calculation of the body mass index (BMI). ABI was performed in both legs to each patient in *ad hoc* scheduled visits, from January 2010 to June 2011. The MD2/SD2 Dopplex High Sensitivity Pocket Doppler was used for our study and all ABI were performed by the same 2 trained physicians working together with each patient. In every patient, 1 ABI was calculated for each leg, the lowest value being chosen. An ABI < 0.9 was considered abnormal.

To evaluate subclinical organ damage, the presence of microalbuminuria and LVH were tested. All patients collected an early morning urine sample to calculate the albumin/creatinine ratio. Data to calculate LVH were extracted from echocardiograms performed during a screening program for detecting pulmonary HTN in the whole Lupus-Cruces cohort[17].

Statistical analysis. The clinical descriptors of the cohort were generated, using means with SD, medians and ranges, or proportions. The total prevalence of PAD was calculated. The relation between the different SCORE categories and the normal/abnormal ABI was tested by McNemar test. To identify associations with PAD, the following independent variables were tested against the dependent variable "ABI lower than 0.9", using chi-square with Yates' correction or Student t-test: age at SLE diagnosis, age at the time of ABI, disease duration, sex, age as a vascular risk factor, abdominal obesity, metabolic syndrome, DM, HTN, hypercholesterolemia, smoking (current or past), any vascular risk factor (DM or HTN or hypercholesterolemia or current/past smoking), exercise, alcohol consumption, family history of premature CV disease, BMI, menopause, previous subclinical organ damage (LVH and microalbuminuria), previous CV events [ischemic heart disease and/or heart failure (IHD/HF), stroke, PAD], chronic renal failure, previous arterial thrombosis (stroke or IHD/HF or PAD), uric acid, vitamin D levels, previous lupus nephritis or antiphospholipid syndrome, anti-DNA, anti-Ro, anti-La, anti-U_1RNP, anti-Sm, and antiphospholipid antibodies (aPL; lupus anticoagulant and/or anticardiolipin antibodies at medium-high levels on at least 2 different determinations 12 weeks apart), SLEDAI, SDI, prednisone (cumulative dose and maximum dose ever received), hydroxychloroquine (yes/no and total dose), cyclophosphamide (cumulative dose), low-dose aspirin (number of months on treatment), anticoagulants (no. mos taking treatment), or statins (no. mos taking treatment) and fibrinogen levels at the time of the ABI. Those variables with a p value ≤ 0.1 in the univariate analysis were subsequently included in a backward stepwise logistic regression model to identify independent associations with PAD.

All statistical analysis was done using the software SPSS 20.0.0 statistical package for Mac OS X (SPSS Inc.).

RESULTS

Demographic and SLE-related variables. Two hundred sixteen patients were studied; 200 were women (92%). Two hundred nine patients (96%) were white, with the remaining consisting of 3 Afro-Caribbeans, 2 Hispanics, and 2 Arabs. The mean (SD) age at SLE diagnosis was 36 years (15). The mean age at the time of the ABI study was 49 (15) years, with a mean (SD) followup after SLE diagnosis of 12 (9) years. The remaining clinical and therapeutic variables are shown on Table 1.

CV risk factors, target organ damage, and previous CV events. Traditional CV risk factors were frequent in our cohort (Table 2). As a whole, 162 patients (74.7%) had at least 1 traditional CV risk factor. In terms of CV risk, 205 patients (95%) had a SCORE between 0 and 4 and 11 patients (5%) had a SCORE ≥ 5, which reveals a high or very high CV risk.

LVH was present in 15 patients (7%) and microalbu-

Table 1. Demographic and clinical characteristics of the cohort (n = 216). Values are expressed as n (%) unless otherwise noted.

Age at study, yrs, mean (SD)	49 (15)
Age at diagnosis of SLE, yrs, mean (SD)	36 (15)
Sex: female	200 (92)
SLE duration, yrs, mean (SD)	12 (9)
Autoantibodies	
Anti-DNA	106 (48.8)
Anti-Ro	70 (32.3)
Anti-La	18 (8)
Anti-RNP	30 (13.8)
Anti-Sm	29 (13.4)
Antiphospholipid antibodies	75 (34.6)
Lupus nephritis	60 (27.6)
Antiphospholipid syndrome	21 (9.7)
SDI at ABI	
0	98 (45.2)
1	53 (24.4)
2	31 (14.3)
3	19 (8.8)
4	11 (5.1)
5	4 (1.8)
8	1 (0.5)
SLEDAI at ABI	
0	104 (48.1)
1–5	91 (42.2)
≥ 6	21 (9.7)
Use of prednisone: y/n	191/25
Average daily dose of prednisone, mg/d, mean (SD)	5.6
Use of hydroxychloroquine:y/n	193/23
Use of immunosuppressive drugs	
Cyclophosphamide: y/n	52/164
Mycophenolate: y/n	34/182
Azathioprine: y/n	64/152
Use of statins: y/n	73/143

ABI: Ankle-brachial index; SDI: Systemic Lupus International Collaborating Clinics damage index; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index.

Table 2. Prevalence of cardiovascular risk factors, organ damage, and cardiovascular events in the full cohort (n = 216). Values are expressed as n (%).

Age as risk factor	41 (18.9)
Family history	25 (11.5)
Current smoking	65 (30)
Smoking (ever)	109 (50.2)
Alcohol	26 (12)
No exercise	97 (44.9)
Abdominal obesity	73 (33.6)
DM	7 (3.2)
Hypertension	71 (32.7)
Hypercholesterolemia	74 (34.1)
MS	21 (9.7)
BMI	
Low weight	20 (9.3)
Normal weight	86 (39.8)
Overweight	69 (31.8)
Obesity	36 (16.6)
Morbid obesity	5 (2.3)
Any vascular risk factor (DM, HBP, DLP, or current smoking)	162 (74.7)
LVH	15 (6.9)
Microalbuminuria*	39 (19.8)
IHD/HF	6 (2.8)
Stroke	19 (8.8)
CRD	22 (10)
PAD	3 (1.4)
Advanced retinopathy	0 (0)
Menopause	103 (50.7)
SCORE	
0	141 (65)
1	31 (14.3)
2	22 (10.1)
3	5 (2.3)
4	7 (3.2)
5	5 (2.3)
6	2 (0.9)
7	2 (0.9)
8	2 (0.9)
Any vascular event (stroke, IHD/HF, PAD, or CRD)	26 (12)

* Total sample: 196 patients, DM: diabetes mellitus; HBP: high blood pressure; DLP: dyslipoproteinemia; MS: metabolic syndrome; BMI: body mass index; LVH: left ventricular hypertrophy; IHD/HF: ischemic heart disease and/or heart failure; CRD: chronic renal disease; PAD: peripheral arterial disease; ABI: ankle-brachial index; SCORE: Systematic Coronary Risk Evaluation.

minuria in 39 of 196 patients (20%); 6 patients (2.8%) had ischemic heart disease and/or heart failure, 19 patients (8.8%) had a stroke, and 3 (1.4%) had symptomatic PAD. Advanced retinopathy was not found in any patient. As a whole, 26 patients (12%) had a history of at least 1 vascular event. In addition, 22 patients (10%) had some degree of chronic renal disease, mostly as a consequence of lupus nephritis.

Frequency and associations of low ABI. Forty-six of the 216 patients studied (21%) had an abnormal ABI (≤ 0.9). Compared with those with normal ABI, patients with low ABI were older at study date (mean age 57 vs 47 years, respectively, $p < 0.001$), were older at SLE diagnosis (mean age 43 vs 34 years, respectively, $p = 0.001$), and had more frequently age as a CV risk factor (32% vs 15%, $p = 0.014$). Women with a low ABI were more often postmenopausal (66% vs 47%, $p = 0.03$). Also, these patients had more traditional CV risk factors such as DM (8.7% vs 1.8%, $p = 0.018$), HTN (52.2% vs 27.5%, $p = 0.002$), and hypercholesterolemia (50% vs 29.8%, $p = 0.018$), and had more previous CV events, including IHD/HF (8.7% vs 1.2%, $p = 0.006$), stroke (17.4% vs 6.4%, $p = 0.02$), and previous arterial thrombosis (ischemic heart disease, stroke or PAD; 28.3% vs 7.6%, $p < 0.001$) than patients with a normal ABI. Patients with low ABI had more frequently at least 1 CV risk factor (presence of HTN, diabetes, hypercholesterolemia, or smoking ever) compared with patients with normal ABI (89.1% vs 70.8%, respectively, $p = 0.011$; Table 3). An increasing proportion of patients with a low ABI was seen paralleling SCORE values ($p = 0.004$; Table 4).

Among SLE-related variables, only higher fibrinogen levels (425 vs 378 mg, $p = 0.002$) and a lower cumulative

Table 3. Relationship between low ABI and cardiovascular variables (univariate analysis). Values are n (%) unless otherwise noted.

	Low ABI, n = 46	Normal ABI, n = 170	p
Age at SLE diagnosis, yrs, mean (SD)	43 (17)	34 (14)	0.001
Age at study, yrs, mean (SD)	57 (15)	47 (14)	< 0.001
Disease duration, yrs, mean (SD)	14 (10)	12 (9)	0.245
Sex (female)	41/46 (89)	158/170 (93)	0.394
Age as a vascular risk factor	15/46 (32)	26/170 (15)	0.007
Abdominal obesity	20/46 (43)	53/170 (31)	0.173
Metabolic syndrome	5/46 (11)	16/170 (9)	0.988
DM	4/46 (8.7)	3/170 (1.8)	0.018
HTN	24/46 (52.2)	47/170 (27.5)	0.002
Hypercholesterolemia	23/46 (50)	51/170 (29.8)	0.018
Current smoking	15,746 (33)	50/170 (29)	0.18
Smoking ever	24/46 (52)	84/170 (49)	0.74
Any vascular risk factor (DM, HTN, hypercholesterolemia, or current smoking)	37/46 (80)	99/170 (58)	0.005
Any vascular risk factor (DM, HTN, hypercholesterolemia, or ever smoking)	41/46 (89.1)	120/170 (70.8)	0.011
No exercise	20/46 (43)	77/170 (45)	0.82
Alcohol	5/46 (11)	21/170 (12)	0.36
Family history of CV disease	6/46 (13)	19/170 (11.2)	0.93
BMI: mean (SD)	26.7 (5.3)	25.5 (5.5)	0.2
Postmenopausal status*	27/41 (66)	75/161 (47)	0.03
Microalbuminuria**	7/40 (17)	32/156 (20)	0.67
Left ventricular hypertrophy	5/46 (11)	10/167 (6)	0.252
IHD/HF	4/46 (8.7)	2/170 (1.2)	0.006
PAD	2/46 (4.3)	1/170 (0.6)	0.052
Stroke	8/46 (17.4)	11/170 (6.4)	0.02
Chronic renal disease	4/46 (9)	18/170 (11)	0.707
Previous arterial thrombosis (stroke, IHD/HF, or PAD)	13/46 (28.3)	13/170 (7.6)	< 0.001
Uric acid, mg/dl: mean (SD)	4.47 (1.2)	4.49 (1.7)	0.94
D vitamin levels, ng/ml: mean (SD)	25.6 (11.7)	29.1 (27.3)	0.414

* Data calculated on 200 women. ** Total sample: 196 patients. SLE: systemic lupus erythematosus; DM: diabetes mellitus; HBP: high blood pressure; DLP: hypercholesterolemia; PAD: peripheral arterial disease; IHD/HF: ischemic heart disease and/or heart failure; ABI: ankle-brachial index; HTN: hypertension; CV: cardiovascular; BMI: body mass index.

Table 4. Prevalence of low ABI in the different SCORE risk groups.

SCORE	Low ABI (%)
0	17/140 (12)
1	11/31 (35)
2	7/22 (35)
3	2/5 (40)
4	3/7 (43)
5	3/5 (60)
6	1/2 (50)
7	1/2 (50)
8	1/2 (50)

p = 0.004. SCORE: Systematic Coronary Risk Evaluation; ABI: ankle- brachial index.

dose of cyclophosphamide (1.15 vs 2.74 g, p = 0.03) were significantly identified in patients with a low ABI compared with those with a normal ABI (Table 5).

After the multivariate analysis, the only independent variables in the final model were the age at the time of the ABI (OR 1.04, 95% CI 1.02–1.07, p < 0.001). There was a tendency for the presence of any vascular risk factor (DM, HTN, hypercholesterolemia, or current smoking; OR 2.3, 95% CI 0.99–5.1, p = 0.053; Table 6).

DISCUSSION

The prevalence of PAD in the general population is not well known, with 25% of patients being symptomatic. PAD is associated with a high frequency of vascular disease in other territories, such as the coronary (with a 4-fold higher risk of suffering a myocardial infarction) and cerebral arterial beds (with a 2-fold to 3-fold increased risk of stroke)[18]. Further, PAD is associated with a 3-fold increased mortality, mainly due to a 6-fold increased risk of coronary death[19]. Thus, the diagnosis of PAD, even in asymptomatic patients, is important to prevent future vascular events. The main risk

Table 5. Relationship between low ABI and SLE variables (univariate analysis). Values are n (%) unless otherwise indicated.

	Low ABI, n = 46	Normal ABI, n = 170	p
Lupus nephritis	11/46 (24)	49/170 (29)	0.635
APS	5/46 (11)	16/170 (9)	0.767
Anti-DNA antibodies	21/46 (46)	85/170 (50)	0.721
Anti-Ro antibodies	13/46 (28)	56/170 (33)	0.67
Anti-La antibodies	3/46 (6)	15/170 (9)	0.616
Anti-RNP antibodies	4/46 (9)	25/170 (15)	0.414
Anti-Sm antibodies	5/46 (11)	24/170 (14)	0.742
aPL	13/46 (28)	61/170 (36)	0.429
SLEDAI: mean (SD)	2 (3)	2 (3)	0.062
SLEDAI categorical:			0.663
0	80 (77)	24 (23)	
1–5	72 (79)	19 (21)	
≥ 6	18 (86)	3 (14)	
SDI: mean (SD)	1.26 (1.3)	1.09 (1.4)	0.453
Prednisone therapy ever	42/46 (91)	149/170 (88)	0.49
Total dose of prednisone, g, mean (SD)	16 (18.6)	23.8 (63.4)	0.678
Maximum dose of prednisone, g, mean (SD)	28.7 (26.2)	26.7 (26.3)	0.644
Hydroxychloroquine ever	40/46 (87)	153/170 (90)	0.553
Total dose of hydroxychloroquine, g, mean (SD)	432.3 (476.8)	409.7 (518.3)	0.79
Cyclophosphamide cumulative dose, g, mean (SD)	1.15 (3.3)	2.74 (6.9)	0.03
Aspirin, mos, mean (SD)	59 (66)	41 (66)	0.104
Statins, mos, mean (SD)	33 (53)	17 (40)	0.069
Anticoagulation, mos, mean (SD)	12 (37)	11 (41)	0.816
Fibrinogen, mg/dl, mean (SD)	425 (94.3)	378 (90.2)	0.002

SLE: systemic lupus erythematosus; APS: antiphospholipid syndrome; aPL: antiphospholipid antibodies; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index; ABI: ankle-brachial index; SDI: Systemic Lupus International Collaborating Clinics damage index.

Table 6. Variables associated with a low ABI (multivariate analysis).

	OR	95% CI	p
Age at study, yrs	1.04	1.02–1.07	< 0.001
Any vascular risk factor (DM, HTN, hypercholesterolemia, or current smoking)	2.3	0.99–5.1	0.053

ABI: ankle-brachial index; DM: diabetes mellitus; HTN: hypertension.

factors for PAD in the general population are smoking, DM, and arterial HTN. ABI testing is recommended in patients with intermittent claudication, in asymptomatic individuals older than 70 or older than 50 with vascular risk factors, and in patients with a Framingham risk score up to 10%, with absence of pedial pulses and/or presence of femoral bruits[20].

We found a high prevalence of mostly asymptomatic PAD in patients with SLE (21%). This prevalence is 10-fold higher than expected according to a recent Spanish population-based cross-sectional survey of 6262 individuals, which showed a 2.1% frequency of an ABI < 0.9 in the subgroup of women 45 to 54 years of age[21]. On the other hand, the frequency of symptomatic PAD in our cohort (1.3%) was similar to that found in the Toronto Lupus cohort (2%)[22].

Few have studied the prevalence of subclinical PAD in patients with SLE. One study from London of 91 patients with SLE younger than 55 years was designed to detect early signs of atheroma by using ABI, whose abnormal cutoff value was set at 1. The authors identified 37% of patients with PAD. Age was the only variable associated with a low ABI[23]. The lower prevalence of abnormal ABI found in our study could be explained in part by the lower cutoff we used, 0.9 instead of 1, according to current guidelines[20].

In a case-control study of 32 Chinese women with SLE who had no previous CV disease or DM, designed to study the correlation between arterial stiffness and disease activity, the authors did not report any cases with an abnormal ABI[24]. Another study of Chinese patients from Taiwan found a 4% frequency of abnormal ABI. That study was focused on the relation between homocysteine and brachial-ankle pulse wave velocity and no specific associations with ABI were sought[25]. The same group studied arterial stiffness by pulse wave velocity in 83 patients with SLE. An ABI was performed on the whole cohort, with 24% of them being abnormal; however, variables potentially related with a low ABI were not analyzed[26].

Like the London study, we found an association between the presence of PAD and age, both at the time of the study

and at SLE diagnosis[23]. The presence of menopause was also associated with a low ABI in the univariate analysis. The association between arterial events and the age at SLE diagnosis has been consistently described[2,4,27,28,29]. An association between CV events and menopause has been found as well[2].

Our study also revealed a strong association between PAD and traditional CV risk factors (DM, HTN, hypercholesterolemia, smoking, and SCORE scale), which persisted as a tendency in the multivariate analysis. A relation with the presence of previous CV events (IHD/HF, stroke, and previous arterial thrombosis) was also seen. Other authors have found associations with some, but not all, vascular risk factors. Petri, *et al* found a relation with serum cholesterol levels and HTN, but not with smoking or DM[4]. Manzi, *et al* described an incidence of myocardial events in women with SLE higher than expected in a population of women of similar age, according to the Framingham Study Cohort[2]. An association with hypercholesterolemia was seen, but not with other classic vascular risk factors[2]. Urowitz, *et al* found a relation between CV events (myocardial infarction, angina, TIA, stroke, PAD, and sudden death) and hypercholesterolemia, smoking, and HTN, but not with DM[30].

Other groups found associations of CV events with longer duration of SLE[2,4], positivity for aPL[27], Raynaud phenomenon, renal disease, neuropsychiatric disease, and vasculitis[30]. In contrast, we found no associations with most SLE-related factors, such as the autoantibody profile, disease activity, chronic organ damage, or treatment with prednisone or antimalarials. In the univariate analysis, higher fibrinogen levels and lower cumulative doses of cyclophosphamide were found in the low ABI group. Despite the loss of statistical significance of both variables in the multivariate analysis, the effect of chronic inflammation in the vascular endothelium is suggested. Accordingly, those therapies suppressing inflammation could have a beneficial effect.

However, studies analyzing the effects of immunosuppressive and antimalarial therapy on vascular disease have obtained heterogeneous results. Urowitz, *et al*[30] found an association between CV events and steroid use as a dichotomic "ever/never" variable, but not with the cumulative dose or the duration of treatment. Surprisingly, antimalarials and immunosuppressive drugs were used more frequently in the group of patients with CV events. Manzi, *et al*[2] and Petri, *et al*[4] found an association of CV disease with longer duration of corticosteroid use. Roman, *et al*[31] identified several variables associated with the presence of plaque: age, disease duration, and damage increased the risk, while positivity for anti-Sm and therapy with hydroxychloroquine and cyclophosphamide had a protective effect. A higher proportion of patients taking prednisone and a higher 5-year mean daily dose of prednisone were seen among patients without plaque. In a Brazilian study[32], hydroxychloroquine was not protective, while cyclophosphamide, methylprednisolone pulses, and the daily dose of prednisone were associated with a lower frequency of plaque. Interestingly, the duration of prednisone therapy was directly related to the presence of plaque, suggesting a somewhat dual effect of glucocorticoids. Such effect was also found in a study of pediatric patients with SLE in whom a beneficial effect of prednisone doses of 0.15–0.40 mg/kg/d on the carotid intima-media thickness was found; however, lower and higher doses were both associated with a higher intima-media thickness[33]. A direct effect of the cumulative dose of prednisone, both unadjusted and adjusted for Framingham risk factors, on the presence of carotid plaque was reported by Doria, *et al*[34] and similar results were obtained by Romero-Diaz, *et al* in Mexico[35].

These heterogeneous results may actually reflect the complex relation between disease activity, drug-associated side effects, and vascular disease. It is possible that a certain degree of immunosuppressive therapy protects from endothelial damage by controlling inflammation, but the proatherosclerotic effects of immunosuppressive drugs, particularly glucocorticoids, may prevail beyond a certain threshold. In addition, it is almost impossible to separate the strong association between SLE severity and more intensive immunosuppressive therapy. Lastly, a number of different endpoints have been used, from crude clinical vascular events to a wide range of noninvasive tests such as carotid ultrasound, CT scan, or arterial stiffness calculations, which can have different clinical implications. Thus, many questions about the effect of SLE therapy on vascular disease are still unresolved.

On the other hand, the effect of traditional CV risk factors on vascular disease in patients with SLE is clear. We found a prevalence of PAD in patients with SLE 10-fold higher than expected[21]. Up to 50% of our cohort was overweight, compared with 39% of the Spanish general population[36]. Thirty-four percent had hypercholesterolemia, compared to 50.5% of individuals in the Spanish general population[37]. The prevalence of HTN in the Spanish general population is 35%, similar to the 33% frequency seen in our patients[38]. However, the age range in epidemiological studies is 18 to 80 years, while the mean age of our cohort was 36 years. This suggests that hypercholesterolemia, HTN, and other vascular risk factors appear earlier in patients with SLE, with the expected clinical effect on the development of vascular disease.

This study has several limitations. First, this is a cross-sectional study, with a wide heterogeneity in variables such as the age, SLE duration, and degree of organ damage. The lack of statistical significance of some SLE-related variables identified in other studies may be partially explained by the confounding effects of this heterogeneity. Eighty-nine percent of our cohort was taking antimalarials, which makes it very difficult to analyze the actual effect of

these drugs, given the lack of a sizable comparison group not taking the therapy. However, the duration of therapy was neither directly nor inversely associated with PAD, remarking that the relation of antimalarials and atherosclerosis is far from clear[39]. The complex relationship between glucocorticoids and arterial disease has already been discussed. In our study, we only considered the cumulative and maximum dose of prednisone received. Given the variation in the time of followup of the individual patients, these glucocorticoid-related variables may not be optimal to analyze the influence of prednisone on PAD. Finally, the lack of a control group without SLE precluded the complete analysis of most SLE-related variables. Likewise, the prevalence of PAD in the general population, as measured by low ABI, was obtained from other studies in the Spanish population, and not directly calculated in a control group of our area. Regarding the effects of SLE activity on ABI, our study is limited by the low number of patients with a SLEDAI ≥ 6 at the time of the study. Also, previous SLEDAI scores were not analyzed. Therefore, we cannot exclude an effect of persistent severe SLE activity on the development of PAD.

On the other hand, this is the first study analyzing the incidence of PAD in patients with SLE using a validated diagnostic technique and a working definition in accordance with current international guidelines. In our descriptive study, we found a high prevalence of PAD in patients with SLE, which was asymptomatic in the vast majority of cases. The clinical implications of our data will be further clarified by future studies and by the longitudinal followup of our cohort.

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5.2.-ESTUDIO 2

Síndrome metabólico en pacientes con lupus eritematoso sistémico: causas y consecuencias.

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Editorial

Síndrome metabólico en pacientes con lupus eritematoso sistémico: causas y consecuencias

Metabolic syndrome in patients with systemic lupus erythematosus: Causes and consequences

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Está bien establecido que los pacientes con lupus eritematoso sistémico (LES) presentan un mayor riesgo de sufrir episodios vasculares tales como enfermedad coronaria, ictus y enfermedad arterial periférica, con su consiguiente significado pronóstico[1,2]. El desarrollo de aterosclerosis subclínica es mayor y más precoz en pacientes con LES en comparación con la población general. Si bien los factores de riesgo tradicionales, como la hipertensión arterial (HTA), la diabetes mellitus (DM), la dislipidemia y el tabaquismo, son más prevalentes en estos pacientes, ello no explica completamente esta mayor prevalencia de vasculopatía aterosclerótica[3].

El síndrome metabólico (SM) agrupa varios factores de riesgo vascular que se traducen en obesidad central y resistencia a la insulina, lo que condiciona un mayor riesgo de desarrollo de DM tipo 2 y enfermedad cardiovascular[4]. No obstante, existen diferentes definiciones de SM, cada una con distintos criterios: la de la Organización Mundial de la Salud, la de la Federación Internacional de Diabetes o la del Panel de Expertos en Detección, Evaluación y Tratamiento de niveles elevados de colesterol en sangre en adultos, del *Adult Treatment Panel III* (ATP III)[5]. Dentro de los criterios incluidos, algunos son factores muy extendidos en la práctica clínica habitual y, por lo tanto, fáciles de evaluar. En cambio, en alguna de las definiciones se incluye la medición de la resistencia a la insulina (HOMA), lo que dificulta su aplicabilidad. La presencia de obesidad abdominal es obligatoria en algunas definiciones de SM, mientras que en otras es solo un criterio de igual peso que otros factores de riesgo vascular, lo que añade dificultades a la hora de identificar a estos pacientes.

A pesar de todo ello, la existencia de SM (independientemente de la definición que se elija) se ha asociado con un mayor riesgo de enfermedad cardiovascular, aunque esta asociación no es tan clara como con los factores de riesgo clásicos. Se sabe que el SM es una herramienta clínica útil en la población para identificar a los pacientes que precisan una mayor intervención cara a prevenir la aparición de episodios vasculares. Parece claro que es un predictor del riesgo relativo de desarrollo a largo plazo de enfermedad cardiovascular y diabetes, pero no predice el riesgo absoluto o global a corto plazo. Por este motivo, diferentes sociedades científicas (Asociación Americana de Diabetes, Asociación Europea para el Estudio de la Diabetes) recomiendan que se calcule el riesgo vascular con calculadoras de riesgo global (SCORE, ecuación de Framingham o el algoritmo de PROCRAM), y posteriormente se investigue la presencia de SM, para obtener el «riesgo cardiometabólico»[6]. Este factor de corrección puede ser determinante en personas jóvenes, en las que estas calculadoras infravaloran el riesgo, como ocurre en los pacientes con LES[3].

La prevalencia de SM en la población general en nuestro país se estima en torno al 15%. En pacientes con LES, Sabio et al. encontraron una prevalencia del 20%, llegando a ser 4 veces mayor en aquellos con LES menores de 40 años[7]. En otros estudios de casos y controles realizados en individuos con LES, en los que se han usado diferentes definiciones de SM, también se ha encontrado una mayor prevalencia de este síndrome que en la población general[8,9].

Entre los pacientes con LES y SM, el factor de riesgo más frecuente es la HTA[5]. Por el contrario, la presencia de perímetro abdominal aumentado es menor que en los controles sanos[7,8]. Este dato puede hacer que se infravalore la prevalencia de SM en los pacientes con lupus, ya que si se eligen definiciones de SM donde la presencia de perímetro abdominal aumentado es necesaria para el diagnóstico, podemos no detectar a un buen número de pacientes. La edad se ha identificado también como un factor de riesgo para presentar SM en los pacientes con LES[8,10].

Además de los factores clásicos, diversos estudios concluyen que la actividad inflamatoria de la enfermedad favorece el desarrollo de SM. Así, los pacientes con mayores puntuaciones en las escalas SLAM-R[11] o SLEDAI-2K[10], los que presentaban mayores niveles de proteína C reactiva (PCR) o velocidad de sedimentación, o niveles más bajos de C3[7–9,11], o aquellos con nefritis lúpica[10], presentan una mayor prevalencia de SM. El daño acumulado en los pacientes con LES también se ha asociado con una mayor probabilidad de desarrollar SM[7,10,12].

En la cohorte internacional SLICC de pacientes con diagnóstico reciente de LES se ha encontrado que determinadas razas o etnias presentan mayor prevalencia de SM, como los coreanos (OR 6,33; IC 95% 3,68-10,86) o los hispanos (OR 6,2; IC 95% 3,78-10,12)[13]. En

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una publicación posterior, después de 2 años de seguimiento, el proceder de ancestros africanos (OR 3,35; IC 95% 1,59-7,01) o ser hispano (OR 2,25; IC 95% 1,28-3,96) se asociaba con un mayor riesgo de SM[10]. En ese mismo trabajo se encontró que la presencia previa de SM es de por sí un factor de riesgo para tener SM, siendo el factor que más riesgo aportaba en el análisis multivariante (OR 14,9; IC 95% 10,7-20,8).

Uno de los elementos que se cree que más influyen en el desarrollo de SM son los fármacos utilizados en el LES, sobre todo los glucocorticoides. Negrón et al.[11], en una cohorte de Puerto Rico, encontraron que haber recibido dosis de prednisona superiores a 10 mg/día se asociaba con SM. Parker et al., en la cohorte SLICC, encontraron asociación entre la prevalencia de SM y el uso de glucocorticoides en general[8], o el uso de dosis medias diarias elevadas[13]. Sin embargo, otros trabajos no han encontrado asociación entre los glucocorticoides y el desarrollo de SM[7,9,10,12].

Es ampliamente conocido que las medidas higiénico-saludables, como la realización de ejercicio aeróbico regular, previenen el desarrollo de SM, tanto en la población general como en los pacientes con LES[11]. Asimismo, se ha encontrado en diversos trabajos que el uso de antipalúdicos en los pacientes con LES tiene un efecto protector frente al desarrollo de SM[7,10,12–14], lo cual, unido a sus efectos protectores frente a las trombosis[15], añade argumentos para el uso generalizado de hidroxicloroquina en estos pacientes.

El LES se ha asociado de manera consistente con aterosclerosis precoz[1]. En 2 trabajos se ha encontrado relación entre la rigidez arterial (medida mediante la velocidad de la onda de pulso), que es la primera manifestación de la aterosclerosis, y el SM. En el trabajo de Sabio et al.[16] la rigidez arterial se relacionaba con la edad, el sexo masculino, el tiempo de evolución del LES, los niveles de PCR y la presencia de SM (OR 2,93; IC 95% 1,05-8,93). En el segundo estudio, Valero-Gonzalez et al.[17] encontraron que el SM aumenta la rigidez arterial (OR 6,6; IC 95% 1,2-38), independientemente de la edad del paciente y los valores de presión arterial. Además, el SDI también se asociaba de forma independiente con una mayor rigidez arterial.

En el artículo publicado en este número de Medicina Clínica por Garcia-Villegas et al.[18] se estudia el valor pronóstico del SM sobre el desarrollo de trombosis en una cohorte de 238 mujeres premenopáusicas con LES. La edad media era de 31 años, con una duración media de la enfermedad de 6,8 años, un MEX-SLEDAI de 2,3 y un SDI de 0,5. Respecto a los tratamientos recibidos, el 76,9% recibía cloroquina y el 93,3% glucocorticoides (a cualquier dosis). Se hizo un seguimiento de la cohorte desde 2001 a 2008, con una prevalencia de SM al inicio del 21,8%, similar a la encontrada en un estudio de población general de México (21,4%)[19], país en el que se llevó a cabo el estudio. Sin embargo, cabe destacar que en este trabajo se utilizan los criterios de ATP III con una modificación, el índice HOMA y/o la glucosa en ayunas, mientras que en el estudio de Aguilar-Salinas et al.[19] se incluyeron ambos sexos y, para el diagnóstico de SM, se utilizó el índice de masa corporal en vez del perímetro abdominal. Por tanto, ambas prevalencias podrían no ser del todo comparables.

El criterio diagnóstico de SM más frecuente fue el nivel de colesterol HDL < 50 mg/dl (55%), seguido de la glucemia en ayunas ≥ 110 mg/dl y/o HOMA $> 2,5$ (31,5%) y del perímetro abdominal > 88 cm (27,7%). Entre los factores de riesgo identificados, las pacientes con SM habían recibido con más frecuencia dosis altas de prednisona (> 30 mg/día) a lo largo de la enfermedad (75 frente a 50,5%, $p < 0,005$). Por otro lado, no se encontraron asociaciones entre el SM y la actividad o el daño crónico, un hecho quizás explicado por las bajas puntuaciones de MEX-SLEDAI y SDI entre las participantes.

Uno de los objetivos de los investigadores fue establecer si el SM se asocia con un aumento de la enfermedad cardiovascular. En este trabajo se confirmó en el análisis multivariante que el SM aumenta el riesgo de padecer enfermedad trombótica (HR 3,8, IC 95% 1,3-10,6), tanto a nivel arterial (infarto agudo de miocardio, ictus, trombosis de la arteria central de la retina, trombosis renal), como venoso (trombosis venosa profunda y tromboembolismo pulmonar [TEP]). Los episodios trombóticos más frecuentes fueron los ictus (9 casos), seguidos de TEP (5 casos). Asimismo, se observó una asociación entre el daño acumulado, medido mediante SDI, y el aumento de riesgo de sufrir trombosis (HR 1,4; IC 95% 1,1-2,1). Es cierto que este trabajo incluyó en la definición de enfermedad cardiovascular, de forma un tanto inusual, tanto trombosis arteriales como venosas. Sin embargo, hay que considerar que, al fin y al cabo, cualquier episodio trombótico implica un incremento de la morbimortalidad. La incidencia acumulada de trombosis en la cohorte fue del 9,2%, lo que representa un riesgo 200 veces superior al esperado en mujeres de 15 a 49 años.

Tomando como base los resultados de este estudio y de otros previos, se puede afirmar que el desarrollo de SM en pacientes con LES es multifactorial, con una serie de variables claramente identificadas: actividad inflamatoria, daño acumulado, edad, determinadas etnias y el tratamiento recibido, fundamentalmente los antipalúdicos (con un efecto protector) y la prednisona[5]. En este último caso, parece claro que sus efectos adversos dependen de la dosis y el tiempo de uso, si bien es difícil establecer de forma concreta los límites de seguridad. Sin embargo, estudios recientes apuntan a que dosis iniciales por debajo de 30 mg/día, con descenso rápido hasta 5 mg/día, acompañadas de bolos intravenosos de metilprednisolona, inmunosupresores e hidroxicloroquina, son efectivas en el control de la enfermedad lúpica grave con mínimos efectos adversos (obesidad, diabetes, dislipidemia, fracturas osteoporóticas, osteonecrosis y cataratas)[20].

En definitiva, se debe realizar una búsqueda activa de SM en los individuos con LES, ya que puede explicar parte del exceso de riesgo vascular que presentan estos pacientes, utilizando definiciones que permitan su detección precoz y eficaz. Una vez identificado, debemos realizar un control estricto de los factores de riesgo tradicionales y promover de forma vehemente la realización de dieta cardiosaludable y ejercicio aeróbico regular, ya que ello constituye la forma más eficaz para su control. Asimismo, se debe conseguir una remisión rápida y duradera de la actividad inflamatoria de la enfermedad, evitando las dosis altas de glucocorticoides orales, y administrar hidroxicloroquina como tratamiento de base en todos los pacientes en los que no haya contraindicaciones[15].

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5.2.-ESTUDIO 3

Predictors of peripheral arterial disease in SLE change with patient's age.

Jose Gabriel Erdozain, Irama Villar, Javier Nieto, Ioana Ruiz-Arruza, Guillermo Ruiz-Irastorza.

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Predictors of peripheral arterial disease in SLE change with patient's age

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ABSTRACT

Objective: To analyse the differential influence of risk factors of peripheral artery disease (PAD) according to age in patients with SLE.

Methods: 216 patients from the Lupus-Cruces cohort were divided in three age groups: ≤34 years, 35–49 years and ≥50 years. A low ankle–brachial index defined PAD. Significant variables were identified by univariant and multivariant analysis in each age group.

Results: Different factors were identified in different age groups: antiphospholipid antibodies/antiphospholipid syndrome and glucocorticoids in patients ≤34 years; in patients 35–49 years old, hypertension was the only statistically significant predictor, although a trend was observed for fibrinogen levels; a trend was observed for hypercholesterolaemia in those ≥50 years.

Conclusions: Age may modulate the influence of risk factors for PAD in patients with SLE.

INTRODUCTION

Cardiovascular disease (CVD) is the main cause of late mortality in patients with SLE.[1] The incidence of CVD has progressively increased within the last decades.[2] CVD can present as coronary artery disease (CAD), cerebrovascular disease and peripheral artery disease (PAD), the first two ones being best studied.[3] The underlying atherosclerotic process can be accelerated by different mechanisms, including inflammation, SLE treatments and traditional cardiovascular risk factors.[3]

Age is the most important unchangeable cardiovascular risk factor, both in the general population and in patients with lupus.[4 5] Indeed, in a previous study in our SLE cohort, age was the only independent predictor of PAD.[6] In a nationwide population-based cohort study in Taiwan, younger (≤34 years) patients with SLE were at a higher risk of symptomatic PAD.[7] In a Swedish population-based study, an increased risk of myocardial infarction and stroke was demonstrated among female patients with SLE compared with the general population. Of note, this extra risk was highest among women aged 40–49 years.[8]

Thus, it is possible that the influence of risk factors, either cardiovascular or SLE-related, varies depending on the age of patients. To test this hypothesis, we aimed to study the influence of risk factors for PAD in different age groups of patients with SLE.

MATERIALS AND METHODS

Study objectives

The objective of this cross-sectional study was to analyse the differential influence, according to age, of several variables in the presence of PAD, defined as a low ankle–brachial index (ABI). Patients were divided in three groups according to age at the time of the ABI, as proposed by Chuang *et al*:[7] ≤34 years (group 1), 35–49 years (group 2) and ≥50 years (group 3).

Study population

Data from the 216 patients who participated in our previous study[6] were further analysed. Detailed characteristics of this population and the variables studied are available.[6] The local institutional review board of the Hospital Universitario Cruces approved the study protocol (CEIC E09/07) in compliance with the Helsinki Declaration. All patients signed an informed consent at the time of enrolment.

Statistical analysis and variables

In order to identify associations with PAD, the following independent variables were tested in each age group against the dependent variable, 'ABI lower than 0.9', using χ^2 with Yate's correction or Student's t-test, as appropriate: age at SLE diagnosis, disease duration, gender, abdominal obesity (≥102 and ≥88 in men and women, respectively), metabolic syndrome according to Adult Treatment Panel III definition,[9] diabetes mellitus (DM), arterial hypertension (HTN), dyslipidaemia, smoking (current or past), any vascular risk factor (DM or HTN or

dyslipidaemia or current/past smoking), exercise, alcohol consumption, family history of premature CVD, body mass index, menopause, previous subclinical organ damage (left ventricular hypertrophy and microalbuminuria), previous CVD (ischaemic heart disease and/or heart failure (IHD/HF), stroke, PAD), chronic renal failure, previous arterial thrombosis (stroke or IHD or PAD), uric acid, vitamin D levels, previous lupus nephritis or antiphospholipid syndrome (APS), anti-DNA, anti-Ro, anti-La, anti-U1RNP, anti-Sm, and antiphospholipid antibodies (aPL) that include lupus anticoagulant and/or anticardiolipin antibodies at medium–high levels on at least two different determinations 12 weeks apart, Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) at the time of diagnosis, SLEDAI at the time of ABI, SLICC/ACR Damage Index (SDI) at the time of ABI, prednisone (cumulative dose, maximum dose ever received, average daily dose <7.5 or ≥7.5), hydroxichloroquine (yes/no and cumulative dose), cyclophosphamide (cumulative dose), mycophenolate (cumulative dose), azathioprine (cumulative dose), low-dose aspirin (number of months on treatment), anticoagulants (number of months on treatment), statins (number of months on treatment) and fibrinogen levels at the time of the ABI.

Those variables with a value of p ≤0.1 in the univariate analysis were subsequently included in a backward stepwise logistic regression model to identify independent associations with PAD for each age subgroup.

All statistical analyses were done using the software SPSS V.20.0 statistical package for MAC OS X (SPSS).

RESULTS

Demographic and SLE-related variables

Two hundred patients (92%) were women. Two hundred and nine patients (96%) were Caucasians of European origin, with the remaining consisting of three Afro-Caribbeans, two Hispanics and two Arabs. The mean (SD) age at SLE diagnosis was 36 years (15). The mean (SD) age at the time of the ABI study was 49 (15) years, with a mean (SD) follow-up after SLE diagnosis of 12 (9) years.

A total of 37 patients were included in group 1, 84 patients in group 2 and 95 patients in group 3. The distribution of traditional cardiovascular risk factors and SLE-related factors in the three age groups is detailed in table 1.

Frequency and associations of low ABI

The prevalence of PAD increased with age: 3/37 (8.1%) in group 1, 12/84 (14.2%) in group 2 and 31/95 (32.6%) in group 3. The variables associated with PAD in each age group are shown in table 2: APS, aPL and cumulative prednisone dose in group 1; DM, hypertension, average daily dose of prednisone <7.5 mg/day, abdominal obesity and fibrinogen levels in group 2; and vitamin D levels, hypercholesterolaemia, any vascular risk factor (DM or hypertension or hypercholesterolaemia or current/past smoking), ischaemic heart disease, aPL, previous arterial thrombosis, cumulative mycophenolote mofetil dose and average daily dose of prednisone <7.5 in group 3.

The final independent predictors of low ABI are shown in table 3. In group 1, the logistic regression

Table 1 Traditional and SLE-related cardiovascular risk factors in different age groups

	Group 1 (≤34 years)	Group 2 (35–49 years)	Group 3 (≥50 years)
HTN, n/N (%)	4/37 (10.8)	20/84 (23.8)	47/95 (49.4)
DM, n/N (%)	0/37 (0)	3/84 (3.5)	4/95 (4.2)
DLP, n/N (%)	3/37 (8.1)	20/84 (23.8)	51/95 (53.6)
Current smoker, n/N (%)	15/37 (40.5)	28/84 (33.3)	22/95 (23.1)
Smoker (ever), n/N (%)	18/37 (48.6)	49/84 (58.3)	41/95 (43.1)
Family history, n/N (%)	2/37 (5.4)	10/84 (11.9)	13/95 (13.6)
Abdominal obesity, n/N (%)	10/37 (27)	25/84 (29.7)	38/95 (40)
BMI, n/N (%) overweight–obesity	13/37 (35.1)	44/84 (52.3)	52/95 (54.7)
Sedentary lifestyle, n/N (%)	20/37 (54)	35/84 (41.6)	42/95 (44.2)
Any vascular risk factor, n/N (%)	22/37 (59.4)	59/84 (70.2)	80/95 (84.2)
MS, n/N (%)	3/37 (8.1)	6/84 (7.1)	12/95 (12.6)
APS, n/N (%)	2/37 (5.4)	10/84 (11.9)	9/95 (9.4)
aPL, n/N (%)	14/37 (29.7)	27/84 (32.1)	33/95 (34.7)
Lupus nephritis, n/N (%)	12/37 (32.4)	30/84 (35.7)	18/95 (18.9)
SLEDAI at dx, mean (SD)	9.83 (7.8)	8.15 (5.3)	6.1 (3.9)
SLEDAI at ABI, mean (SD)	3.08 (3.7)	2.05 (2.9)	1.5 (2.2)
SDI at ABI, mean (SD)	0.4 (0.8)	0.98 (1.2)	1.5 (1.5)
Age at SLE dx, years, mean (SD)	21.4 (6.1)	30.2 (9.2)	47.4 (15.6)
Disease duration, years, mean (SD)	6.2 (5.3)	11.7 (8.5)	15 (10.5)

Any vascular risk factor: DLP, hypercholesterolaemia; HTN, DM, dyslipidaemia or smoking exposed. ABI, ankle–brachial index; aPL, antiphospholipid antibodies (anticardiolipin and/or lupus anticoagulant); APS, antiphospholipid syndrome; BMI, body mass index; DM, diabetes mellitus; dx, diagnosis; HTN, arterial hypertension; MS, metabolic syndrome according to ATPIII.

Table 2 Univariate analysis showing variables with p<0.1

	Low ABI	Normal ABI	p Value
Group 1 (≤34 years)	N=3	N=34	
APS, n/N (%)	2/3 (66)	0/34 (0)	0.005
aPL, n/N (%)	3/3 (100)	11/34 (32.3)	0.047
Cumulative prednisone, g, mean (SD)	21.25 (1.89)	7.70 (1.08)	0.058
Group 2 (35–49 years)	N=12	N=72	
DM, n/N (%)	2/12 (16.6)	1/72 (1.3)	0.052
HTN, n/N (%)	6/12 (50)	14/72 (19.4)	0.021
Average prednisone <7.5 mg/day, n/N (%)	11/11 (100)	50/68 (73.5)	0.046
Abdominal obesity, cm, mean (SD)	90.46 (14.9)	82.50 (12.2)	0.047
Fibrinogen levels, mg/dL, mean (SD)	454 (100)	388 (83.2)	0.021
Group 3 (≥50 years)	N=31	N=64	
Vitamin D levels, ng/mL, mean (SD)	22.2 (8.7)	35.9 (41.4)	0.018
Hypercholesterolaemia, n/N (%)	21/31 (67.7)	30/64 (46.8)	0.056
Any vascular risk factor (ever smoking), n/N (%)	30/31 (96.7)	50/64 (78.1)	0.015
Any vascular risk factor (current smoking), n/N (%)	28/31 (90.3)	44/64 (68.7)	0.023
Ischaemic heart disease, n/N (%)	4/31 (12.9)	2/64 (3.1)	0.086
aCL, n/N (%)	4/31 (12.9)	24/64 (37.5)	0.011
aPL, n/N (%)	6/31 (19.3)	27/64 (42.1)	0.028
Arterial thrombosis, n/N (%)	11/31 (35.4)	11/64 (17.1)	0.047
Cumulative MMF, g, mean (SD)	0 (0)	111 (442.8)	0.049
Average prednisone <7.5 mg/day, n/N (%)	28/30 (93.3)	48/63 (76.1)	0.038

ABI, ankle–brachial index; aCL, anticardiolipin antibodies; aPL, antiphospholipid antibodies (anticardiolipin and/or lupus anticoagulant); APS, antiphospholipid syndrome; DM, diabetes mellitus; HTN, arterial hypertension; MMF, mycophenolate mofetil.

Table 3 Variables associated with a low ABI in different age groups (multivariate analysis)

Variables	OR	95% CI	p Value
Group 1			
N/A			
Group 2			
Hypertension	4.61	1.15 to 18.44	0.031
Group 3			
Hypercholesterolaemia	2.49	0.97 to 6.4	0.057

ABI, ankle–brachial index; N/A, not applicable.

model could not be built due to the absolute absence of any patients with APS in the subgroup with normal ABI and the 100% frequency of aPL positivity among those with abnormal ABI; thus, the results of the univariate analysis could not be adjusted. In group 2, hypertension was the only statistically significant predictor, although a trend was observed for fibrinogen levels. In group 3, a trend was observed for hypercholesterolaemia.

DISCUSSION

Age is among the most important cardiovascular risk factors; indeed, many of the cardiovascular risk estimation models are actually based on age.[4 5] In a cohort of more than 3.6 million individuals undergoing self-referred screening for CVD (ABI, carotid duplex ultrasound and abdominal ultrasound), the prevalence of any vascular disease increased progressively after 40 years of age: from 2% in those aged 40–50 years to 13% among those aged 71–80 years. After adjusting for traditional risk factors, each additional decade of life doubled the risk for vascular disease (OR 2.14 for PAD).[10]

Moreover, the differential influence of cardiovascular risk factors changes throughout life. In the general population, the Framingham study found that the relative effect of systolic, diastolic and pulse pressure changed with age. In patients younger than 50 years, diastolic blood pressure was the strongest predictor of coronary heart disease (CHD) risk; in those aged 50–59 years old, all three variables contributed equally to CHD risk; among those older than 60 years, pulse pressure was the strongest predictor.[11]

Our results suggest that age may modulate the effect of risk factors for CVD also in patients with SLE. aPL/APS and higher glucocorticoid load seem to increase the risk of PAD in younger patients, although a multivariant analysis could not be performed. In group 2, an average daily dose of prednisone <7.5 mg was associated with PAD in the univariate but not in the multivariate analysis. Moreover, since more than 75% of patients in this age group were taking low-dose prednisone, this result is likely to be misleading. As age increased, more traditional risk factors such as hypertension and hypercholesterolaemia played a significant role. We identified factors associated with PAD (and, probably, by extension with CVD) hidden by the large influence of age. This could be particularly important among younger patients, in whom the prevalence of arterial disease was low, however very much unrelated to classical cardiovascular risk factors.

This study has a number of limitations, which have been already acknowledged.[6] This is a cross-sectional study, with different disease duration among patients. This makes it difficult to fully address the effects of some time-varying variables such as glucocorticoid exposure, lupus activity and cardiovascular risk factors. In addition, almost 90% of our cohort was on hydroxychloroquine, which precludes analysis of the actual effect of this drug. On the other hand, the sizeable number of patients has allowed a differential analysis per different age groups using a large variety of demographic, cardiovascular, lupus-related and therapeutic variables. This is, to our knowledge, the first study of this kind.

Based on our results, a number of practical considerations can be made. First, it is important to regularly check patients with lupus for the presence of aPL, especially in the early phases of the disease, given the possible association with PAD in young patients with SLE. We have previously shown that aPL increase the risk of damage in SLE,[12] particularly by the occurrence of thrombotic events.[13] Since the addition of low-dose aspirin seems to be protective in aPL-positive patients with SLE according to a recent systematic review,[14] the detection of persistently positive aPL should call for early antiplatelet therapy. Second, the doses of prednisone should be reduced as much as possible, especially in young patients, given the possible association with PAD in this group and, in general, with damage in patients with SLE.[15] Third, especial attention should be paid to controlling traditional cardiovascular risk factors, especially in older patients.

Contributors J-GE: substantial contributions to the conception, design of the work, acquisition, analysis and interpretation of data for the work; drafting the work and revising it critically for important intellectual content; final approval of the version to be published; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. IV: Substantial contributions to the conception and design of the work; analysis and interpretation of data for the work; Drafting the work or revising it critically for important intellectual content; final approval of the version to be published; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. JN: Substantial contributions to the conception and design of the work; analysis and interpretation of data for the work; drafting the work or revising it critically for important intellectual content; final approval of the version to be published; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. IR-A: Substantial contributions to the analysis and interpretation of data for the work; drafting the work or revising it critically for important intellectual content; final approval of the version to be published; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. GR-I: Substantial contributions to the conception and design of the work; analysis and interpretation of data for the work; drafting the work or revising it critically for important intellectual content; final approval of the version to be published; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Competing interests None declared.

Patient consent Obtained.

Ethics approval The local institutional review board of the Hospital Universitario Cruces approved the study protocol (CEIC E09/07).

Provenance and peer review Not commissioned; externally peer reviewed.

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5.3.-ESTUDIO 4

Ankle-brachial index and arterial vascular events in systemic lupus erythematosus patients: a 5-year prospective cohort

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Ankle-brachial index and arterial vascular events in systemic lupus erythematosus patients: a 5-year prospective cohort

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Abstract

Objective

To determine the potential predictive value in patients with systemic lupus erythematous of the ankle-brachial index (ABI) for the occurrence of arterial vascular events.

Methods

216 lupus patients from a prospective clinical cohort were evaluated using the ABI at the start of the study and then followed up for 5 years. Abnormal ABI was defined as an index ≤0.9 or >1.4. Several potential vascular risk factors were also evaluated. Arterial vascular events (AVE): coronary events, cerebrovascular events, peripheral arterial disease and death related to vascular disease. Survival analysis was performed using a competitive risk regression approach, considering non-vascular death as a competitive event.

Results

18 arterial events and 14 deaths were identified. In the competitive risk regression analysis, independent predictors of higher risk were identified: family history of early AVE [subdistribution hazard ratio (SHR) 5.44, 95% confidence interval (CI) 1.69-17.50, p=0.004)], cumulative prednisone (grams) (SHR 1.01, 95% CI 1.01-1.03, p=0.007) and a personal history of arterial thrombosis (SHR 5.44, 95% CI 1.45-14.59, p=0.004). Female gender was a protective factor (SHR 0.22, 95% CI 0.07-0.77, p=0.017). A statistical trend was detected with abnormal ABI (SHR 2.65, 95% CI 0.86-8.14, p=0.089).

Conclusion

Male gender, exposure to high cumulative doses of prednisone, family history of early arterial vascular disease and occurrence of previous arterial thrombosis are independent risk predictors of arterial vascular events in patients with systemic lupus erythematosus. Abnormal ABI may be related to high risk for arterial vascular events.

Key words

systemic lupus erythematosus, cardiovascular disease, peripheral arterial disease, atherosclerosis, ankle brachial index

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Competing interests: none declared.

Introduction

Patients with systemic lupus erythematous (SLE) are known to be at increased risk for arterial vascular events (AVE), mainly ischaemic heart disease (IHD) and cerebrovascular disease (CVD) (1), but also peripheral arterial disease (PAD), either symptomatic or asymptomatic (2, 3). Such an increased risk is greatest among young patients (3-5). Early atherosclerosis has been demonstrated in lupus patients (6), with a prevalence of 41% in a recent Danish study that included the coronary, carotid, and lower-extremity territories (7). The premature atherosclerosis observed in SLE patients has been related to traditional cardiovascular risk factors, like arterial hypertension, diabetes, hypercholesterolaemia, tobacco use and obesity, however, some lupus-related factors, such as lupus activity itself, treatments (steroids, azathioprine) and inflammatory molecules may play an additional role (6).

AVE are one of the leading causes of increased morbidity and mortality in SLE patients (8) and detection of patients at high risk for cardiovascular disease is one of the priorities during follow-up, although these identification in clinical practice is sometimes not very adequate (9). In the general population, some specific actions could reduce the rate of AVE among high-risk patients (10). Likewise, preventing the occurrence of cardiovascular disease is one of the main objectives in SLE patients. A range of procedures have been developed for the early identification of subjects at increased vascular risk: duplex sonography of carotid arteries for the detection of plaques or to calculate intima/media thickening; coronary computed tomography to quantify coronary calcium burden; and ankle-brachial index (ABI) test.

Abnormal ABI, defined as ≤0.9 or >1.4, has been related with an increased morbidity and mortality in the general population, and ABI has been proposed to be a useful tool to identify a high cardiovascular risk population (11, 12).

SLE patients have been studied in many cross-sectional studies, even with control groups, with duplex sonography of carotid artery, detection of coronary calcium and the ABI test. A number of studies have shown an increased presence of carotid plaques, low ABI and increased coronary-calcium index in SLE patients (2, 13, 14). To date, there is only one published prospective follow-up study in patients with SLE using the carotid duplex sonography to identify patients at increased risk for AVE; in this study, the presence of carotid plaque was associated with an increased risk for coronary and cerebrovascular events (HR 4.67, 95% CI 1.41–15.53, p=0.001) (15).

Thus, we designed a prospective follow-up study of a SLE cohort with a baseline ABI previously reported (2) to determine its utility as a predictor of AVE. The secondary objective of our study was to analyse the relationship between other risk factors and the occurrence of AVE.

Material and methods

Study population

Follow-up data from 216 patients at the Autoimmune Diseases Unit, Department of Internal Medicine, Cruces University Hospital, a tertiary teaching centre in Baracaldo (Basque Country, Spain) associated with the University of the Basque Country. All patients fulfilled the 1997 classification criteria of the American College of Rheumatology and had participated in a previous cross-sectional study between January 2010 and June 2011 (2, 16).

Variables

The following variables were recorded at the time of enrolment for each patient:

1) Demographic characteristics: age, sex, race.
2) Clinical and immunological SLE variables: disease duration (years), SLE manifestations (lupus nephritis, antiphospholipid syndrome, neuropsychiatric lupus), autoantibody profile (anti-DNA, anti-Ro, anti-La, anti-RNP, anti-Sm, antiphospholipid), treatments received (corticosteroids, immunosuppressives, anti-malarials), the Systemic Lupus International Collaborating Clinics (SLICC) damage index (SDI) (17) and the SLE Disease Activity Index (SLEDAI) (18).
3) Cardiovascular (CV) risk factors:

age (defined as more than 55 and 65 years in men and women, respectively), arterial hypertension (HTN, defined as 2 consecutive measurements of at least 140/90 mmHg or antihypertensive therapy), diabetes mellitus (DM, defined as 2 consecutive fasting blood glucose determinations ≥126 mg/dl or treatment with antidiabetic drugs), hypercholesterolaemia (defined as total blood cholesterol fasting levels >200 mg/dl on 2 consecutive determinations or treatment with cholesterol-lowering drugs), metabolic syndrome according to the Adult Treatment Panel III definition (19), current or past smoking, degree of physical exercise (aerobic exercise 1 h/day, at least 3 days a week), and menopause in females. The size, weight, and waist and hip circumference were determined in each patient at the time of performing the ABI, along with calculation of the body mass index (BMI). We included in the study the levels of uric acid, vitamin D and fibrinogen at the time of the ABI.

4) Previous subclinical organ damage or CV events: left ventricular hypertrophy (LVH), microalbuminuria (presence in urine of albumin excretion between 30 and 300 mg/day, determined in spot urine sample), coronary disease, heart failure, cerebrovascular disease, chronic kidney disease, PAD, advanced retinopathy. CV events were defined as the presence of compatible clinical signs and symptoms and eventually confirmed by complementary tests: myocardial infarction was defined as typical chest pain with characteristic electrocardiographic features and elevated levels of creatine kinase (MB fraction) and/or T troponine; stroke by computed tomography (CT) scanning or magnetic resonance imaging; cerebral transient ischaemic attacks (TIA) were diagnosed in the setting of acute focal neurologic symptoms/signs lasting <24 h; chronic kidney disease is defined based on the presence of either kidney damage or decreased kidney function for three or more months, irrespective of cause; PAD, specifically atherosclerotic disease leading to peripheral artery obstruction, may be silent or present with a variety of symptoms and signs indicative of extremity ischaemia; advanced retinopathy is characterised by retinal haemorrhages, exudates, and papilloedema.
5) CV disease-related treatments received for at least 6 months: antiaggregants, statins, anticoagulants.
6) CV risk stratification was performed using the European Vascular Risk Systematic Coronary Risk Evaluation (SCORE) scale for the Mediterranean population (20).

Ankle-brachial index

ABI was performed in both legs of each patient in ad hoc scheduled visits, from January 2010 to June 2011. The MD2/SD2 Dopplex High Sensitivity Pocket Doppler was used for our study and all ABI were performed by the same 2 trained physicians working together with each patient. In every patient, 1 ABI was calculated for each leg. For the purposes of this study, the ABI variable was coded as abnormal ABI: ≤0.9 or >1.4, according to the previously mentioned evidences (11, 12).

Follow-up

A 5-year follow-up was planned for all study participants. Patients were routinely assessed every 3 to 6 months, unless clinical status demanded more frequent visits. Lupus flares (defined as any clinical manifestation of lupus that involves the use of high doses of corticosteroids, use of a new immunosuppressant or increasing the dose of some immunosuppressant previously used) were recorded. Arterial vascular events (AVE) were systematically investigated at each visit through a standardised interview. The AVE were defined as coronary events (angina pectoris, acute myocardial infarction, coronary revascularisation by angioplasty or surgery), cerebrovascular events (transient ischaemic attack, ischaemic or haemorrhagic stroke), PAD (symptomatic intermittent claudication, distal ischaemia, revascularisation by angioplasty or surgery), and vascular death. Follow-up ended when the patient attended the 5-year follow-up visit or due to death. The cause of death was established for all patients who deceased during the follow-up period.

Statistical analysis

Continuous data were described using mean and standard deviation (SD) or median and range, if it does not present a normal distribution; categorical variables with relative frequencies and percentages. The normality of the continuous variables analysed was confirmed with the appropriate statistical studies.

To identify associations with AVE, the following independent variables were tested against the dependent variable "incidence of AVE", using chi-square with Yates' correction or Student *t*-test: age at SLE diagnosis, age at the time of ABI, disease duration, sex, age as a vascular risk factor, abdominal obesity, metabolic syndrome, DM, HTN, hypercholesterolaemia, smoking (current or past), any vascular risk factor (DM or HTN or hypercholesterolaemia or current/past smoking), exercise, alcohol consumption, family history of premature CV disease, BMI, menopause, previous subclinical organ damage (LVH and microalbuminuria), previous CV events [ischaemic heart disease and/or heart failure (IHD/HF), stroke, PAD], chronic kidney disease, previous arterial thrombosis (stroke or IHD/HF or PAD), uric acid levels, vitamin D levels, previous lupus nephritis, previous antiphospholipid syndrome (APS), previous neuropsychiatric lupus (NPSLE), lupus flares during follow-up, anti-DNA, anti-Ro, anti-La, anti-U1RNP, anti-Sm, and antiphospholipid antibodies (aPL; lupus anticoagulant and/or anticardiolipin antibodies at medium-high levels on at least 2 different determinations 12 weeks apart), SLEDAI, SDI value (categorised: 0 *vs.* ≥1), prednisone (cumulative dose in grams and maximum dose ever received), hydroxychloroquine (yes/no and total dose), cyclophosphamide (cumulative dose), low-dose aspirin (number of months on treatment), anticoagulants (number of months taking treatment), or statins (number of months taking treatment) and fibrinogen levels (continuous variable).

Given the fact that the probability of occurrence of the outcomes of interest

(AVE) was influenced by other alternative events (non-vascular death) a competing risk regression (CRR) approach was adopted to obtain more accurate estimates of the 5-year cumulative risk of AVE (21). The model proposed by Fine *et al*. (22) was implemented, as it does not depend upon the independence between both the competing event and the event of interest. Accordingly, subdistribution hazard ratios (SHR) were obtained as estimates of the relative effect of a putative risk factor on the occurrence of the AVE, and subdistribution cumulative hazard functions as estimates of the adjusted 5-year risks. Ninety five percent confidence intervals were also provided.

Those variables with a p-value <0.1 in the univariate analysis were subsequently included as potential predictors of AVE: sex, age at the time of ABI, disease duration in years, family history of premature CV disease, HTN, hypercholesterolemia, SDI value, APS, fibrinogen levels at the time of the ABI, previous arterial thrombosis, prednisone cumulative dose at baseline and abnormal ABI.

Regarding the model selection, we followed a manual backward procedure, starting with the full model and removing variables based on the lack of statistically significant association using likelihood ratio tests, until all the remaining variables were statistically significant. The proportionality of risks assumption was assessed through the introduction of time-dependent covariates and the use of graphical tools. As abnormal ABI was the factor of main interest, it was kept in all the models. Departures from linearity in the log-odds for continuous variables were assessed creating and statistically testing squared and cubic terms.

Stata 14.2 for Windows was used for all analyses (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP).

Ethics

The Ethics Committee for Clinical Research at Cruces University Hospital approved the study protocol in accordance with the Helsinki Declaration (CEIC E09/07). All patients signed an informed consent at the time of enrolment.

Table I. Baseline variables.

Female	200	(92%)
Race	Caucasian: 209	(96%)
Afro-Caribbeans:	3	(1.3%)
Hispanic:	2	(0.9%)
Arabic:	2	(0.9%)
Age at ABI	49	(15) years.
SLE duration at ABI	11	(0-37) years.
APS	21	(9.7%)
Lupus nephritis	60	(27.6%)
NPSLE	5	(2.3%)
Lupus flares	39	(18.3%)
SLEDAI at ABI	0: 104	(48.1%)
	1-5: 91	(42.2%)
	≥6: 21	(9.7%)
SDI at ABI	0: 98	(45.2%)
	1: 53	(24.4%)
	>1: 65	(30.4%)
Use of prednisone	191	(88.4%)
Maximum dose of prednisone	30.8	(25.9) mg
Average daily dose of prednisone	5.6	(8.2) mg
Cumulative dose of prednisone: mean (SD)	18.7	(57) g
Cumulative dose of prednisone: median (IQR)	7.32	(0-177.6) g
Hydroxychloroquine	193	(89.3%)
Cyclophosphamide	52	(24%)
Mycophenolate	34	(15.7%)
Azathioprine	64	(29.7%)
Family history of early vascular disease	25	(11.5%)
Current smoking at ABI	65	(30%)
Smoking (ever)	109	(50.2%)
Diabetes mellitus	7	(3.2%)
Hypertension	71	(32.7%)
Hypercholesterolaemia	74	(34.1%)
Statins	72	(33.3%)
Antiaggregants	103	(47.7%)
Anticoagulants	26	(12%)
Body mass index	Low-normal weight: 106	(49.1%)
	Overweight-obesity: 110	(50.9%)
SCORE	0-4: 205	(95%)
	≥5: 11	(5%)
Previous vascular disease	IHD: 6	(2.8%)
	CVD: 19	(8.8%)
	PAD: 3	(1.4%)

ABI: ankle-brachial index; SLE: systemic lupus erythematosus; APS: antiphospholipid syndrome; NPSLE: neuropsychiatric lupus; SDI: SLICC Damage Index; IHD: ischaemic heart disease; CVD: cerebrovascular disease; PAD: peripheral arterial disease.

Results

Baseline demographic variables

Two hundred sixteen patients started the follow-up. One hundred ninety-nine (92%) were women. Two hundred nine patients (96%) were white, with the remaining consisting of 3 Afro-Caribbeans, 2 Hispanics, and 2 Arabic. The age at baseline was 49 (15) years, and the follow-up after SLE diagnosis was 11 (0–37) years (Table I).

Cardiovascular risk factors

Traditional CV risk factors were frequent in our cohort, with 162 (74.7%) patients presenting at least one CVRF: HTN 32.7%, hypercholesterolaemia 34.1%, tobacco use 50.2%, overweight-obesity 50.9%, family history of premature CV disease 11.5%, DM 3.2%. 205 patients (95%) had a SCORE between 0 and 4 and 11 patients (5%) had a SCORE ≥5. Previous CV events were present in 26 (12%) patients: CVD in 19 (8.8%), IHD in 6 (2.8%) and PAD in 3 (1.4%). Two patients suffered two or more CV events: one with PAD and CVD and another with IHD and CVD; 72 (33.3%) patients had been treated with statins, 103 (47.7%) with antiaggregants and 26 (12%) with anticoagulants (Table I).

Baseline SLE-related variables and lupus flares

At baseline, 21 (9.7%) patients had an SLEDAI ≥6 and 104 (48.1%) were inactive with a SLEDAI score of 0. APS was diagnosed in 21 (9.7%) patients. 60 (27.6%) patients had been diagnosed of lupus nephritis (in 6 patients, lupus nephritis was active at the time of inclusion in the study). 5 (2.3%) patients had been previously diagnosed of NPSLE. The baseline SDI was 0 in 98 (45.2%) patients, 53 (24.4%) patients had a SDI index of 1 and 65 (30.4%) patients had a SDI >1. Thirty-nine patients suffered at least one lupus flare during follow-up (range 1 to 4 lupus flares).

Regarding SLE treatments, 191 (88.4%) patients had received prednisone with a mean maximum dose ever received 30.8 (25.9) mg/d, mean daily dose at baseline 5.6 (8.2) mg/d and median cumulative prednisone dose 7.32 (0–177.6) g. Hydroxychloroquine was used in 193 (89.3%), cyclophosphamide in 52 (24%), mycophenolate in 34 (15.7%) and azathioprine in 64 (29.7%) (Table I).

Cardiovascular events and mortality

Follow-up data were available for 212 (98.1%) patients, with 1016 patient/year observation; 4 patients discontinued follow-up. Among them, 186 (88%) patients survived during the whole follow-up period without suffering any AVE. 18 AVE were identified in 17 patients: 11 cerebrovascular events, 4 coronary events, 2 peripheral arterial disease events and 1 sudden death, with one patient presenting two angina pectoris episodes requiring percutaneous coronary interventions during follow-up. Fourteen patients died during the follow-up: 6 because of AVE or their sequelae, 4 due to cancer and 4 due to cardio-respiratory failure (Table II). The age at the time of death was 74 (14) years, and the age at the time of the AVE was 66 (16) years (Table II).

Ankle-brachial index

The baseline prevalence of abnormal ABI was 24.1%, being more prevalent in males (6/17, 35.3%) than females (46/199, 23.1%). In patients who suffered AVE during follow-up, 41.2% had a normal ABI while 58.8% had an abnormal ABI. In patients who remained free of AVE during follow-up, 79% had a normal ABI while 21% had an abnormal ABI. In the analysis structured by the type of AVE we observe the following findings: in patients with IHD and sudden death 100% had an abnormal ABI; in patients with CVD 54.5% had a normal ABI and 45.5% had an abnormal ABI; and in patients with PAD 50% had a normal ABI and 50% had an abnormal ABI (Table III).

Table II. Mortality causes.

Death causes	n (%)	Types
Arterial vascular events	6	4 cerebrovascular events 1 acute myocardial infarction 1 sudden death
Malignant neoplasm	4	2 lung cancer 1 gastrointestinal cancer 1 lymphoma
Other causes	4	1 interstitial lung disease 1 pulmonary hypertension 1 disseminated infection 1 multiple organ failure (at 90 years of age)

Table III. Arterial vascular events and ABI.

	Patients	Normal ABI	Abnormal ABI
All vascular events	17/212 (8.01%)	7/17 (41.2%)	10/17 (58.8%)
Cerebrovascular event: - Cerebrovascular accident (10) - Transient ischaemic attack (1)	11/212 (5.18%)	6/11 (54.5%)	5/11 (45.5%)
Coronary events (3 patients) - Acute myocardial infarction (2) - Angina pectoris with angioplasty (2)	4/212 (1.88%)	0/3 (0%)	3/3 (100%)
Peripheral arterial disease	2/212 (0.94%)	1/2 (50%)	1/2 (50%)
Sudden death	1/212 (0.47%)	0/1 (0%)	1/1 (100%)
No vascular event during follow-up	**195/212 (91.98%)**	**154/195 (79%)**	**41/195 (21%)**

Table IV. Competing risk regression: abnormal ABI.

Variable	SHR	*p*-value	95% CI
Female	0.22	0.017	0.07-0.77
Family history of early thrombosis	5.44	0.004	1.69-17.51
Previous thrombosis	5.01	0.007	1.55-16.19
Cumulative dose of prednisone	1.01	0.007	1.005-1.031
Abnormal ABI	2.65	0.089	0.86-8.14

SHR: subdistribution hazard ratio; ABI: ankle-brachial index.

Multivariate analysis

In the final model, the risk factors associated to cardiovascular events were family history of early thrombosis (SHR 5.44 [1.69-17.51]; p=0.004), personal history of previous arterial thrombosis (SHR 5.01 [1.55-16.19]; p=0.007) and cumulative dose of corticosteroids (in prednisone gram equivalents) (SHR 1.01 [1.005-1.031]; p=0.007). An abnormal baseline ABI showed a SHR 2.65 [95% confidence interval 0.86-8.14]; p=0.089. As a protective factor we identify the female sex (SHR 0.22 [0.07-0.77]; p=0.017) (Table IV).

Discussion

In the main objective of the study, we have found a clear statistical trend but not an association between abnormal ABI and risk of AVE. As secondary objectives of the study, we identified a set of risk factors to suffer AVE in SLE patients: family history of premature AVE, previous cardiovascular disease, male gender and higher cumulative glucocorticoids dose.

Although the results do not conclusively confirm the utility of the ABI as a predictor of AVE, we think that this

clear statistical trend observed should be taken into consideration, bearing in mind the relatively low power of the study, due to the small number of patients included in the study and the small number of events occurring during the 5-year follow-up time. In the studies that found association in the general population between the abnormal ABI and the risk of AVE, the number of participants was much higher, including thousands of patients, and with a longer follow-up, as can be seen in different cohorts or systematic reviews (23-26). For all these reasons we can neither confirm nor rule out a possible association between an abnormal ABI and a higher risk of AVE in SLE patients.

In the lupus population, only one study had, to our knowledge, a similar design. In a prospective cohort study, Kao *et al*. (15) investigated the association between the presence of carotid plaque, detected by using B-model ultrasound, and incident cardiovascular events: myocardial infarction, coronary angioplasty, coronary artery bypass graft, fatal cardiac arrest and cerebrovascular accident. All patients were women without previous cardiovascular disease, unlike our study cohort. The presence of carotid plaque (HR 4.67, 95% CI 1.41–15.53, p=0.01) and the duration of corticosteroid use (HR 1.08, 95% CI 1.03–1.13, p<0.01) were both associated with an increased risk for vascular events. The family history of AVE was analysed but was found non-significant.

In Schoenfeld's systematic review, only 9/20 of the studies took into account family history of premature AVE (1), and only in one of them a statistically significant association with IHD was shown in the multivariable analysis (26). In our cohort, family history of premature AVE was actually the predictor with the highest SHR. This is in keeping with large cohorts studies in the general population, in which this variable has been related to an increased risk of arterial events; indeed, family history of premature cardiovascular disease has been used for the stratification of total cardiovascular risk in the 2013 European Society of Hypertension (ESH) and the European Society of Cardiology (ESC) guidelines for the management of arterial hypertension (27).

In many studies designed to identify risk factors for AVE in SLE patients, patients with previous vascular disease have been excluded, whilst in the general population a history of arterial thrombosis conferred a very high cardiovascular risk (27). Patients with previous thrombosis had a 5-fold higher risk of AVE in the final model of our study.

Also, male gender was independently associated with an increased risk of arterial events. This finding is not reported in many of the studies of vascular disease in SLE because have been conducted in exclusively female populations (1), but is consistent with the results obtained in some SLE cohort and population-based studies (28-30), in the general population (31) and in other inflammatory rheumatic diseases (32).

The effect of glucocorticoids on the cardiovascular risk of SLE patients is complex. On the one hand, glucocorticoids can control lupus activity, which is a cause of premature atherosclerosis. On the other hand, the metabolic side effects of glucocorticoid can themselves increase cardiovascular risk (33), taking into account that the dose/toxicity gradient is not linear: damage risk increases with doses of prednisone over 7.5 mg/d, reaching maximum levels with doses over 30 mg/d (34). Thus, it is not surprising that studies analysing the relation of glucocorticoid therapy with cardiovascular disease have yielded heterogeneous results (1). In this study we built three different variables to model the effect of glucocorticoids on AVE: the maximum dose received during the follow-up, the average daily dose and the total cumulative dose. Only the cumulative total dose was identified as a risk factor, with each increase of 10 g over the mean of the whole cohort, 18.7g, resulting in an increased risk for AVE of around 2%. This is in keeping with a recent study from our cohort, in which a reduced dose glucocorticoid regime resulted in a significant decrease in cardiovascular damage after 5 years of follow-up (35). More recently, a longitudinal cohort study in Chinese SLE patients from Hong-Kong has shown that those receiving doses of prednisone ≥0.6 mg/kg/day for 4 weeks or longer were 14-fold more likely to die during the follow-up (36).

Our study has some limitations. When interpreting our results it must be taken into account the fact that our population was mainly constituted by Caucasians living in a country with a low general cardiovascular risk. Almost 90% of our patients received treatment with hydroxychloroquine, and the doses of prednisone were low compared with other cohorts (33). In probable relation with all this, the absolute number of AVE was low, a fact that could have reduced the study power to identify risk factors for arterial events. Another limitation is the number of patients included and the time of follow-up. Probably these two factors also limit the study power.

Among the strengths of our study, it should be emphasised the use of detailed information on clinical and immunological SLE variables, treatments administered and internationally agreed upon cardiovascular risk factors. Follow-up data were available for more than 98% of the 216 patients included in the original study. The statistical analysis was performed using the CRR approach, which substantially reduces bias associated with unreliable assumptions about the censoring profiles common in classical survival studies.

Of course, the findings obtained should be confirmed by other cohorts. A longer follow-up of this cohort can give us a future answer to the question of the prognostic utility of ABI for AVE in patients with SLE.

In summary, we have found that male gender, higher cumulative prednisone dose, family history of early vascular disease and personal history of arterial vascular disease are related to a higher risk for AVE in SLE patients. Regarding the ABI, we can consider carrying out this test, because could be useful to identify patients with SLE with a possible higher risk of AVE. In patients who present the previous factors, a more aggressive control of modifiable cardiovascular risk factors should be accomplished.

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Sección 6

DISCUSIÓN

6.1.-PREVALENCIA DE EAP EN PACIENTES CON LES

HIPÓTESIS 1: La prevalencia de EAP en los pacientes con LES podría ser superior a la de la población general, al igual que otras manifestaciones ateroscleróticas.

OBJETIVO 1: Analizar la prevalencia de EAP en pacientes con LES.

La prevalencia de EAP definida como un ITB ≤0,9 hallada en esta cohorte de 216 pacientes con LES ha sido del 21%. La edad media (DE) de los pacientes era de 49 (15) años. La prevalencia de EAP sintomática fue del 3,2% y la de EAP asintomática del 17,8%.

La prevalencia observada en este estudio es muy superior a la hallada en estudios en la población general española, que oscila entre el 4,5-8,5%, aunque incluyen cohortes con edades mayores a la de la cohorte estudiada por lo que no son directamente comparables [12]. En aquellos estudios que incluyen pacientes menores de 55 años, la prevalencia de EAP en población general es menor; por ejemplo, un estudio transversal sobre una población de 6.262 individuos de la población general realizado en Girona encontró que en el subgrupo de pacientes de entre 45-54 años la prevalencia de EAP hallada mediante ITB era del 2,1% en mujeres y del 1,1% en hombres [107]. Los hallazgos de nuestro estudio muestran claramente que la prevalencia de EAP en pacientes con LES es superior a la de la población general en conjunto y que podría ser entre 5 y 10 veces superior cuando se compara con grupos de edad similar.

Los estudios de prevalencia de EAP en pacientes con LES son escasos y con diseños heterogéneos, lo que explica el hallazgo de resultados dispares. Un estudio en 32 pacientes chinas con LES sin enfermedad vascular conocida ni diabetes mellitus, diseñado para analizar la correlación entre rigidez de la pared arterial y EAP, no

encontró ningún caso de ITB alterado, mientras que otro estudio realizado en 58 pacientes de Taiwan halló un 4% de ITB patológicos [103-104]. Los resultados de nuestro estudio muestran una prevalencia claramente superior, como la que se halló en un estudio realizado en Londres en 91 pacientes con LES menores de 55 años, en los que el ITB era anormal en el 37% de los casos (aunque se consideró un punto de corte <1 y no ≤0,9, por lo que los resultados tampoco son directamente comparables) [99]. Respecto a la prevalencia de EAP sintomática, nuestros resultados se aproximan a los hallados en la Toronto Lupus Cohort (3,2% y 2% respectivamente) [108].

Recientemente, dos meta-análisis han aportado datos sobre la prevalencia de EAP en pacientes con LES en comparación con la población general. En el de Forte et al, publicado en 2020 y que incluía 8 estudios con 263258 pacientes, se observó una prevalencia de EAP en pacientes con LES del 15,8%, 4 veces mayor que los controles sin LES (3,9%); a la hora de interpretar estos resultados, hay que señalar que este meta-análisis presenta una elevada heterogeneidad (I2 98,1%) e incluye estudios poblacionales de prevalencia de aneurisma de aorta abdominal [106]. Stewart et al, en otro meta-análisis publicado en 2019 en el que se incluyeron 11 publicaciones con un total de 1030 pacientes, observaron que el riesgo de tener un ITB patológico era tres veces superior en los pacientes con LES que los controles sin LES, esta vez con una baja heterogeneidad (I2 13%) [105].

En resumen, este estudio muestra que un porcentaje muy importante (21%) de pacientes con LES presenta EAP definida con un ITB ≤0,9, si bien sólo una pequeña parte de los pacientes con LES tienen EAP sintomática (3,2%). Aunque nuestro estudio no incluye grupo control de comparación, tras la revisión bibliográfica esta prevalencia parece claramente superior a la de la población general, especialmente respecto a la población general con edad por debajo de 55 años.

6.2.-SÍNDROME METABÓLICO EN PACIENTES CON LES

En esta editorial se realiza una revisión sobre el riesgo aumentado de eventos aterotrombóticos que presentan los pacientes con LES y los factores de riesgo asociados y se discute el papel que el síndrome metabólico (SM) puede jugar en este contexto, con las siguientes consideraciones:

- Los factores de riesgo cardiovascular tradicionales, como la HTA, la diabetes mellitus, la dislipidemia y el tabaquismo, son más prevalentes en estos pacientes; sin embargo, su presencia no explica completamente la mayor prevalencia de vasculopatía aterosclerótica.
- El SM agrupa varios factores de riesgo vascular que se traducen en obesidad central y resistencia a la insulina, lo que condiciona un mayor riesgo de desarrollo de DM tipo 2 y enfermedad cardiovascular. Existen diferentes definiciones de SM, cada una con distintos criterios (Organización Mundial de la Salud, Federación Internacional de Diabetes, Adult Treatment Panel III -ATP III-). La existencia de SM (independientemente de la definición que se elija) se ha asociado con un mayor riesgo de enfermedad cardiovascular, aunque esta asociación no es tan clara como con los factores de riesgo clásicos. El SM es una herramienta clínica útil en la población general para identificar a los pacientes que precisan una mayor intervención, ya que es un predictor de un mayor riesgo relativo de desarrollo a largo plazo de enfermedad cardiovascular y diabetes.
- En pacientes con LES la prevalencia de SM es superior a la población general; en pacientes menores de 40 años puede ser hasta cuatro veces más frecuente. Entre los pacientes con LES y SM, el factor de riesgo más frecuente es la HTA, mientras que la presencia de perímetro abdominal aumentado es menor que en los controles sanos. Este hecho puede hacer que se infravalore la prevalencia de SM en los pacientes con LES, ya que si se eligen definiciones de SM donde la presencia de perímetro abdominal aumentado es necesaria para el

diagnóstico de SM. Además de los factores clásicos, diversos estudios concluyen que la presencia de SM se asocia con la actividad inflamatoria de la enfermedad (mayores puntuaciones en la escala SLEDAI, mayores niveles plasmáticos de PCR, elevación de la VSG, niveles bajos de C3), el daño acumulado y el empleo de ciertos fármacos como los glucocorticoides.

Teniendo en cuenta estas consideraciones, se ha incluido el síndrome metabólico entre las variables a estudio, siguiendo la definición del ATP III, que incluye factores clínicos y analíticos que se utilizan habitualmente en la práctica diaria y no tiene en consideración la demostración de la resistencia a la insulina o hiperinsulinemia (tabla 6.1). La definición de la ATP III considera la obesidad central (determinada por el perímetro abdominal) como un factor más entre cinco y no como un factor necesario para el diagnóstico de SM, por lo que no debería infravalorar la prevalencia de SM en pacientes con LES. Tal y como se ha mostrado en el apartado 4.2. 'VARIABLES RELACIONADAS CON EL RIESGO CARDIOVASCULAR, DAÑO EN ÓRGANO DIANA Y EVENTOS CARDIOVASCULARES PREVIOS' la prevalencia de SM en nuestra cohorte es del 9.7%.

Tabla 6.1: Diagnóstico de SM según el ATP III
Tres o más de los factores siguientes:
1.-Obesidad central: Perímetro abdominal ≥102 cm en hombres y ≥88 cm en mujeres.
2.-Hipertrigliceridemia: Triglicéridos ≥1,7 mmol/l (150 mg/dl).
3.-Disminución de HDL colesterol: HDL colesterol <1,0 mmol/l (40 mg/dl) en hombres y <1,3 mmol/l (50 mg/dl) en mujeres.
4.-Hipertensión arterial: Presión arterial ≥130/85 o tratamiento medicamentoso.
5.-Glucemia en ayunas ≥6,1 mmol/l (110 mg/dl).

6.3.-FACTORES DE RIESGO DE EAP EN PACIENTES CON LES

HIPÓTESIS 2: La presencia de EAP en pacientes con LES se asocia probablemente con una serie de factores de riesgo cardiovascular, tanto tradicionales (por ejemplo, tabaquismo, HTA, dislipemia, diabetes mellitus) como específicos del LES (por ejemplo, actividad inflamatoria de la enfermedad o tratamiento con corticoides).

OBJETIVO 2: Analizar los factores de riesgo potencialmente asociados a la EAP en pacientes con LES.

En los análisis univariantes realizados en el primer trabajo se identificaron varias variables asociadas con la presencia de un ITB ≤0,9: edad, hipertensión arterial, hipercolesterolemia, diabetes mellitus, menopausia, antecedente de enfermedad coronaria, antecedente de enfermedad cerebrovascular y las variables combinadas 'cualquier factor de riesgo vascular' y 'cualquier evento arterial previo' (tabla 6.2); estos hallazgos en los análisis univariantes son congruentes con lo publicado en estudios previos. Sin embargo, esta asociación no se ha mantenido en los análisis multivariantes, en los que únicamente la edad se ha asociado de forma independiente con ITB ≤0,9, mientras que la variable combinada 'cualquier factor de riesgo vascular' (diabetes, hipertensión arterial, hipercolesterolemia o tabaquismo activo) ha mostrado una tendencia estadística en el límite de significación (tabla 6.3). Se ha observado también una asociación significativa entre un ITB ≤0,9 y la puntuación en la escala SCORE (Tabla 6.4).

Tabla 6.2. Análisis univariantes: variables cardiovasculares asociadas a ITB ≤ 0,9

Variable	ITB <0.9 n=46	ITB normal n=170	p
Edad al diagnóstico de LES*	43 (17)	34 (17)	0,001
Edad al ITB*	57 (15)	47 (14)	<0,001
Diabetes mellitus	4/46 (8,7)	3/179 (1,8)	0,018
Hipertensión arterial	24/46 (52,2)	47/170 (27,5)	0,002
Hipercolesterolemia	23/46 (50)	51/170 (29,8)	0,018
Cualquier factor de riesgo vascular (diabetes, hipertensión, hipercolesterolemia, tabaquismo activo)	37/46 (80)	99/170 (58)	0,005
Cualquier factor de riesgo vascular (diabetes, hipertensión, hipercolesterolemia, tabaquismo activo o previo)	41/46 (89,1)	120/170 (70,8)	0,011
Menopausia*	27/41 (66)	75/161 (47)	0,03
Enfermedad coronaria/insuficiencia cardiaca	4/46 (8,7)	2/170 (1,2)	0,006
Enfermedad cerebrovascular	8/46 (17,4)	11/170 (6,4)	0,02
Cualquier EVA previo	13/46 (28,3)	13/170 (7,6)	<0,001

*Años (DE). El resto de valores se muestran como n (%).
**200 mujeres.
EVA: Evento vascular arterial. IC: Insuficiencia cardiaca; ITB: índice tobillo-brazo; LES: lupus eritematoso sistémico.

Tabla 6.3. Análisis multivariantes: variables cardiovasculares asociadas a ITB ≤ 0,9

Variable	OR	IC 95%	p
Edad al ITB	1,04	1,01 – 1,07	<0,001
Cualquier factor de riesgo vascular (diabetes, hipertensión, hipercolesterolemia, tabaquismo activo)	2,3	0,99 – 5,1	0,053

Tabla 6.4. Asociación entre escala SCORE e ITB ≤0,9

Puntuación SCORE	ITB patológico: n/N (%)
0	17/140 (12%)
1	11/31 (35%)
2	7/22 (35%)
3	2/5 (40%)
4	3/7 (43%)
≥5	6/11 (54%)

p = 0,004. SCORE: Systematic Coronary Risk Evaluation.

Cuando comencé este estudio en 2010, la EAP había sido poco estudiada en los pacientes con LES. El primer trabajo al respecto es un estudio de Londres [99] en el que se incluyeron 91 pacientes con LES, menores de 55 años y se definió un punto de corte <1 en el ITB para establecer la EAP. Los autores identificaron un 37% de paciente con EAP. La edad fue la única variable asociada con un ITB<1. En otros estudios realizados con similar diseño (realización de ITB en una cohorte de pacientes con LES), en cambio, no se ha identificado la edad como factor de riesgo para EAP en estos pacientes [105-106].

Otros autores han encontrado asociación entre la aterosclerosis y/o enfermedad cardiovascular con algunos factores de riesgo tradicionales, pero no con todos ellos. Petri *et al* encontraron asociación entre la enfermedad coronaria (angina, infarto agudo de miocardio y/o muerte súbita) y los niveles de colesterol, obesidad y la hipertensión arterial, pero no con la diabetes o el tabaco [82]. Manzi *et al* describen una incidencia de infarto agudo de miocardio en mujeres con LES mayor de lo esperado según el Framingham Study Cohort. En ese trabajo observan una asociación con la hipercolesterolemia, pero no con otros factores de riesgo vascular tradicionales; las mujeres en estado post-menopaúsico sufrieron con más frecuencia eventos coronarios frente a las premenopaúsicas [67]. Urowitz *et al* demostraron una relación entre eventos cardiovasculares (infarto agudo de miocardio, AIT, ictus, EAP o muerte súbita) y la hipercolesterolemia, tabaquismo e hipertensión arterial, pero no con la diabetes [94].

La influencia de los factores de riesgo vascular tradicionales en los pacientes con LES parece clara. Hemos encontrado una prevalencia de EAP 10 veces mayor de lo esperado respecto a población general y la presencia de ITB ≤0,9 se asocia claramente con una puntuación elevada en la escala SCORE, y la puntuación en la escala SCORE, que calcula el riesgo vascular en función de edad, sexo, diabetes mellitus,

tabaquismo, hipertensión arterial e hipercolesterolemia. Más de la mitad de nuestra cohorte tiene sobrepeso, comparado con el 39% descrito en la población general española [109]. El 34% de la cohorte tiene hipercolesterolemia, comparado con el 50% de la población general española [110]; y el 33% de nuestros pacientes tiene hipertensión arterial, comparado con el 35% en la población general [111]. Hay que señalar que el rango de edad de estos estudios epidemiológicos es de 18 a 80 años, mientras que en nuestro trabajo la edad media es de 36 años. Esto nos sugiere que la hipercolesterolemia, la hipertensión arterial y otros factores de riesgo vascular pueden aparecer de forma más precoz en los pacientes con LES, como demostraron en su trabajo Bruce *et al* [112], con el efecto clínico esperado en el desarrollo de la enfermedad vascular.

Otros grupos han encontrado asociación entre aterosclerosis y/o enfermedad cardiovascular y factores relacionados con el LES como la duración de la enfermedad [67,82], la presencia de anticuerpos antifosfolípido [113, 114], el fenómeno de Raynaud, la enfermedad renal, la afectación neuropsiquiátrica y la vasculitis [115]. Por el contrario, nosotros no hemos encontrado asociación entre tener ITB ≤0,9 y la mayoría de los factores relacionados con el LES, como el perfil de autoanticuerpos, la actividad de la enfermedad, el daño crónico o los tratamientos recibidos, como los corticoides o los antimaláricos u otros inmunosupresores. En el análisis univariante los niveles de fibrinógeno eran más elevados en el grupo de ITB patológico. A pesar de perderse la significación estadística en el análisis multivariable, este dato podría sugerir una relación entre la inflamación crónica en el endotelio vascular y el desarrollo de aterosclerosis.

6.4.-VARIACION SEGÚN LA EDAD DE LA INFLUENCIA DE LOS FACTORES DE RIESGO DE EAP EN PACIENTES CON LES

HIPÓTESIS 3: La influencia de los factores de riesgo vascular asociados a EAP en pacientes con LES podría variar dependiendo de la edad, siendo más importantes los específicos del LES en los pacientes más jóvenes y los factores de riesgo tradicionales en los pacientes de mayor edad.

OBJETIVO 3: Analizar la influencia de los factores de riesgo para la EAP en diferentes grupos de edad de pacientes con LES.

Los resultados del segundo trabajo muestran que la prevalencia de la EAP en pacientes con LES se incrementa con la edad: 3/37 (8,1%) en el grupo 1 (edad ≤34 años), 12/84 (14,2%) en el grupo 2 (35-49 años) y 31/95 (32,6%) en el grupo 3 (edad ≥50 años). Asimismo, la prevalencia de los factores de riesgo vascular también se incrementa con la edad (tabla 6.5)

Las variables asociadas en los análisis univariantes con la presencia de un ITB ≤0,9 en cada uno de los grupos de edad fueron los siguientes (tabla 6.6):

- Grupo 1 (≤34 años): Síndrome antifosfolípido, presencia de anticuerpos antifosfolípido, dosis acumulada de prednisona.
- Grupo 2 (35-49 años): Diabetes mellitus, hipertensión arterial, dosis de prednisona media diaria menor de 7,5 mg, obesidad abdominal y niveles de fibrinógeno.
- Grupo 3 (≥50 años): Niveles de vitamina D, hipercolesterolemia, cualquier factor de riesgo vascular (diabetes, hipertensión, hipercolesterolemia, tabaquismo activo o previo), enfermedad coronaria, cualquier evento arterial previo, anticuerpos anticardiolipina, anticuerpos

antifosfolípido, dosis de prednisona media diaria menor de 7,5 mg, dosis acumulada de micofenolato.

Tabla 6.5. Distribución de los factores tradicionales de riesgo vascular y relacionados con el LES por grupos de edad.

Los valores se expresan en n/N (%), salvo que se indique de otra manera.

Variable	Grupo 1 (≤34 años)	Grupo 2 (35-49 años)	Grupo 3 (≥50 años)
Hipertensión arterial	4/37 (10,8)	20/84 (23,8)	47/95 (49,4)
Diabetes mellitus	0/37 (0)	3/84 (3,5)	4/95 (4,2)
Hipercolesterolemia	3/37 (8,1)	20/84 (23,8)	51/95 (53,6)
Tabaquismo (activo)	15/37 (40,5)	28/84 (33,3)	22/95 (23,1)
Tabaquismo (activo o previo)	18/37 (48,6)	49/84 (58,3)	41/95 (43,1)
Obesidad abdominal	10/37 (27)	25/84 (29,7)	38/95 (40)
IMC: sobrepeso-obesidad	13/37 (35,1)	44/84 (52,3)	52/95 (54,7)
Sedentarismo	20/37 (54)	35/84 (41,6)	42/95 (44,2)
Algún factor de riesgo vascular	22/37 (59,4)	59/84 (70,2)	80/95 (84,2)
Síndrome metabólico	3/37 (8,1)	6/84 (7,1)	12/95 (12,6)
SAF	2/37 (5,4)	10/84 (11,9)	9/95 (9,4)
aFL	14/37 (29,7)	27/84 (32,1)	33/95 (34,7)
Nefritis lúpica	12/37 (32,4)	30/84 (35,7)	18/95 (18,9)
SLEDAI al diagnóstico; media (DE)	9,83 (7,8)	8,15 (5,3)	6,1 (3,9)
SLEDAI al ITB; media (DE)	3,08 (3,7)	2,05 (2,9)	1,5 (2,2)
SDI al ITB; media (DE)	0,4 (0,8)	0,98 (1,2)	1,5 (1,5)
Edad diagnóstico LES, años; media (DE)	21,4 (6,1)	30,2 (9,2)	47,4 (15,6)
Duración del LES, años; media (DE)	6,2 (5,3)	11,7 (8,5)	15 (10,5)

aFL: anticuerpos antifosfolipido; IMC: índice masa corporal; ITB: índice tobillo-brazo; LES: lupus eritematoso sistémico; SAF: síndrome antifosfolipido; SDI: SLICC Damage Index; SLEDAI: SLE Disease Activity Index.

Los análisis multivariantes mostraron la asociación con ITB ≤0,9 de la hipertensión arterial en el grupo 2 y de la hipercolesterolemia en el grupo 3; no pudo realizarse análisis multivariante en el grupo 1 por la ausencia de casos de SAF en el grupo de ITB normal frente a 66% en el grupo de ITB patológico y por la presencia de anticuerpos antifosfolípido en el 100% de los pacientes con ITB patológico (tabla 6.7).

Tabla 6.6. Análisis univariantes. Asociaciones con ITB ≤0,9 (se muestran las variables con p<0,1)

Los valores se expresan en n/N (%), salvo que se indique de otra manera.

	ITB patológico	ITB normal	p
Grupo 1 (≤34 años): N=37	**N=3**	**N=34**	
SAF	2/3 (66)	0/34 (0)	0,005
aFL	3/3 (100)	11/34 (32,3)	0,047
Prednisona acumulada, gramos; media (DE)	21,25 (1,89)	7,70 (1,08)	0,058
Grupo 2 (35-49 años): N=84	**N=12**	**N=72**	
Diabetes mellitus	2/12 (16,6)	1/72 (1,3)	0,052
Hipertensión arterial	6/12 (50)	14/72 (19,4)	0,021
Dosis media diaria prednisona <7,5	11/11 (100)	50/68 (73,5)	0,046
Obesidad abdominal, cm; media (DE)	90,46 (14,9)	82,50 (12,2)	0,047
Niveles de fibrinógeno, mg/dl; media (DE)	454 (100)	388 (83,2)	0,021
Grupo 3 (≥50 años): N=95	**N=31**	**N=64**	
Dosis acumulada MF, gramos; media (DE)	0 (0)	111 (442,8)	0,049
Niveles vitamina D, ng/ml; media (DE)	22,2 (8,7)	35,9 (41,4)	0,018
Hipercolesterolemia	21/31 (67,7)	30/64 (46,8)	0,056
Variable combinada (diabetes, hipertensión, hipercolesterolemia, tabaco previo o activo)	30/31 (96,7)	50/64 (78,1)	0,015
Variable combinada (diabetes, hipertensión, hipercolesterolemia, tabaquismo activo)	28/31 (90,3)	44/64 (68,7)	0,023
Enfermedad coronaria/insuficiencia cardiaca	4/31 (12,9)	2/64 (3,1)	0,086
aCL	4/31 (12,9)	24/64 (37,5)	0,011
aFL	6/31 (19,3)	27/64 (42,1)	0,028
Evento arterial previo	11/31 (35,4)	11/64 (17,1)	0,047
Dosis media diaria prednisona <7,5	28/30 (93,3)	48/63 (76,1)	0,038

SAF: síndrome antifosfolipido; aFL: anticuerpos antifosfolípido; aCL: anticuerpos anticardiolipina: MF: Micofenolato.

Tabla 6.7. Variables asociadas con ITB patológico en los diferentes grupos de edad (análisis multivariante)

Variable	OR	IC 95%	p
Grupo 1 N/A			
Grupo 2 Hipertensión arterial Niveles de Fibrinógeno	 4,61 1,007	 1,15-18,44 0,99-1,014	 0,031 0,073
Grupo 3 Hipercolesterolemia	 2,49	 0,97-6,4	 0,057

N/A: no aplicable; ITB: Índice tobillo-brazo.

La edad es uno de los principales factores de riesgo vascular; de hecho, la mayoría de las escalas de riesgo vascular se basan en la edad, como el SCORE o la escala de Framingham [17; 116]. En una cohorte de más de 3.6 millones de personas a los que se les realizan una valoración de enfermedad cardiovascular con diferentes técnicas (ITB, Doppler carotideo y Doppler abdominal), la prevalencia de cualquier enfermedad vascular se incrementa de forma progresiva después de los 40 años: del 2% en el grupo de 41-50 años hasta el 13% en el grupo de 71-80 años. Después de realizar un ajuste por los factores de riesgo tradicionales, en este estudio identifican que cada década adicional dobla el riesgo de enfermedad arterial periférica (OR 2,14; IC 95% 2,12-2,15) [117].

La influencia de los factores de riesgo vascular puede cambiar a lo largo de la vida. En un estudio realizado en población general, dentro del estudio de la cohorte de Framingham, se observó que la influencia de la presión arterial sistólica, diastólica y la presión de pulso en el riesgo de presentar enfermedad coronaria se modificaba con la edad. En los pacientes menores de 50 años el predictor más potente de enfermedad coronaria era la presión arterial diastólica; en los pacientes entre 50-59 años, los tres parámetros contribuían de igual manera como factores de riesgo para la enfermedad coronaria; y en los pacientes mayores de 60 años, la presión de pulso era el predictor más potente para la enfermedad coronaria [118].

Está claro que la edad influye en la enfermedad vascular; el hallazgo en nuestro estudio de un incremento de la prevalencia de ITB patológico con la edad es concordarte con este hecho. En el segundo trabajo publicado observamos además que los diferentes factores de riesgo pueden actuar con diferente intensidad según la edad de los pacientes. La aterosclerosis comienza ya a desarrollarse en los pacientes con LES desde edades tempranas, siendo mucho más prevalente en los pacientes con LES que en la población general, como

se puede ver en los trabajos realizados en diferentes territorios vasculares, incluidos estudios poblacionales [40, 68-71, 119, 120]. En nuestro trabajo observamos que en el grupo de pacientes de ≤34 años el SAF, los anticuerpos antifosfolípido y la dosis acumulada de corticoides son factores de riesgo para tener un ITB patológico, aunque no hemos podido hacer un análisis multivariante; conforme aumenta la edad de los pacientes observamos que la influencia de los factores de riesgo vascular más tradicionales adquieren una mayor importancia, concretamente la hipertensión arterial en el grupo de 35-49 años y la hipercolesterolemia en el grupo de ≥50. Estos hallazgos sugieren que a lo largo de la vida de los pacientes con LES los factores de riesgo vascular modulan su efecto en el desarrollo de aterosclerosis. Parece que son más importantes los relacionados con el LES (como el SAF o la presencia de aFL o el tratamiento con corticoides) en los pacientes más jóvenes. Y conforme la edad avanza, influyen más los factores de riesgo vascular convencionales, como la hipertensión arterial o la hipercolesterolemia.

6.5. VALOR PREDICTIVO DEL ITB PARA LA APARICION DE EVENTOS VASCULARES ARTERIALES EN PACIENTES CON LES

HIPÓTESIS 4: La presencia de un ITB patológico podría permitir la identificación de un subgrupo de pacientes con LES con un mayor riesgo de eventos vasculares arteriales a largo plazo.

OBJETIVO 4: Determinar el potencial valor predictivo del ITB para la aparición de eventos vasculares arteriales en pacientes con LES.

Los datos del seguimiento a 5 años estuvieron disponibles para 212 (98.1%) pacientes (1016 pacientes/año). 186 pacientes (88%) sobrevivieron durante los 5 años de seguimiento sin sufrir ningún evento vascular arterial (EVA). Durante el periodo de seguimiento se produjeron 14 fallecimientos (cuyas causas se muestran en la tabla 6.8) y se produjeron 18 eventos vasculares arteriales (EVA) en 17 (8%) de los pacientes: 11 eventos cerebrovasculares (10 ictus isquémicos y 1 AIT), 4 eventos coronarios (2 IAM, 2 anginas que precisaron revascularización percutánea), 2 eventos arteriales periféricos y una muerte súbita en un paciente con antecedente de cardiopatía isquémica que había precisado revascularización coronaria percutánea previa. La edad media en el momento del fallecimiento fue de 74 (14 años) y la edad media en el momento del EVA fue de 66 (16) años.

Tabla 6.8. Causas de mortalidad

Causas de muerte	N	Tipos
EVA	6	4 eventos cerebrovasculares
		1 IAM
		1 muerte súbita
Neoplasias	4	2 cáncer de pulmón
		1 cáncer gastrointestinal
		1 linfoma
Otras causas	4	1 enfermedad pulmonar intersticial
		1 hipertensión pulmonar
		1 infección diseminada
		1 fallo multiorgánico (90 años de edad)

EVA: eventos vasculares arteriales; IAM: infarto agudo miocardio.

A pesar del relativamente bajo número de EVA que se produjeron durante el seguimiento, en los análisis multivariantes hemos identificado una tendencia estadística (sin llegar a una asociación significativa) entre la existencia de un ITB anormal (≤0,9 o > 1,4) y el riesgo de sufrir un evento vascular arterial [SHR 2,65 (IC 95% 0,86-8,14, p 0,089)]. Además, el sexo masculino, la dosis acumulada de prednisona, una historia familiar de enfermedad vascular precoz y la enfermedad vascular previa se identificaron como predictores independientes de eventos vasculares arteriales (EVA) (tabla 6.9).

Tabla 6.9. Regresión de riesgos competitivos: EVA durante seguimiento

Variable	SHR	p	IC 95%
Sexo femenino	0,22	0,017	0,07-0,77
Historia familiar de enfermedad vascular precoz	5,44	0,004	1,69-17,51
EVA previo	5,01	0,007	1,55-16,19
Dosis acumulada de prednisona	1,01	0,007	1,005-1,031
ITB anormal	2,65	0,089	0,86-8,14

SHR: *Sub-distribution Hazard Ratio*; EVA: Evento vascular arterial; ITB: índice tobillo brazo.

Este trabajo muestra, por primera vez en pacientes con LES, que un ITB anormal se puede relacionar con un mayor riesgo de padecer EVA (tabla 6.10). Si bien la significación estadística fue límite (SHR

2,65, IC95% 0,86-8,14, p=0,089), un hecho que probablemente podría explicarse por el número de enfermos incluidos en la cohorte y el pequeño número de eventos que se producen durante los 5 años de seguimiento, las implicaciones clínicas de nuestros resultados están en consonancia con los datos provenientes de estudios poblacionales: la presencia de un ITB anormal implica un mayor riesgo de sufrir eventos vasculares arteriales [22-25].

Tabla 6.10. Eventos vasculares arteriales (EVA) e ITB

	N	**ITB normal**	**ITB anormal**
Todos los EVA	17/212 (8,01%)	7/17 (41,2%)	10/17 (58,8%)
Sin EVA durante el seguimiento	195/212 (91,98%)	154/195 (79%)	41/195 (21%)

Hay dos estudios publicados previamente al nuestro con un diseño similar: realizar una técnica que permita identificar pacientes con alteraciones vasculares y seguirles en el tiempo, de cara a demostrar que los pacientes con esa técnica patológica tienen un mayor riesgo de sufrir eventos vasculares.

En el primer trabajo, Nikpour et al, utilizan la gammagrafía de perfusión miocárdica en una población de 122 mujeres con LES sin enfermedad coronaria previa. En las variables estudiadas relacionadas con el LES incluyen datos de actividad del LES mediante el SLEDAI-2K, daño con el SLICC Damage Index (SDI), presencia de anticuerpos antifosfolípido y los tratamientos: uso/no uso de corticoides, antimaláricos e inmunosupresores. Respecto a los factores de riesgo vascular tradicionales, calculan el riesgo de cada paciente mediante la escala de Framingham a 10 años. La edad media es de 45 años, con un seguimiento medio de 8.7 años. El 37,7% de las mujeres presentaban defectos de perfusión miocárdica, y observan 15 eventos

coronarios (1 IAM y 14 ángor) a lo largo del seguimiento. En el modelo de Cox identifican que los defectos de perfusión miocárdicos son un potente predictor independiente de eventos coronarios, con una HR de 13 (IC 95% 2,8-60,1, p=0,001). Además, la media de los valores obtenidos con la escala de Framingham son un predictor de eventos coronario, con un HR de 1,8 (IC 95% 1,1-2,9, p=0,01). Hay que señalar que los valores del Framingham obtenidos corresponden a valores de bajo riesgo (media de 2,39 en el grupo con defectos), por lo que realmente no parece que esta escala aporte mucho en la identificación de pacientes de mayor riesgo. En este trabajo concluyen que los defectos de perfusión miocárdicos identificados con gammagrafía son predictores de eventos coronarios, y puede ser útil en la identificación de los pacientes con mayor riesgo de sufrir un evento coronario [121].

En el segundo trabajo, de Kao et al, utilizan el eco-Doppler de carótidas para medir el engrosamiento de íntima-media y detectar la presencia de placas de ateroma. Estudian una cohorte proveniente de dos centros (Pittsburg y Chicago) con 392 mujeres sin enfermedad vascular previa. En las variables estudiadas relacionadas con el LES incluyen datos de actividad del LES mediante el SLAM (*Systemic Lupus Activity Measure*), daño con el SLICC Damage Index (SDI), presencia de anticuerpos antifosfolipido y los tratamientos: uso/no uso de corticoides y dosis, uso/no uso de antimaláricos y uso/no uso de inmunosupresores. Respecto a los factores de riesgo vascular tradicionales, evalúan de forma exhaustiva todos ellos y calculan el riesgo de cada paciente mediante la escala de Framingham a 8 años, ajustándolo asumiendo el principio de proporcionalidad. La edad media es de 44 años y les siguen una media de 8 años. EL 32% de los pacientes tenía placa de ateroma, y el engrosamiento de íntima-media era de 0,65 mm. Durante el seguimiento 38 pacientes sufren un evento vascular (ángor, IAM, angioplastia coronaria percutánea, *bypass*

coronario, muerte súbita, AIT e ictus), siendo un evento duro en 17 pacientes (IAM, angioplastia coronaria percutánea, *bypass* coronario, muerte súbita e ictus). En el modelo de Cox identifican que el engrosamiento basal de íntima media es un predictor independiente de evento vascular duro, con un HR de 1,35 (IC 95% 1,12-1,64, p<0,01), así como la presencia de placa de ateroma, con un HR de 4,26 (IC 95% 1,23-14,83, p=0,01). En este trabajo concluyen que la presencia de placas de ateroma y el engrosamiento de íntima-media son predictores de eventos vasculares. Y consideran que la eco-Doppler de carótidas puede ser una herramienta útil para la estratificación del riesgo vascular en los pacientes con LES [122].

Además de un ITB anormal, en nuestro estudio se han identificado otros factores predictivos de EVA (sexo masculino, dosis acumuladas de prednisona, historia familiar de enfermedad vascular precoz y enfermedad vascular previa). En la revisión sistemática de Schoenfeld, solo 9/20 de los estudios tuvieron en cuenta los antecedentes familiares de enfermedad vascular precoz [85], y solo en uno de ellos se mostró una asociación estadísticamente significativa con la enfermedad coronaria en el análisis multivariable [91]. En nuestra cohorte, el tener antecedentes familiares de enfermedad vascular precoz fue el predictor con el SHR más alto. Esto es congruente con estudios de cohortes de gran tamaño en la población general, en los cuales esta variable se ha relacionado con un mayor riesgo de eventos arteriales; de hecho, los antecedentes familiares de enfermedad cardiovascular se han utilizado para la estratificación del riesgo cardiovascular total en las directrices de la Sociedad Europea de Hipertensión (ESH) y la Sociedad Europea de Cardiología (ESC) de 2013 para el tratamiento de la hipertensión arterial [16].

En muchos estudios diseñados para identificar los factores de riesgo de EVA en pacientes con LES, se excluyeron a los pacientes con enfermedad vascular previa, mientras que en la población general los

antecedentes de trombosis arterial confirieron un riesgo cardiovascular muy alto [16]. En nuestro estudio los pacientes con trombosis arteriales previas tenían un riesgo 5 veces mayor de EVA en el modelo final.

El sexo masculino se asoció de forma independiente con un mayor riesgo de eventos arteriales. Este hallazgo es consistente con lo descrito en otros estudios de cohortes y en un estudio poblacional [94, 123, 124]. Muchos de los estudios de enfermedad vascular en el LES se han realizado exclusivamente en poblaciones de mujeres [85], y esta es una de las razones por las que hay tan poca evidencia. Estos hallazgos encajan con lo que se ha demostrado en la población general. El sexo masculino tiene un mayor riesgo vascular per se [125].

Por último, quiero dedicar un apartado específico a los tratamientos farmacológicos empleados en el LES, y su posible implicación (en aumento o reducción) en el desarrollo de aterosclerosis y el riesgo de trombosis arteriales.

Si estudiamos la influencia de los tratamientos recibidos para el LES en la aterosclerosis, como los corticoides, inmunosupresores o antimaláricos, nos encontramos con una gran heterogeneidad de resultados en los estudios publicados.

Roman *et al* [69] identificaron diferentes variables asociadas a tener placas de ateroma en las arterias carótidas: la edad, la duración de la enfermedad, mayor daño del LES medido con SDI; e identificaron como factores protectores de tener placa de ateroma el anticuerpo Sm, recibir tratamiento con hidroxicloroquina y ciclofosfamida. Como dato, los pacientes sin placa de ateroma tenían una mayor proporción de tratamiento con prednisona y una mayor media diaria de prednisona en los últimos 5 años. En un estudio realizado en Brasil [126] el uso de ciclofosfamida, los pulsos de metilprednisolona y una mayor dosis media diaria de prednisona se asoció con una menor frecuencia de

placa de ateroma en las carótidas. Una mayor duración del tratamiento con prednisona se asoció con mayor riesgo de presencia de placa de ateroma, sugiriendo estos datos un posible efecto dual de los esteroides sobre la aterosclerosis. Este efecto se observó en un estudio realizado en una población de pacientes pediátricos con LES. Los efectos beneficiosos de la prednisona en el engrosamiento de íntima-media se obtenían entre las dosis de prednisona de 0,15 mg/kg-0,40mg/kg. En cambio, las dosis inferiores o superiores a estos límites se asociaban con mayor riesgo de engrosamiento de intima media. En este estudio la azatioprina se asoció con un engrosamiento de la íntima media [127]. Un efecto directo de la dosis acumulada de prednisona en la presencia de placas de ateroma en las carótidas, tanto sin ajustar como ajustado a los factores de riesgo tradicionales, se demostró en un trabajo de Doria *et al* [128] y también en un estudio en México de Romero-Díaz *et al* [93].

El efecto de los glucocorticoides sobre la enfermedad cardiovascular de los pacientes con LES es complejo. Por un lado, los glucocorticoides pueden controlar la actividad del lupus, que puede ser una de las causas de la aterosclerosis prematura. Por otro lado, los efectos secundarios metabólicos de los glucocorticoides pueden aumentar el riesgo cardiovascular [129], teniendo en cuenta que el gradiente de dosis/toxicidad parece que no es lineal: el riesgo de daño aumenta con dosis de prednisona superiores a 7,5 mg/día, alcanzando niveles máximos con dosis superiores a 30 mg/día [130]. Por lo tanto, no es sorprendente que los estudios que analizan la relación entre la terapia con glucocorticoides y la enfermedad cardiovascular hayan arrojado resultados heterogéneos [85]. En este estudio construimos tres variables diferentes para modelar el efecto de los glucocorticoides en el EVA: la dosis máxima recibida durante el seguimiento, la dosis diaria promedio y la dosis acumulada total. Solo la dosis total acumulada se identificó como un factor de riesgo, con cada aumento de 10 g sobre

la media de toda la cohorte, 18,7 g, lo que resulta en un aumento del riesgo de AVE de alrededor del 2%. Esto concuerda con un estudio reciente de nuestra cohorte, en el que una dosis reducida de régimen de glucocorticoides dio lugar a una disminución significativa del daño cardiovascular después de 5 años de seguimiento [44]. Más recientemente, un estudio de cohorte longitudinal en pacientes con LES chinos de Hong Kong ha demostrado que los que recibieron dosis de prednisona ≥0,6 mg / kg / día durante 4 semanas o más tuvieron 14 veces más probabilidades de morir (por diferentes causas: infecciones, EVA, cáncer) durante el seguimiento [131].

Estos resultados reflejan la compleja relación existente entre la actividad de la enfermedad, los efectos protectores o adversos de los fármacos utilizados, y la enfermedad vascular. Es posible que cierto grado de inmunosupresión proteja frente al desarrollo de aterosclerosis producido por el daño endotelial asociado a la inflamación crónica, pero también existe un efecto pro ateroscleró tico de los fármacos inmunosupresores, particularmente los corticoides y la azatioprina, que puede prevalecer más allá de un cierto umbral. Además, es casi imposible separar la fuerte asociación que existe entre la severidad de la enfermedad y una mayor inmunosupresión. Por último, en los trabajos publicados se han utilizado y comparado diferentes variables finales, desde eventos vasculares crudos hasta diferentes técnicas que identifican presencia de aterosclerosis, lo que conlleva muy diferentes implicaciones clínicas. Por esto, muchas preguntas sobre el efecto del tratamiento del LES en la enfermedad vascular permanecen sin respuesta.

6.6 FORTALEZAS Y LIMITACIONES DEL ESTUDIO

Para una interpretación adecuada de los resultados, creo que es necesario tener en cuenta las limitaciones y fortalezas del estudio.

6.5.1.-Limitaciones del estudio

- No disponemos de grupo control, para poder comparar prevalencias en grupos de pacientes emparejados.
- La población estudiada es muy homogénea desde el punto de vista étnico, está constituida principalmente por personas caucásicas que viven en un país con un bajo riesgo cardiovascular general.
- Se trata además de una cohorte de pacientes que proviene de un centro especializado, lo que puede conllevar un sesgo de selección de pacientes más graves, dejando fuera de los análisis pacientes con manifestaciones clínicas de LES menos graves.
- El número de enfermos incluidos y el tiempo de seguimiento realizado en esta cohorte puede ser bajo para obtener una adecuada potencia estadística.
- Casi el 90% de nuestros pacientes recibió tratamiento con hidroxicloroquina y las dosis de prednisona fueron bajas en comparación con otras cohortes [129], lo que podría explicar al menos en parte el bajo número de EVA que se produjeron durante el seguimiento.

6.5.2.-Fortalezas del estudio

- El hecho de que la cohorte proceda de un único centro permite que el seguimiento haya sido muy homogéneo y minimiza la pérdida de casos.
- Recogida de información muy detallada sobre las variables clínicas e inmunológicas del LES, los tratamientos administrados y los factores de riesgo cardiovascular.
- El análisis estadístico de la fase prospectiva se realizó mediante el enfoque CRR, que reduce sustancialmente el sesgo asociado con suposiciones poco confiables sobre los perfiles de censura comunes en los estudios de supervivencia clásicos.

6.7.-APLICACIÓN DEL ESTUDIO EN LA PRÁCTICA CLÍNICA

La principal aplicación práctica de este trabajo es la incorporación del ITB (una prueba sencilla, no invasiva y que puede realizarse en la consulta) en la valoración del riesgo cardiovascular de los pacientes con LES, añadida a la historia clínica y a la utilización de las escalas de cálculo de riesgo vascular (SCORE), para identificar a los pacientes que tengan un mayor riesgo de sufrir eventos vasculares.

CONCLUSIONES

En base a las cuatro hipótesis y objetivos planteados en esta tesis doctoral, las conclusiones son las siguientes:

1) La prevalencia de EAP (definida como ITB <0.9) es mayor en los pacientes con LES que en la población general.

2) La edad es el principal factor de riesgo asociado a la presencia de EAP (definida como un ITB ≤0,9). Otros factores de riesgo probablemente asociados son la diabetes mellitus, la hipertensión arterial, la hipercolesterolemia y el tabaquismo activo.

3) La influencia de los diferentes factores de riesgo vascular en el riesgo de EAP (definida como un ITB ≤0,9) es diferente según la edad de los pacientes. En pacientes menores de 35 años probablemente tienen más importancia los factores de riesgo relacionados con la enfermedad (presencia de anticuerpos antifosfolípido o de síndrome antifosfolípido, dosis acumulada de prednisona), mientras que en pacientes mayores de 35 años son más importantes los factores de riesgo convencionales (especialmente hipertensión arterial e hipercolesterolemia).

4) La presencia de un ITB anormal (≤0,9 o >1,4) podría tener un valor predictivo de riesgo incrementado de EVA. El sexo masculino, la historia personal de EVA previos, los antecedentes familiares de enfermedad vascular precoz y una mayor dosis acumulada de prednisona se asocian con un riesgo aumentado de EVA.

ÍNDICE DE ABREVIATURAS

aCL	Anticuerpos anticardiolipina
aFL	Anticuerpos antifosfolípido
AIT	Accidente isquémico transitorio
ANA	Antinuclear antibodies
ATP III	Adult Treatment Panel III
DE	Desviación estándar
DM	Diabetes mellitus
EAP	Enfermedad arterial periférica
ECG	Electrocardiograma
ESC	European Society of Cardiology
ESH	European Society of Hypertension
EULAR/ACR	European League Against Rheumatism / American College of Rheumatology
HDL	High Density Lipoprotein
HR	Hazard ratio
HTA	Hipertensión arterial
IAM	Infarto agudo de miocardio
ICAM-1	Intercellular Adhesion Molecule 1
IL-1	Interleucina I
IL-8	Interleucina 8
ITB	Índice tobillo-brazo
LDL	Low Density Lipoprotein
LES	Lupus eritematoso sistémico
MCP-1	Monocyte Chemoattractant Protein-1
M-CSF	Macrophage colony-stimulating factor
OSI	Organización sanitaria integrada
RIQ	Rango intercuartil
RM	Resonancia magnética
SAF	Síndrome antifosfolípido
SCORE	European Vascular Risk Systematic Coronary Risk Evaluation
SDI	SLICC Damage Index
SHR	Sub-distribution Hazard Ratio
SLAM	Systemic Lupus Activity Measure
SLEDAI	Systemic Lupus Erythematosus Disease Activity Index
SLICC	Systemic Lupus Erythematosus International Collaborating Clinics Damage Index
SNC	Sistema nervioso central
SM	Síndrome metabólico
TC	Tomografía computerizada
TNFα	Tumor Necrosis Factor alfa
VCAM-1	Vascular Cell Adhesion Molecule 1

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Peripheral Arterial Disease in Systemic Lupus Erythematosus: Prevalence and Risk Factors

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Peripheral Arterial Disease in Systemic Lupus Erythematosus: Prevalence and Risk Factors

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ABSTRACT. ***Objective.*** To analyze the prevalence of peripheral arterial disease (PAD) and cardiovascular (CV) risk factors in a cohort of patients with systemic lupus erythematosus (SLE) and to identify variables potentially related to PAD.

Methods. The study included 216 patients with SLE from the Lupus-Cruces prospective observational cohort. The ankle brachial index (ABI) was determined in each patient, with values < 0.9 considered diagnostic of PAD. Demographic and clinical variables, presence of traditional risk factors and CV events, cardiovascular risk calculated by Systematic Coronary Risk Evaluation (SCORE), and treatments received by each patient were analyzed.

Results. Ninety-two percent of patients were women. The mean age (SD) was 49 years (15), with a mean followup (SD) of 12 years (9). The prevalence of low ABI was 21%. CV risk factors were frequent: smoking, 30% of patients; high blood pressure, 32.7%; diabetes mellitus, 3.2%; hypercholesterolemia, 34.1%; and metabolic syndrome, 9.7%. The following variables were associated with low ABI in the univariate analysis: age ($p < 0.001$), hypertension ($p = 0.002$), diabetes ($p = 0.018$), hypercholesterolemia ($p = 0.018$), CV events ($p < 0.001$), SCORE ($p = 0.004$), cumulative dose of cyclophosphamide ($p = 0.03$), and fibrinogen levels ($p = 0.002$). In the multivariate analysis, the only independent variable in the final model was age (OR 1.04, 95% CI 1.02–1.07, $p < 0.001$), with a tendency for the presence of any vascular risk factor (diabetes, hypertension, hypercholesterolemia, or current smoking; OR 2.3, 95% CI 0.99–5.1, $p = 0.053$).

Conclusion. The prevalence of low ABI in patients with SLE is higher than expected. While the association with CV risk factors and vascular disease in other territories was strong, we could not identify SLE-specific variables independently associated with PAD. (First Release Jan 15 2014; J Rheumatol 2014;41:310–17; doi:10.3899/jrheum.130817)

Key Indexing Terms:
SYSTEMIC LUPUS ERYTHEMATOSUS VASCULAR DISEASE HYPERTENSION
CARDIOVASCULAR RISK FACTORS ATHEROSCLEROSIS HYPERCHOLESTEROLEMIA

Patients with systemic lupus erythematosus (SLE) have an increased prevalence of cardiovascular (CV) disease. The bimodal pattern of mortality proposed by Urowitz, *et al* in 1976 described a late peak of mortality mainly due to atherosclerotic heart disease[1]. In different series, the prevalence of symptomatic coronary artery disease (CAD) ranged from 6 to 10%[1,2,3,4]. Women younger than 55 years of age with SLE have a 5-fold to 8-fold higher risk of developing CAD compared to women in the general population[2]. The risk of hospitalization for stroke has been shown to be 2-fold higher in patients with SLE[3].

Premature atherosclerosis has been primarily related to traditional vascular risk factors[2,4]. However [and despite the higher prevalence of hypertension (HTN) and hypercholesterolemia in patients with SLE compared with the general population], traditional Framingham CV risk factors fail to fully explain the increased CV morbidity and mortality seen in SLE[5]. Several studies have found an association between premature atherosclerosis and some SLE-related factors, such as disease duration, steroid therapy, or irreversible organ damage[2,4,5,6].

Peripheral arterial disease (PAD) is frequently asymptomatic and can be difficult to diagnose[7]. The development of noninvasive, simple techniques with low intraobserver and interobserver variability, such as the ankle-brachial index (ABI), has facilitated the detection of subclinical PAD[8]. An ABI lower than 0.9 is diagnostic of PAD with 95–99% accuracy[9]. Moreover, a low ABI has been related to a higher incidence of myocardial infarction and stroke and higher

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mortality, both vascular and nonvascular, in studies in the general European and North American populations[10,11].

The incidence, risk factors, and consequences of PAD have not been well studied in patients with SLE. Given the high risk for atherosclerotic disease in patients with SLE, subclinical PAD is possibly frequent and underdiagnosed, with potential prognostic implications. We aimed to study the prevalence of PAD in the Lupus-Cruces cohort and to analyze the associated vascular and nonvascular risk factors.

MATERIALS AND METHODS

Study objectives. The primary objective in this cross-sectional study was to determine the prevalence of PAD in patients with SLE. The secondary objective was to identify factors potentially associated with PAD.

Study population and variables. Consecutive patients within the Lupus-Cruces longitudinal observational cohort, at the Autoimmune Diseases Unit, Hospital Universitario Cruces (a tertiary teaching center in Barakaldo, Spain, associated with the University of the Basque Country), were invited to participate in our study between January 2010 and June 2011. All patients fulfilled the 1997 classification criteria of the American College of Rheumatology[12]. The local institutional review board of the Hospital Universitario Cruces approved the study protocol in compliance with the Helsinki Declaration. All patients signed an informed consent at the time of enrollment.

Patients were routinely assessed every 3 to 6 months, unless clinical status demands more frequent visits. On the other hand, patients on longterm remission were seen on a yearly basis. At each followup visit, a number of clinical and immunological variables from every patient were routinely collected in a database: demographic characteristics (age, sex, race, year of diagnosis), SLE manifestations, autoantibody profile (anti-DNA, anti-Ro, anti-La, anti-RNP, anti-Sm, antiphospholipid), treatments received (corticosteroids, immunosuppressives, antimalarials, anticoagulants, etc.), complications of the disease and/or treatment. Date of death and cause of death were recorded when appropriate. This database was completed with CV variables: presence of CV risk factors [age, defined as more than 55 and 65 years in men and women, respectively; arterial HTN, defined as 2 consecutive measurements of at least 140/90 mmHg or antihypertensive therapy; diabetes mellitus (DM), defined as 2 consecutive fasting blood glucose determinations ≥ 126 mg/dl or treatment with antidiabetic drugs; hypercholesterolemia, defined as total blood cholesterol fasting levels > 200 mg/dl on 2 consecutive determinations or treatment with cholesterol-lowering drugs; metabolic syndrome according to the Adult Treatment Panel III definition[13]; and current or past smoking], degree of physical exercise (aerobic exercise 1 h/day, at least 3 days a week), presence of previous subclinical organ damage [left ventricular hypertrophy (LVH), presence of microalbuminuria], previous CV events (previous coronary events, heart failure, cerebrovascular disease, renal disease, PAD, or advanced retinopathy), and CV disease-related treatments (aspirin, statins). CV events were defined as the presence of compatible clinical signs and symptoms and eventually confirmed by complementary tests: myocardial infarction was defined as typical chest pain with characteristic electrocardiographic features and elevated levels of creatine kinase (MB fraction) and/or T troponine; stroke by computed tomography (CT) scanning or magnetic resonance imaging; cerebral transient ischemic attacks (TIA) were diagnosed in the setting of acute focal neurologic symptoms/signs lasting < 24 h. CV risk stratification was performed using the European Vascular Risk Systematic Coronary Risk Evaluation (SCORE) scale for the Mediterranean population[14]. The Systemic Lupus International Collaborating Clinics damage index (SDI)[15] and the SLE Disease Activity Index (SLEDAI)[16] were calculated at the time of enrollment for each patient.

The size, weight, and waist and hip circumference were determined in each patient at the time of performing the ABI, along with calculation of the body mass index (BMI). ABI was performed in both legs to each patient in *ad hoc* scheduled visits, from January 2010 to June 2011. The MD2/SD2 Dopplex High Sensitivity Pocket Doppler was used for our study and all ABI were performed by the same 2 trained physicians working together with each patient. In every patient, 1 ABI was calculated for each leg, the lowest value being chosen. An ABI < 0.9 was considered abnormal.

To evaluate subclinical organ damage, the presence of microalbuminuria and LVH were tested. All patients collected an early morning urine sample to calculate the albumin/creatinine ratio. Data to calculate LVH were extracted from echocardiograms performed during a screening program for detecting pulmonary HTN in the whole Lupus-Cruces cohort[17].

Statistical analysis. The clinical descriptors of the cohort were generated, using means with SD, medians and ranges, or proportions. The total prevalence of PAD was calculated. The relation between the different SCORE categories and the normal/abnormal ABI was tested by McNemar test. To identify associations with PAD, the following independent variables were tested against the dependent variable "ABI lower than 0.9", using chi-square with Yates' correction or Student t-test: age at SLE diagnosis, age at the time of ABI, disease duration, sex, age as a vascular risk factor, abdominal obesity, metabolic syndrome, DM, HTN, hypercholesterolemia, smoking (current or past), any vascular risk factor (DM or HTN or hypercholesterolemia or current/past smoking), exercise, alcohol consumption, family history of premature CV disease, BMI, menopause, previous subclinical organ damage (LVH and microalbuminuria), previous CV events [ischemic heart disease and/or heart failure (IHD/HF), stroke, PAD], chronic renal failure, previous arterial thrombosis (stroke or IHD/HF or PAD), uric acid, vitamin D levels, previous lupus nephritis or antiphospholipid syndrome, anti-DNA, anti-Ro, anti-La, anti-U_1RNP, anti-Sm, and antiphospholipid antibodies (aPL; lupus anticoagulant and/or anticardiolipin antibodies at medium-high levels on at least 2 different determinations 12 weeks apart), SLEDAI, SDI, prednisone (cumulative dose and maximum dose ever received), hydroxychloroquine (yes/no and total dose), cyclophosphamide (cumulative dose), low-dose aspirin (number of months on treatment), anticoagulants (no. mos taking treatment), or statins (no. mos taking treatment) and fibrinogen levels at the time of the ABI. Those variables with a p value ≤ 0.1 in the univariate analysis were subsequently included in a backward stepwise logistic regression model to identify independent associations with PAD.

All statistical analysis was done using the software SPSS 20.0.0 statistical package for Mac OS X (SPSS Inc.).

RESULTS

Demographic and SLE-related variables. Two hundred sixteen patients were studied; 200 were women (92%). Two hundred nine patients (96%) were white, with the remaining consisting of 3 Afro-Caribbeans, 2 Hispanics, and 2 Arabs. The mean (SD) age at SLE diagnosis was 36 years (15). The mean age at the time of the ABI study was 49 (15) years, with a mean (SD) followup after SLE diagnosis of 12 (9) years. The remaining clinical and therapeutic variables are shown on Table 1.

CV risk factors, target organ damage, and previous CV events. Traditional CV risk factors were frequent in our cohort (Table 2). As a whole, 162 patients (74.7%) had at least 1 traditional CV risk factor. In terms of CV risk, 205 patients (95%) had a SCORE between 0 and 4 and 11 patients (5%) had a SCORE ≥ 5, which reveals a high or very high CV risk.

LVH was present in 15 patients (7%) and microalbu-

Table 1. Demographic and clinical characteristics of the cohort (n = 216). Values are expressed as n (%) unless otherwise noted.

Age at study, yrs, mean (SD)	49 (15)
Age at diagnosis of SLE, yrs, mean (SD)	36 (15)
Sex: female	200 (92)
SLE duration, yrs, mean (SD)	12 (9)
Autoantibodies	
Anti-DNA	106 (48.8)
Anti-Ro	70 (32.3)
Anti-La	18 (8)
Anti-RNP	30 (13.8)
Anti-Sm	29 (13.4)
Antiphospholipid antibodies	75 (34.6)
Lupus nephritis	60 (27.6)
Antiphospholipid syndrome	21 (9.7)
SDI at ABI	
0	98 (45.2)
1	53 (24.4)
2	31 (14.3)
3	19 (8.8)
4	11 (5.1)
5	4 (1.8)
8	1 (0.5)
SLEDAI at ABI	
0	104 (48.1)
1–5	91 (42.2)
≥ 6	21 (9.7)
Use of prednisone: y/n	191/25
Average daily dose of prednisone, mg/d, mean (SD)	5.6
Use of hydroxychloroquine:y/n	193/23
Use of immunosuppressive drugs	
Cyclophosphamide: y/n	52/164
Mycophenolate: y/n	34/182
Azathioprine: y/n	64/152
Use of statins: y/n	73/143

ABI: Ankle-brachial index; SDI: Systemic Lupus International Collaborating Clinics damage index; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index.

Table 2. Prevalence of cardiovascular risk factors, organ damage, and cardiovascular events in the full cohort (n = 216). Values are expressed as n (%).

Age as risk factor	41 (18.9)
Family history	25 (11.5)
Current smoking	65 (30)
Smoking (ever)	109 (50.2)
Alcohol	26 (12)
No exercise	97 (44.9)
Abdominal obesity	73 (33.6)
DM	7 (3.2)
Hypertension	71 (32.7)
Hypercholesterolemia	74 (34.1)
MS	21 (9.7)
BMI	
Low weight	20 (9.3)
Normal weight	86 (39.8)
Overweight	69 (31.8)
Obesity	36 (16.6)
Morbid obesity	5 (2.3)
Any vascular risk factor (DM, HBP, DLP, or current smoking)	162 (74.7)
LVH	15 (6.9)
Microalbuminuria*	39 (19.8)
IHD/HF	6 (2.8)
Stroke	19 (8.8)
CRD	22 (10)
PAD	3 (1.4)
Advanced retinopathy	0 (0)
Menopause	103 (50.7)
SCORE	
0	141 (65)
1	31 (14.3)
2	22 (10.1)
3	5 (2.3)
4	7 (3.2)
5	5 (2.3)
6	2 (0.9)
7	2 (0.9)
8	2 (0.9)
Any vascular event (stroke, IHD/HF, PAD, or CRD)	26 (12)

* Total sample: 196 patients, DM: diabetes mellitus; HBP: high blood pressure; DLP: dyslipoproteinemia; MS: metabolic syndrome; BMI: body mass index; LVH: left ventricular hypertrophy; IHD/HF: ischemic heart disease and/or heart failure; CRD: chronic renal disease; PAD: peripheral arterial disease; ABI: ankle-brachial index; SCORE: Systematic Coronary Risk Evaluation.

minuria in 39 of 196 patients (20%); 6 patients (2.8%) had ischemic heart disease and/or heart failure, 19 patients (8.8%) had a stroke, and 3 (1.4%) had symptomatic PAD. Advanced retinopathy was not found in any patient. As a whole, 26 patients (12%) had a history of at least 1 vascular event. In addition, 22 patients (10%) had some degree of chronic renal disease, mostly as a consequence of lupus nephritis.

Frequency and associations of low ABI. Forty-six of the 216 patients studied (21%) had an abnormal ABI (≤ 0.9). Compared with those with normal ABI, patients with low ABI were older at study date (mean age 57 vs 47 years, respectively, $p < 0.001$), were older at SLE diagnosis (mean age 43 vs 34 years, respectively, $p = 0.001$), and had more frequently age as a CV risk factor (32% vs 15%, $p = 0.014$). Women with a low ABI were more often postmenopausal (66% vs 47%, $p = 0.03$). Also, these patients had more traditional CV risk factors such as DM (8.7% vs 1.8%, $p = 0.018$), HTN (52.2% vs 27.5%, $p = 0.002$), and hypercholesterolemia (50% vs 29.8%, $p = 0.018$), and had more previous CV events, including IHD/HF (8.7% vs 1.2%, $p = 0.006$), stroke (17.4% vs 6.4%, $p = 0.02$), and previous arterial thrombosis (ischemic heart disease, stroke or PAD; 28.3% vs 7.6%, $p < 0.001$) than patients with a normal ABI. Patients with low ABI had more frequently at least 1 CV risk factor (presence of HTN, diabetes, hypercholesterolemia, or smoking ever) compared with patients with normal ABI (89.1% vs 70.8%, respectively, $p = 0.011$; Table 3). An increasing proportion of patients with a low ABI was seen paralleling SCORE values ($p = 0.004$; Table 4).

Among SLE-related variables, only higher fibrinogen levels (425 vs 378 mg, $p = 0.002$) and a lower cumulative

Table 3. Relationship between low ABI and cardiovascular variables (univariate analysis). Values are n (%) unless otherwise noted.

	Low ABI, n = 46	Normal ABI, n = 170	p
Age at SLE diagnosis, yrs, mean (SD)	43 (17)	34 (14)	0.001
Age at study, yrs, mean (SD)	57 (15)	47 (14)	< 0.001
Disease duration, yrs, mean (SD)	14 (10)	12 (9)	0.245
Sex (female)	41/46 (89)	158/170 (93)	0.394
Age as a vascular risk factor	15/46 (32)	26/170 (15)	0.007
Abdominal obesity	20/46 (43)	53/170 (31)	0.173
Metabolic syndrome	5/46 (11)	16/170 (9)	0.988
DM	4/46 (8.7)	3/170 (1.8)	0.018
HTN	24/46 (52.2)	47/170 (27.5)	0.002
Hypercholesterolemia	23/46 (50)	51/170 (29.8)	0.018
Current smoking	15,746 (33)	50/170 (29)	0.18
Smoking ever	24/46 (52)	84/170 (49)	0.74
Any vascular risk factor (DM, HTN, hypercholesterolemia, or current smoking)	37/46 (80)	99/170 (58)	0.005
Any vascular risk factor (DM, HTN, hypercholesterolemia, or ever smoking)	41/46 (89.1)	120/170 (70.8)	0.011
No exercise	20/46 (43)	77/170 (45)	0.82
Alcohol	5/46 (11)	21/170 (12)	0.36
Family history of CV disease	6/46 (13)	19/170 (11.2)	0.93
BMI: mean (SD)	26.7 (5.3)	25.5 (5.5)	0.2
Postmenopausal status*	27/41 (66)	75/161 (47)	0.03
Microalbuminuria**	7/40 (17)	32/156 (20)	0.67
Left ventricular hypertrophy	5/46 (11)	10/167 (6)	0.252
IHD/HF	4/46 (8.7)	2/170 (1.2)	0.006
PAD	2/46 (4.3)	1/170 (0.6)	0.052
Stroke	8/46 (17.4)	11/170 (6.4)	0.02
Chronic renal disease	4/46 (9)	18/170 (11)	0.707
Previous arterial thrombosis (stroke, IHD/HF, or PAD)	13/46 (28.3)	13/170 (7.6)	< 0.001
Uric acid, mg/dl: mean (SD)	4.47 (1.2)	4.49 (1.7)	0.94
D vitamin levels, ng/ml: mean (SD)	25.6 (11.7)	29.1 (27.3)	0.414

* Data calculated on 200 women. ** Total sample: 196 patients. SLE: systemic lupus erythematosus; DM: diabetes mellitus; HBP: high blood pressure; DLP: hypercholesterolemia; PAD: peripheral arterial disease; IHD/HF: ischemic heart disease and/or heart failure; ABI: ankle-brachial index; HTN: hypertension; CV: cardiovascular; BMI: body mass index.

Table 4. Prevalence of low ABI in the different SCORE risk groups.

SCORE	Low ABI (%)
0	17/140 (12)
1	11/31 (35)
2	7/22 (35)
3	2/5 (40)
4	3/7 (43)
5	3/5 (60)
6	1/2 (50)
7	1/2 (50)
8	1/2 (50)

p = 0.004. SCORE: Systematic Coronary Risk Evaluation; ABI: ankle- brachial index.

dose of cyclophosphamide (1.15 vs 2.74 g, p = 0.03) were significantly identified in patients with a low ABI compared with those with a normal ABI (Table 5).

After the multivariate analysis, the only independent variables in the final model were the age at the time of the ABI (OR 1.04, 95% CI 1.02–1.07, p < 0.001). There was a tendency for the presence of any vascular risk factor (DM, HTN, hypercholesterolemia, or current smoking; OR 2.3, 95% CI 0.99–5.1, p = 0.053; Table 6).

DISCUSSION

The prevalence of PAD in the general population is not well known, with 25% of patients being symptomatic. PAD is associated with a high frequency of vascular disease in other territories, such as the coronary (with a 4-fold higher risk of suffering a myocardial infarction) and cerebral arterial beds (with a 2-fold to 3-fold increased risk of stroke)[18]. Further, PAD is associated with a 3-fold increased mortality, mainly due to a 6-fold increased risk of coronary death[19]. Thus, the diagnosis of PAD, even in asymptomatic patients, is important to prevent future vascular events. The main risk

Table 5. Relationship between low ABI and SLE variables (univariate analysis). Values are n (%) unless otherwise indicated.

	Low ABI, n = 46	Normal ABI, n = 170	p
Lupus nephritis	11/46 (24)	49/170 (29)	0.635
APS	5/46 (11)	16/170 (9)	0.767
Anti-DNA antibodies	21/46 (46)	85/170 (50)	0.721
Anti-Ro antibodies	13/46 (28)	56/170 (33)	0.67
Anti-La antibodies	3/46 (6)	15/170 (9)	0.616
Anti-RNP antibodies	4/46 (9)	25/170 (15)	0.414
Anti-Sm antibodies	5/46 (11)	24/170 (14)	0.742
aPL	13/46 (28)	61/170 (36)	0.429
SLEDAI: mean (SD)	2 (3)	2 (3)	0.062
SLEDAI categorical:			0.663
0	80 (77)	24 (23)	
1–5	72 (79)	19 (21)	
≥ 6	18 (86)	3 (14)	
SDI: mean (SD)	1.26 (1.3)	1.09 (1.4)	0.453
Prednisone therapy ever	42/46 (91)	149/170 (88)	0.49
Total dose of prednisone, g, mean (SD)	16 (18.6)	23.8 (63.4)	0.678
Maximum dose of prednisone, g, mean (SD)	28.7 (26.2)	26.7 (26.3)	0.644
Hydroxychloroquine ever	40/46 (87)	153/170 (90)	0.553
Total dose of hydroxychloroquine, g, mean (SD)	432.3 (476.8)	409.7 (518.3)	0.79
Cyclophosphamide cumulative dose, g, mean (SD)	1.15 (3.3)	2.74 (6.9)	0.03
Aspirin, mos, mean (SD)	59 (66)	41 (66)	0.104
Statins, mos, mean (SD)	33 (53)	17 (40)	0.069
Anticoagulation, mos, mean (SD)	12 (37)	11 (41)	0.816
Fibrinogen, mg/dl, mean (SD)	425 (94.3)	378 (90.2)	0.002

SLE: systemic lupus erythematosus; APS: antiphospholipid syndrome; aPL: antiphospholipid antibodies; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index; ABI: ankle-brachial index; SDI: Systemic Lupus International Collaborating Clinics damage index.

Table 6. Variables associated with a low ABI (multivariate analysis).

	OR	95% CI	p
Age at study, yrs	1.04	1.02–1.07	< 0.001
Any vascular risk factor (DM, HTN, hypercholesterolemia, or current smoking)	2.3	0.99–5.1	0.053

ABI: ankle-brachial index; DM: diabetes mellitus; HTN: hypertension.

factors for PAD in the general population are smoking, DM, and arterial HTN. ABI testing is recommended in patients with intermittent claudication, in asymptomatic individuals older than 70 or older than 50 with vascular risk factors, and in patients with a Framingham risk score up to 10%, with absence of pedial pulses and/or presence of femoral bruits[20].

We found a high prevalence of mostly asymptomatic PAD in patients with SLE (21%). This prevalence is 10-fold higher than expected according to a recent Spanish population-based cross-sectional survey of 6262 individuals, which showed a 2.1% frequency of an ABI < 0.9 in the subgroup of women 45 to 54 years of age[21]. On the other hand, the frequency of symptomatic PAD in our cohort (1.3%) was similar to that found in the Toronto Lupus cohort (2%)[22].

Few have studied the prevalence of subclinical PAD in patients with SLE. One study from London of 91 patients with SLE younger than 55 years was designed to detect early signs of atheroma by using ABI, whose abnormal cutoff value was set at 1. The authors identified 37% of patients with PAD. Age was the only variable associated with a low ABI[23]. The lower prevalence of abnormal ABI found in our study could be explained in part by the lower cutoff we used, 0.9 instead of 1, according to current guidelines[20].

In a case-control study of 32 Chinese women with SLE who had no previous CV disease or DM, designed to study the correlation between arterial stiffness and disease activity, the authors did not report any cases with an abnormal ABI[24]. Another study of Chinese patients from Taiwan found a 4% frequency of abnormal ABI. That study was focused on the relation between homocysteine and brachial-ankle pulse wave velocity and no specific associations with ABI were sought[25]. The same group studied arterial stiffness by pulse wave velocity in 83 patients with SLE. An ABI was performed on the whole cohort, with 24% of them being abnormal; however, variables potentially related with a low ABI were not analyzed[26].

Like the London study, we found an association between the presence of PAD and age, both at the time of the study

and at SLE diagnosis[23]. The presence of menopause was also associated with a low ABI in the univariate analysis. The association between arterial events and the age at SLE diagnosis has been consistently described[2,4,27,28,29]. An association between CV events and menopause has been found as well[2].

Our study also revealed a strong association between PAD and traditional CV risk factors (DM, HTN, hypercholesterolemia, smoking, and SCORE scale), which persisted as a tendency in the multivariate analysis. A relation with the presence of previous CV events (IHD/HF, stroke, and previous arterial thrombosis) was also seen. Other authors have found associations with some, but not all, vascular risk factors. Petri, *et al* found a relation with serum cholesterol levels and HTN, but not with smoking or DM[4]. Manzi, *et al* described an incidence of myocardial events in women with SLE higher than expected in a population of women of similar age, according to the Framingham Study Cohort[2]. An association with hypercholesterolemia was seen, but not with other classic vascular risk factors[2]. Urowitz, *et al* found a relation between CV events (myocardial infarction, angina, TIA, stroke, PAD, and sudden death) and hypercholesterolemia, smoking, and HTN, but not with DM[30].

Other groups found associations of CV events with longer duration of SLE[2,4], positivity for aPL[27], Raynaud phenomenon, renal disease, neuropsychiatric disease, and vasculitis[30]. In contrast, we found no associations with most SLE-related factors, such as the autoantibody profile, disease activity, chronic organ damage, or treatment with prednisone or antimalarials. In the univariate analysis, higher fibrinogen levels and lower cumulative doses of cyclophosphamide were found in the low ABI group. Despite the loss of statistical significance of both variables in the multivariate analysis, the effect of chronic inflammation in the vascular endothelium is suggested. Accordingly, those therapies suppressing inflammation could have a beneficial effect.

However, studies analyzing the effects of immunosuppressive and antimalarial therapy on vascular disease have obtained heterogeneous results. Urowitz, *et al*[30] found an association between CV events and steroid use as a dichotomic "ever/never" variable, but not with the cumulative dose or the duration of treatment. Surprisingly, antimalarials and immunosuppressive drugs were used more frequently in the group of patients with CV events. Manzi, *et al*[2] and Petri, *et al*[4] found an association of CV disease with longer duration of corticosteroid use. Roman, *et al*[31] identified several variables associated with the presence of plaque: age, disease duration, and damage increased the risk, while positivity for anti-Sm and therapy with hydroxychloroquine and cyclophosphamide had a protective effect. A higher proportion of patients taking prednisone and a higher 5-year mean daily dose of prednisone were seen among patients without plaque. In a Brazilian study[32], hydroxychloroquine was not protective, while cyclophosphamide, methylprednisolone pulses, and the daily dose of prednisone were associated with a lower frequency of plaque. Interestingly, the duration of prednisone therapy was directly related to the presence of plaque, suggesting a somewhat dual effect of glucocorticoids. Such effect was also found in a study of pediatric patients with SLE in whom a beneficial effect of prednisone doses of 0.15–0.40 mg/kg/d on the carotid intima-media thickness was found; however, lower and higher doses were both associated with a higher intima-media thickness[33]. A direct effect of the cumulative dose of prednisone, both unadjusted and adjusted for Framingham risk factors, on the presence of carotid plaque was reported by Doria, *et al*[34] and similar results were obtained by Romero-Diaz, *et al* in Mexico[35].

These heterogeneous results may actually reflect the complex relation between disease activity, drug-associated side effects, and vascular disease. It is possible that a certain degree of immunosuppressive therapy protects from endothelial damage by controlling inflammation, but the proatherosclerotic effects of immunosuppressive drugs, particularly glucocorticoids, may prevail beyond a certain threshold. In addition, it is almost impossible to separate the strong association between SLE severity and more intensive immunosuppressive therapy. Lastly, a number of different endpoints have been used, from crude clinical vascular events to a wide range of noninvasive tests such as carotid ultrasound, CT scan, or arterial stiffness calculations, which can have different clinical implications. Thus, many questions about the effect of SLE therapy on vascular disease are still unresolved.

On the other hand, the effect of traditional CV risk factors on vascular disease in patients with SLE is clear. We found a prevalence of PAD in patients with SLE 10-fold higher than expected[21]. Up to 50% of our cohort was overweight, compared with 39% of the Spanish general population[36]. Thirty-four percent had hypercholesterolemia, compared to 50.5% of individuals in the Spanish general population[37]. The prevalence of HTN in the Spanish general population is 35%, similar to the 33% frequency seen in our patients[38]. However, the age range in epidemiological studies is 18 to 80 years, while the mean age of our cohort was 36 years. This suggests that hypercholesterolemia, HTN, and other vascular risk factors appear earlier in patients with SLE, with the expected clinical effect on the development of vascular disease.

This study has several limitations. First, this is a cross-sectional study, with a wide heterogeneity in variables such as the age, SLE duration, and degree of organ damage. The lack of statistical significance of some SLE-related variables identified in other studies may be partially explained by the confounding effects of this heterogeneity. Eighty-nine percent of our cohort was taking antimalarials, which makes it very difficult to analyze the actual effect of

these drugs, given the lack of a sizable comparison group not taking the therapy. However, the duration of therapy was neither directly nor inversely associated with PAD, remarking that the relation of antimalarials and atherosclerosis is far from clear[39]. The complex relationship between glucocorticoids and arterial disease has already been discussed. In our study, we only considered the cumulative and maximum dose of prednisone received. Given the variation in the time of followup of the individual patients, these glucocorticoid-related variables may not be optimal to analyze the influence of prednisone on PAD. Finally, the lack of a control group without SLE precluded the complete analysis of most SLE-related variables. Likewise, the prevalence of PAD in the general population, as measured by low ABI, was obtained from other studies in the Spanish population, and not directly calculated in a control group of our area. Regarding the effects of SLE activity on ABI, our study is limited by the low number of patients with a SLEDAI ≥ 6 at the time of the study. Also, previous SLEDAI scores were not analyzed. Therefore, we cannot exclude an effect of persistent severe SLE activity on the development of PAD.

On the other hand, this is the first study analyzing the incidence of PAD in patients with SLE using a validated diagnostic technique and a working definition in accordance with current international guidelines. In our descriptive study, we found a high prevalence of PAD in patients with SLE, which was asymptomatic in the vast majority of cases. The clinical implications of our data will be further clarified by future studies and by the longitudinal followup of our cohort.

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Editorial

Síndrome metabólico en pacientes con lupus eritematoso sistémico: causas y consecuencias

Metabolic syndrome in patients with systemic lupus erythematosus: Causes and consequences

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Está bien establecido que los pacientes con lupus eritematoso sistémico (LES) presentan un mayor riesgo de sufrir episodios vasculares tales como enfermedad coronaria, ictus y enfermedad arterial periférica, con su consiguiente significado pronóstico[1,2]. El desarrollo de aterosclerosis subclínica es mayor y más precoz en pacientes con LES en comparación con la población general. Si bien los factores de riesgo tradicionales, como la hipertensión arterial (HTA), la diabetes mellitus (DM), la dislipidemia y el tabaquismo, son más prevalentes en estos pacientes, ello no explica completamente esta mayor prevalencia de vasculopatía aterosclerótica[3].

El síndrome metabólico (SM) agrupa varios factores de riesgo vascular que se traducen en obesidad central y resistencia a la insulina, lo que condiciona un mayor riesgo de desarrollo de DM tipo 2 y enfermedad cardiovascular[4]. No obstante, existen diferentes definiciones de SM, cada una con distintos criterios: la de la Organización Mundial de la Salud, la de la Federación Internacional de Diabetes o la del Panel de Expertos en Detección, Evaluación y Tratamiento de niveles elevados de colesterol en sangre en adultos, del *Adult Treatment Panel III* (ATP III)[5]. Dentro de los criterios incluidos, algunos son factores muy extendidos en la práctica clínica habitual y, por lo tanto, fáciles de evaluar. En cambio, en alguna de las definiciones se incluye la medición de la resistencia a la insulina (HOMA), lo que dificulta su aplicabilidad. La presencia de obesidad abdominal es obligatoria en algunas definiciones de SM, mientras que en otras es solo un criterio de igual peso que otros factores de riesgo vascular, lo que añade dificultades a la hora de identificar a estos pacientes.

A pesar de todo ello, la existencia de SM (independientemente de la definición que se elija) se ha asociado con un mayor riesgo de enfermedad cardiovascular, aunque esta asociación no es tan clara como con los factores de riesgo clásicos. Se sabe que el SM es una herramienta clínica útil en la población para identificar a los pacientes que precisan una mayor intervención cara a prevenir la aparición de episodios vasculares. Parece claro que es un predictor del riesgo relativo de desarrollo a largo plazo de enfermedad cardiovascular y diabetes, pero no predice el riesgo absoluto o global a corto plazo. Por este motivo, diferentes sociedades científicas (Asociación Americana de Diabetes, Asociación Europea para el Estudio de la Diabetes) recomiendan que se calcule el riesgo vascular con calculadoras de riesgo global (SCORE, ecuación de Framingham o el algoritmo de PROCRAM), y posteriormente se investigue la presencia de SM, para obtener el «riesgo cardiometabólico»[6]. Este factor de corrección puede ser determinante en personas jóvenes, en las que estas calculadoras infravaloran el riesgo, como ocurre en los pacientes con LES[3].

La prevalencia de SM en la población general en nuestro país se estima en torno al 15%. En pacientes con LES, Sabio et al. encontraron una prevalencia del 20%, llegando a ser 4 veces mayor en aquellos con LES menores de 40 años[7]. En otros estudios de casos y controles realizados en individuos con LES, en los que se han usado diferentes definiciones de SM, también se ha encontrado una mayor prevalencia de este síndrome que en la población general[8,9].

Entre los pacientes con LES y SM, el factor de riesgo más frecuente es la HTA[5]. Por el contrario, la presencia de perímetro abdominal aumentado es menor que en los controles sanos[7,8]. Este dato puede hacer que se infravalore la prevalencia de SM en los pacientes con lupus, ya que si se eligen definiciones de SM donde la presencia de perímetro abdominal aumentado es necesaria para el diagnóstico, podemos no detectar a un buen número de pacientes. La edad se ha identificado también como un factor de riesgo para presentar SM en los pacientes con LES[8,10].

Además de los factores clásicos, diversos estudios concluyen que la actividad inflamatoria de la enfermedad favorece el desarrollo de SM. Así, los pacientes con mayores puntuaciones en las escalas SLAM-R[11] o SLEDAI-2K[10], los que presentaban mayores niveles de proteína C reactiva (PCR) o velocidad de sedimentación, o niveles más bajos de C3[7–9,11], o aquellos con nefritis lúpica[10], presentan una mayor prevalencia de SM. El daño acumulado en los pacientes con LES también se ha asociado con una mayor probabilidad de desarrollar SM[7,10,12].

En la cohorte internacional SLICC de pacientes con diagnóstico reciente de LES se ha encontrado que determinadas razas o etnias presentan mayor prevalencia de SM, como los coreanos (OR 6,33; IC 95% 3,68-10,86) o los hispanos (OR 6,2; IC 95% 3,78-10,12)[13]. En

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una publicación posterior, después de 2 años de seguimiento, el proceder de ancestros africanos (OR 3,35; IC 95% 1,59-7,01) o ser hispano (OR 2,25; IC 95% 1,28-3,96) se asociaba con un mayor riesgo de SM[10]. En ese mismo trabajo se encontró que la presencia previa de SM es de por sí un factor de riesgo para tener SM, siendo el factor que más riesgo aportaba en el análisis multivariante (OR 14,9; IC 95% 10,7-20,8).

Uno de los elementos que se cree que más influyen en el desarrollo de SM son los fármacos utilizados en el LES, sobre todo los glucocorticoides. Negrón et al.[11], en una cohorte de Puerto Rico, encontraron que haber recibido dosis de prednisona superiores a 10 mg/día se asociaba con SM. Parker et al., en la cohorte SLICC, encontraron asociación entre la prevalencia de SM y el uso de glucocorticoides en general[8], o el uso de dosis medias diarias elevadas[13]. Sin embargo, otros trabajos no han encontrado asociación entre los glucocorticoides y el desarrollo de SM[7,9,10,12].

Es ampliamente conocido que las medidas higiénico-saludables, como la realización de ejercicio aeróbico regular, previenen el desarrollo de SM, tanto en la población general como en los pacientes con LES[11]. Asimismo, se ha encontrado en diversos trabajos que el uso de antipalúdicos en los pacientes con LES tiene un efecto protector frente al desarrollo de SM[7,10,12–14], lo cual, unido a sus efectos protectores frente a las trombosis[15], añade argumentos para el uso generalizado de hidroxicloroquina en estos pacientes.

El LES se ha asociado de manera consistente con aterosclerosis precoz[1]. En 2 trabajos se ha encontrado relación entre la rigidez arterial (medida mediante la velocidad de la onda de pulso), que es la primera manifestación de la aterosclerosis, y el SM. En el trabajo de Sabio et al.[16] la rigidez arterial se relacionaba con la edad, el sexo masculino, el tiempo de evolución del LES, los niveles de PCR y la presencia de SM (OR 2,93; IC 95% 1,05-8,93). En el segundo estudio, Valero-Gonzalez et al.[17] encontraron que el SM aumenta la rigidez arterial (OR 6,6; IC 95% 1,2-38), independientemente de la edad del paciente y los valores de presión arterial. Además, el SDI también se asociaba de forma independiente con una mayor rigidez arterial.

En el artículo publicado en este número de Medicina Clínica por Garcia-Villegas et al.[18] se estudia el valor pronóstico del SM sobre el desarrollo de trombosis en una cohorte de 238 mujeres premenopáusicas con LES. La edad media era de 31 años, con una duración media de la enfermedad de 6,8 años, un MEX-SLEDAI de 2,3 y un SDI de 0,5. Respecto a los tratamientos recibidos, el 76,9% recibía cloroquina y el 93,3% glucocorticoides (a cualquier dosis). Se hizo un seguimiento de la cohorte desde 2001 a 2008, con una prevalencia de SM al inicio del 21,8%, similar a la encontrada en un estudio de población general de México (21,4%)[19], país en el que se llevó a cabo el estudio. Sin embargo, cabe destacar que en este trabajo se utilizan los criterios de ATP III con una modificación, el índice HOMA y/o la glucosa en ayunas, mientras que en el estudio de Aguilar-Salinas et al.[19] se incluyeron ambos sexos y, para el diagnóstico de SM, se utilizó el índice de masa corporal en vez del perímetro abdominal. Por tanto, ambas prevalencias podrían no ser del todo comparables.

El criterio diagnóstico de SM más frecuente fue el nivel de colesterol HDL < 50 mg/dl (55%), seguido de la glucemia en ayunas ≥ 110 mg/dl y/o HOMA $> 2,5$ (31,5%) y del perímetro abdominal > 88 cm (27,7%). Entre los factores de riesgo identificados, las pacientes con SM habían recibido con más frecuencia dosis altas de prednisona (> 30 mg/día) a lo largo de la enfermedad (75 frente a 50,5%, $p < 0,005$). Por otro lado, no se encontraron asociaciones entre el SM y la actividad o el daño crónico, un hecho quizás explicado por las bajas puntuaciones de MEX-SLEDAI y SDI entre las participantes.

Uno de los objetivos de los investigadores fue establecer si el SM se asocia con un aumento de la enfermedad cardiovascular. En este trabajo se confirmó en el análisis multivariante que el SM aumenta el riesgo de padecer enfermedad trombótica (HR 3,8, IC 95% 1,3-10,6), tanto a nivel arterial (infarto agudo de miocardio, ictus, trombosis de la arteria central de la retina, trombosis renal), como venoso (trombosis venosa profunda y tromboembolismo pulmonar [TEP]). Los episodios trombóticos más frecuentes fueron los ictus (9 casos), seguidos de TEP (5 casos). Asimismo, se observó una asociación entre el daño acumulado, medido mediante SDI, y el aumento de riesgo de sufrir trombosis (HR 1,4; IC 95% 1,1-2,1). Es cierto que este trabajo incluyó en la definición de enfermedad cardiovascular, de forma un tanto inusual, tanto trombosis arteriales como venosas. Sin embargo, hay que considerar que, al fin y al cabo, cualquier episodio trombótico implica un incremento de la morbimortalidad. La incidencia acumulada de trombosis en la cohorte fue del 9,2%, lo que representa un riesgo 200 veces superior al esperado en mujeres de 15 a 49 años.

Tomando como base los resultados de este estudio y de otros previos, se puede afirmar que el desarrollo de SM en pacientes con LES es multifactorial, con una serie de variables claramente identificadas: actividad inflamatoria, daño acumulado, edad, determinadas etnias y el tratamiento recibido, fundamentalmente los antipalúdicos (con un efecto protector) y la prednisona[5]. En este último caso, parece claro que sus efectos adversos dependen de la dosis y el tiempo de uso, si bien es difícil establecer de forma concreta los límites de seguridad. Sin embargo, estudios recientes apuntan a que dosis iniciales por debajo de 30 mg/día, con descenso rápido hasta 5 mg/día, acompañadas de bolos intravenosos de metilprednisolona, inmunosupresores e hidroxicloroquina, son efectivas en el control de la enfermedad lúpica grave con mínimos efectos adversos (obesidad, diabetes, dislipidemia, fracturas osteoporóticas, osteonecrosis y cataratas)[20].

En definitiva, se debe realizar una búsqueda activa de SM en los individuos con LES, ya que puede explicar parte del exceso de riesgo vascular que presentan estos pacientes, utilizando definiciones que permitan su detección precoz y eficaz. Una vez identificado, debemos realizar un control estricto de los factores de riesgo tradicionales y promover de forma vehemente la realización de dieta cardiosaludable y ejercicio aeróbico regular, ya que ello constituye la forma más eficaz para su control. Asimismo, se debe conseguir una remisión rápida y duradera de la actividad inflamatoria de la enfermedad, evitando las dosis altas de glucocorticoides orales, y administrar hidroxicloroquina como tratamiento de base en todos los pacientes en los que no haya contraindicaciones[15].

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Predictors of peripheral arterial disease in SLE change with patient's age

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ABSTRACT

Objective: To analyse the differential influence of risk factors of peripheral artery disease (PAD) according to age in patients with SLE.

Methods: 216 patients from the Lupus-Cruces cohort were divided in three age groups: ≤34 years, 35–49 years and ≥50 years. A low ankle–brachial index defined PAD. Significant variables were identified by univariant and multivariant analysis in each age group.

Results: Different factors were identified in different age groups: antiphospholipid antibodies/antiphospholipid syndrome and glucocorticoids in patients ≤34 years; in patients 35–49 years old, hypertension was the only statistically significant predictor, although a trend was observed for fibrinogen levels; a trend was observed for hypercholesterolaemia in those ≥50 years.

Conclusions: Age may modulate the influence of risk factors for PAD in patients with SLE.

INTRODUCTION

Cardiovascular disease (CVD) is the main cause of late mortality in patients with SLE.[1] The incidence of CVD has progressively increased within the last decades.[2] CVD can present as coronary artery disease (CAD), cerebrovascular disease and peripheral artery disease (PAD), the first two ones being best studied.[3] The underlying atherosclerotic process can be accelerated by different mechanisms, including inflammation, SLE treatments and traditional cardiovascular risk factors.[3]

Age is the most important unchangeable cardiovascular risk factor, both in the general population and in patients with lupus.[4 5] Indeed, in a previous study in our SLE cohort, age was the only independent predictor of PAD.[6] In a nationwide population-based cohort study in Taiwan, younger (≤34 years) patients with SLE were at a higher risk of symptomatic PAD.[7] In a Swedish population-based study, an increased risk of myocardial infarction and stroke was demonstrated among female patients with SLE compared with the general population. Of note, this extra risk was highest among women aged 40–49 years.[8]

Thus, it is possible that the influence of risk factors, either cardiovascular or SLE-related, varies depending on the age of patients. To test this hypothesis, we aimed to study the influence of risk factors for PAD in different age groups of patients with SLE.

MATERIALS AND METHODS

Study objectives

The objective of this cross-sectional study was to analyse the differential influence, according to age, of several variables in the presence of PAD, defined as a low ankle–brachial index (ABI). Patients were divided in three groups according to age at the time of the ABI, as proposed by Chuang *et al*:[7] ≤34 years (group 1), 35–49 years (group 2) and ≥50 years (group 3).

Study population

Data from the 216 patients who participated in our previous study[6] were further analysed. Detailed characteristics of this population and the variables studied are available.[6] The local institutional review board of the Hospital Universitario Cruces approved the study protocol (CEIC E09/07) in compliance with the Helsinki Declaration. All patients signed an informed consent at the time of enrolment.

Statistical analysis and variables

In order to identify associations with PAD, the following independent variables were tested in each age group against the dependent variable, 'ABI lower than 0.9', using χ^2 with Yate's correction or Student's t-test, as appropriate: age at SLE diagnosis, disease duration, gender, abdominal obesity (≥102 and ≥88 in men and women, respectively), metabolic syndrome according to Adult Treatment Panel III definition,[9] diabetes mellitus (DM), arterial hypertension (HTN), dyslipidaemia, smoking (current or past), any vascular risk factor (DM or HTN or

dyslipidaemia or current/past smoking), exercise, alcohol consumption, family history of premature CVD, body mass index, menopause, previous subclinical organ damage (left ventricular hypertrophy and microalbuminuria), previous CVD (ischaemic heart disease and/or heart failure (IHD/HF), stroke, PAD), chronic renal failure, previous arterial thrombosis (stroke or IHD or PAD), uric acid, vitamin D levels, previous lupus nephritis or antiphospholipid syndrome (APS), anti-DNA, anti-Ro, anti-La, anti-U1RNP, anti-Sm, and antiphospholipid antibodies (aPL) that include lupus anticoagulant and/or anticardiolipin antibodies at medium–high levels on at least two different determinations 12 weeks apart, Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) at the time of diagnosis, SLEDAI at the time of ABI, SLICC/ACR Damage Index (SDI) at the time of ABI, prednisone (cumulative dose, maximum dose ever received, average daily dose <7.5 or ≥7.5), hydroxichloroquine (yes/no and cumulative dose), cyclophosphamide (cumulative dose), mycophenolate (cumulative dose), azathioprine (cumulative dose), low-dose aspirin (number of months on treatment), anticoagulants (number of months on treatment), statins (number of months on treatment) and fibrinogen levels at the time of the ABI.

Those variables with a value of p ≤0.1 in the univariate analysis were subsequently included in a backward stepwise logistic regression model to identify independent associations with PAD for each age subgroup.

All statistical analyses were done using the software SPSS V.20.0 statistical package for MAC OS X (SPSS).

RESULTS

Demographic and SLE-related variables

Two hundred patients (92%) were women. Two hundred and nine patients (96%) were Caucasians of European origin, with the remaining consisting of three Afro-Caribbeans, two Hispanics and two Arabs. The mean (SD) age at SLE diagnosis was 36 years (15). The mean (SD) age at the time of the ABI study was 49 (15) years, with a mean (SD) follow-up after SLE diagnosis of 12 (9) years.

A total of 37 patients were included in group 1, 84 patients in group 2 and 95 patients in group 3. The distribution of traditional cardiovascular risk factors and SLE-related factors in the three age groups is detailed in table 1.

Frequency and associations of low ABI

The prevalence of PAD increased with age: 3/37 (8.1%) in group 1, 12/84 (14.2%) in group 2 and 31/95 (32.6%) in group 3. The variables associated with PAD in each age group are shown in table 2: APS, aPL and cumulative prednisone dose in group 1; DM, hypertension, average daily dose of prednisone <7.5 mg/day, abdominal obesity and fibrinogen levels in group 2; and vitamin D levels, hypercholesterolaemia, any vascular risk factor (DM or hypertension or hypercholesterolaemia or current/past smoking), ischaemic heart disease, aPL, previous arterial thrombosis, cumulative mycophenolote mofetil dose and average daily dose of prednisone <7.5 in group 3.

The final independent predictors of low ABI are shown in table 3. In group 1, the logistic regression

Table 1 Traditional and SLE-related cardiovascular risk factors in different age groups

	Group 1 (≤34 years)	Group 2 (35–49 years)	Group 3 (≥50 years)
HTN, n/N (%)	4/37 (10.8)	20/84 (23.8)	47/95 (49.4)
DM, n/N (%)	0/37 (0)	3/84 (3.5)	4/95 (4.2)
DLP, n/N (%)	3/37 (8.1)	20/84 (23.8)	51/95 (53.6)
Current smoker, n/N (%)	15/37 (40.5)	28/84 (33.3)	22/95 (23.1)
Smoker (ever), n/N (%)	18/37 (48.6)	49/84 (58.3)	41/95 (43.1)
Family history, n/N (%)	2/37 (5.4)	10/84 (11.9)	13/95 (13.6)
Abdominal obesity, n/N (%)	10/37 (27)	25/84 (29.7)	38/95 (40)
BMI, n/N (%) overweight–obesity	13/37 (35.1)	44/84 (52.3)	52/95 (54.7)
Sedentary lifestyle, n/N (%)	20/37 (54)	35/84 (41.6)	42/95 (44.2)
Any vascular risk factor, n/N (%)	22/37 (59.4)	59/84 (70.2)	80/95 (84.2)
MS, n/N (%)	3/37 (8.1)	6/84 (7.1)	12/95 (12.6)
APS, n/N (%)	2/37 (5.4)	10/84 (11.9)	9/95 (9.4)
aPL, n/N (%)	14/37 (29.7)	27/84 (32.1)	33/95 (34.7)
Lupus nephritis, n/N (%)	12/37 (32.4)	30/84 (35.7)	18/95 (18.9)
SLEDAI at dx, mean (SD)	9.83 (7.8)	8.15 (5.3)	6.1 (3.9)
SLEDAI at ABI, mean (SD)	3.08 (3.7)	2.05 (2.9)	1.5 (2.2)
SDI at ABI, mean (SD)	0.4 (0.8)	0.98 (1.2)	1.5 (1.5)
Age at SLE dx, years, mean (SD)	21.4 (6.1)	30.2 (9.2)	47.4 (15.6)
Disease duration, years, mean (SD)	6.2 (5.3)	11.7 (8.5)	15 (10.5)

Any vascular risk factor: DLP, hypercholesterolaemia; HTN, DM, dyslipidaemia or smoking exposed. ABI, ankle–brachial index; aPL, antiphospholipid antibodies (anticardiolipin and/or lupus anticoagulant); APS, antiphospholipid syndrome; BMI, body mass index; DM, diabetes mellitus; dx, diagnosis; HTN, arterial hypertension; MS, metabolic syndrome according to ATPIII.

Table 2 Univariate analysis showing variables with p<0.1

	Low ABI	Normal ABI	p Value
Group 1 (≤34 years)	N=3	N=34	
APS, n/N (%)	2/3 (66)	0/34 (0)	0.005
aPL, n/N (%)	3/3 (100)	11/34 (32.3)	0.047
Cumulative prednisone, g, mean (SD)	21.25 (1.89)	7.70 (1.08)	0.058
Group 2 (35–49 years)	N=12	N=72	
DM, n/N (%)	2/12 (16.6)	1/72 (1.3)	0.052
HTN, n/N (%)	6/12 (50)	14/72 (19.4)	0.021
Average prednisone <7.5 mg/day, n/N (%)	11/11 (100)	50/68 (73.5)	0.046
Abdominal obesity, cm, mean (SD)	90.46 (14.9)	82.50 (12.2)	0.047
Fibrinogen levels, mg/dL, mean (SD)	454 (100)	388 (83.2)	0.021
Group 3 (≥50 years)	N=31	N=64	
Vitamin D levels, ng/mL, mean (SD)	22.2 (8.7)	35.9 (41.4)	0.018
Hypercholesterolaemia, n/N (%)	21/31 (67.7)	30/64 (46.8)	0.056
Any vascular risk factor (ever smoking), n/N (%)	30/31 (96.7)	50/64 (78.1)	0.015
Any vascular risk factor (current smoking), n/N (%)	28/31 (90.3)	44/64 (68.7)	0.023
Ischaemic heart disease, n/N (%)	4/31 (12.9)	2/64 (3.1)	0.086
aCL, n/N (%)	4/31 (12.9)	24/64 (37.5)	0.011
aPL, n/N (%)	6/31 (19.3)	27/64 (42.1)	0.028
Arterial thrombosis, n/N (%)	11/31 (35.4)	11/64 (17.1)	0.047
Cumulative MMF, g, mean (SD)	0 (0)	111 (442.8)	0.049
Average prednisone <7.5 mg/day, n/N (%)	28/30 (93.3)	48/63 (76.1)	0.038

ABI, ankle–brachial index; aCL, anticardiolipin antibodies; aPL, antiphospholipid antibodies (anticardiolipin and/or lupus anticoagulant); APS, antiphospholipid syndrome; DM, diabetes mellitus; HTN, arterial hypertension; MMF, mycophenolate mofetil.

Table 3 Variables associated with a low ABI in different age groups (multivariate analysis)

Variables	OR	95% CI	p Value
Group 1			
N/A			
Group 2			
Hypertension	4.61	1.15 to 18.44	0.031
Group 3			
Hypercholesterolaemia	2.49	0.97 to 6.4	0.057

ABI, ankle–brachial index; N/A, not applicable.

model could not be built due to the absolute absence of any patients with APS in the subgroup with normal ABI and the 100% frequency of aPL positivity among those with abnormal ABI; thus, the results of the univariate analysis could not be adjusted. In group 2, hypertension was the only statistically significant predictor, although a trend was observed for fibrinogen levels. In group 3, a trend was observed for hypercholesterolaemia.

DISCUSSION

Age is among the most important cardiovascular risk factors; indeed, many of the cardiovascular risk estimation models are actually based on age.[4 5] In a cohort of more than 3.6 million individuals undergoing self-referred screening for CVD (ABI, carotid duplex ultrasound and abdominal ultrasound), the prevalence of any vascular disease increased progressively after 40 years of age: from 2% in those aged 40–50 years to 13% among those aged 71–80 years. After adjusting for traditional risk factors, each additional decade of life doubled the risk for vascular disease (OR 2.14 for PAD).[10]

Moreover, the differential influence of cardiovascular risk factors changes throughout life. In the general population, the Framingham study found that the relative effect of systolic, diastolic and pulse pressure changed with age. In patients younger than 50 years, diastolic blood pressure was the strongest predictor of coronary heart disease (CHD) risk; in those aged 50–59 years old, all three variables contributed equally to CHD risk; among those older than 60 years, pulse pressure was the strongest predictor.[11]

Our results suggest that age may modulate the effect of risk factors for CVD also in patients with SLE. aPL/APS and higher glucocorticoid load seem to increase the risk of PAD in younger patients, although a multivariant analysis could not be performed. In group 2, an average daily dose of prednisone <7.5 mg was associated with PAD in the univariate but not in the multivariate analysis. Moreover, since more than 75% of patients in this age group were taking low-dose prednisone, this result is likely to be misleading. As age increased, more traditional risk factors such as hypertension and hypercholesterolaemia played a significant role. We identified factors associated with PAD (and, probably, by extension with CVD) hidden by the large influence of age. This could be particularly important among younger patients, in whom the prevalence of arterial disease was low, however very much unrelated to classical cardiovascular risk factors.

This study has a number of limitations, which have been already acknowledged.[6] This is a cross-sectional study, with different disease duration among patients. This makes it difficult to fully address the effects of some time-varying variables such as glucocorticoid exposure, lupus activity and cardiovascular risk factors. In addition, almost 90% of our cohort was on hydroxychloroquine, which precludes analysis of the actual effect of this drug. On the other hand, the sizeable number of patients has allowed a differential analysis per different age groups using a large variety of demographic, cardiovascular, lupus-related and therapeutic variables. This is, to our knowledge, the first study of this kind.

Based on our results, a number of practical considerations can be made. First, it is important to regularly check patients with lupus for the presence of aPL, especially in the early phases of the disease, given the possible association with PAD in young patients with SLE. We have previously shown that aPL increase the risk of damage in SLE,[12] particularly by the occurrence of thrombotic events.[13] Since the addition of low-dose aspirin seems to be protective in aPL-positive patients with SLE according to a recent systematic review,[14] the detection of persistently positive aPL should call for early antiplatelet therapy. Second, the doses of prednisone should be reduced as much as possible, especially in young patients, given the possible association with PAD in this group and, in general, with damage in patients with SLE.[15] Third, especial attention should be paid to controlling traditional cardiovascular risk factors, especially in older patients.

Contributors J-GE: substantial contributions to the conception, design of the work, acquisition, analysis and interpretation of data for the work; drafting the work and revising it critically for important intellectual content; final approval of the version to be published; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. IV: Substantial contributions to the conception and design of the work; analysis and interpretation of data for the work; Drafting the work or revising it critically for important intellectual content; final approval of the version to be published; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. JN: Substantial contributions to the conception and design of the work; analysis and interpretation of data for the work; drafting the work or revising it critically for important intellectual content; final approval of the version to be published; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. IR-A: Substantial contributions to the analysis and interpretation of data for the work; drafting the work or revising it critically for important intellectual content; final approval of the version to be published; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. GR-I: Substantial contributions to the conception and design of the work; analysis and interpretation of data for the work; drafting the work or revising it critically for important intellectual content; final approval of the version to be published; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Competing interests None declared.

Patient consent Obtained.

Ethics approval The local institutional review board of the Hospital Universitario Cruces approved the study protocol (CEIC E09/07).

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Ankle-brachial index and arterial vascular events in systemic lupus erythematosus patients: a 5-year prospective cohort

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Abstract

Objective

To determine the potential predictive value in patients with systemic lupus erythematous of the ankle-brachial index (ABI) for the occurrence of arterial vascular events.

Methods

216 lupus patients from a prospective clinical cohort were evaluated using the ABI at the start of the study and then followed up for 5 years. Abnormal ABI was defined as an index ≤0.9 or >1.4. Several potential vascular risk factors were also evaluated. Arterial vascular events (AVE): coronary events, cerebrovascular events, peripheral arterial disease and death related to vascular disease. Survival analysis was performed using a competitive risk regression approach, considering non-vascular death as a competitive event.

Results

18 arterial events and 14 deaths were identified. In the competitive risk regression analysis, independent predictors of higher risk were identified: family history of early AVE [subdistribution hazard ratio (SHR) 5.44, 95% confidence interval (CI) 1.69-17.50, p=0.004)], cumulative prednisone (grams) (SHR 1.01, 95% CI 1.01-1.03, p=0.007) and a personal history of arterial thrombosis (SHR 5.44, 95% CI 1.45-14.59, p=0.004). Female gender was a protective factor (SHR 0.22, 95% CI 0.07-0.77, p=0.017). A statistical trend was detected with abnormal ABI (SHR 2.65, 95% CI 0.86-8.14, p=0.089).

Conclusion

Male gender, exposure to high cumulative doses of prednisone, family history of early arterial vascular disease and occurrence of previous arterial thrombosis are independent risk predictors of arterial vascular events in patients with systemic lupus erythematosus. Abnormal ABI may be related to high risk for arterial vascular events.

Key words

systemic lupus erythematosus, cardiovascular disease, peripheral arterial disease, atherosclerosis, ankle brachial index

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Introduction

Patients with systemic lupus erythematous (SLE) are known to be at increased risk for arterial vascular events (AVE), mainly ischaemic heart disease (IHD) and cerebrovascular disease (CVD) (1), but also peripheral arterial disease (PAD), either symptomatic or asymptomatic (2, 3). Such an increased risk is greatest among young patients (3-5). Early atherosclerosis has been demonstrated in lupus patients (6), with a prevalence of 41% in a recent Danish study that included the coronary, carotid, and lower-extremity territories (7). The premature atherosclerosis observed in SLE patients has been related to traditional cardiovascular risk factors, like arterial hypertension, diabetes, hypercholesterolaemia, tobacco use and obesity, however, some lupus-related factors, such as lupus activity itself, treatments (steroids, azathioprine) and inflammatory molecules may play an additional role (6).

AVE are one of the leading causes of increased morbidity and mortality in SLE patients (8) and detection of patients at high risk for cardiovascular disease is one of the priorities during follow-up, although these identification in clinical practice is sometimes not very adequate (9). In the general population, some specific actions could reduce the rate of AVE among high-risk patients (10). Likewise, preventing the occurrence of cardiovascular disease is one of the main objectives in SLE patients. A range of procedures have been developed for the early identification of subjects at increased vascular risk: duplex sonography of carotid arteries for the detection of plaques or to calculate intima/media thickening; coronary computed tomography to quantify coronary calcium burden; and ankle-brachial index (ABI) test.

Abnormal ABI, defined as ≤0.9 or >1.4, has been related with an increased morbidity and mortality in the general population, and ABI has been proposed to be a useful tool to identify a high cardiovascular risk population (11, 12).

SLE patients have been studied in many cross-sectional studies, even with control groups, with duplex sonography of carotid artery, detection of coronary calcium and the ABI test. A number of studies have shown an increased presence of carotid plaques, low ABI and increased coronary-calcium index in SLE patients (2, 13, 14). To date, there is only one published prospective follow-up study in patients with SLE using the carotid duplex sonography to identify patients at increased risk for AVE; in this study, the presence of carotid plaque was associated with an increased risk for coronary and cerebrovascular events (HR 4.67, 95% CI 1.41–15.53, p=0.001) (15).

Thus, we designed a prospective follow-up study of a SLE cohort with a baseline ABI previously reported (2) to determine its utility as a predictor of AVE. The secondary objective of our study was to analyse the relationship between other risk factors and the occurrence of AVE.

Material and methods

Study population

Follow-up data from 216 patients at the Autoimmune Diseases Unit, Department of Internal Medicine, Cruces University Hospital, a tertiary teaching centre in Baracaldo (Basque Country, Spain) associated with the University of the Basque Country. All patients fulfilled the 1997 classification criteria of the American College of Rheumatology and had participated in a previous cross-sectional study between January 2010 and June 2011 (2, 16).

Variables

The following variables were recorded at the time of enrolment for each patient:

1) Demographic characteristics: age, sex, race.
2) Clinical and immunological SLE variables: disease duration (years), SLE manifestations (lupus nephritis, antiphospholipid syndrome, neuropsychiatric lupus), autoantibody profile (anti-DNA, anti-Ro, anti-La, anti-RNP, anti-Sm, antiphospholipid), treatments received (corticosteroids, immunosuppressives, anti-malarials), the Systemic Lupus International Collaborating Clinics (SLICC) damage index (SDI) (17) and the SLE Disease Activity Index (SLEDAI) (18).
3) Cardiovascular (CV) risk factors:

age (defined as more than 55 and 65 years in men and women, respectively), arterial hypertension (HTN, defined as 2 consecutive measurements of at least 140/90 mmHg or antihypertensive therapy), diabetes mellitus (DM, defined as 2 consecutive fasting blood glucose determinations ≥126 mg/dl or treatment with antidiabetic drugs), hypercholesterolaemia (defined as total blood cholesterol fasting levels >200 mg/dl on 2 consecutive determinations or treatment with cholesterol-lowering drugs), metabolic syndrome according to the Adult Treatment Panel III definition (19), current or past smoking, degree of physical exercise (aerobic exercise 1 h/day, at least 3 days a week), and menopause in females. The size, weight, and waist and hip circumference were determined in each patient at the time of performing the ABI, along with calculation of the body mass index (BMI). We included in the study the levels of uric acid, vitamin D and fibrinogen at the time of the ABI.

4) Previous subclinical organ damage or CV events: left ventricular hypertrophy (LVH), microalbuminuria (presence in urine of albumin excretion between 30 and 300 mg/day, determined in spot urine sample), coronary disease, heart failure, cerebrovascular disease, chronic kidney disease, PAD, advanced retinopathy. CV events were defined as the presence of compatible clinical signs and symptoms and eventually confirmed by complementary tests: myocardial infarction was defined as typical chest pain with characteristic electrocardiographic features and elevated levels of creatine kinase (MB fraction) and/or T troponine; stroke by computed tomography (CT) scanning or magnetic resonance imaging; cerebral transient ischaemic attacks (TIA) were diagnosed in the setting of acute focal neurologic symptoms/signs lasting <24 h; chronic kidney disease is defined based on the presence of either kidney damage or decreased kidney function for three or more months, irrespective of cause; PAD, specifically atherosclerotic disease leading to peripheral artery obstruction, may be silent or present with a variety of symptoms and signs indicative of extremity ischaemia; advanced retinopathy is characterised by retinal haemorrhages, exudates, and papilloedema.
5) CV disease-related treatments received for at least 6 months: antiaggregants, statins, anticoagulants.
6) CV risk stratification was performed using the European Vascular Risk Systematic Coronary Risk Evaluation (SCORE) scale for the Mediterranean population (20).

Ankle-brachial index

ABI was performed in both legs of each patient in ad hoc scheduled visits, from January 2010 to June 2011. The MD2/SD2 Dopplex High Sensitivity Pocket Doppler was used for our study and all ABI were performed by the same 2 trained physicians working together with each patient. In every patient, 1 ABI was calculated for each leg. For the purposes of this study, the ABI variable was coded as abnormal ABI: ≤0.9 or >1.4, according to the previously mentioned evidences (11, 12).

Follow-up

A 5-year follow-up was planned for all study participants. Patients were routinely assessed every 3 to 6 months, unless clinical status demanded more frequent visits. Lupus flares (defined as any clinical manifestation of lupus that involves the use of high doses of corticosteroids, use of a new immunosuppressant or increasing the dose of some immunosuppressant previously used) were recorded. Arterial vascular events (AVE) were systematically investigated at each visit through a standardised interview. The AVE were defined as coronary events (angina pectoris, acute myocardial infarction, coronary revascularisation by angioplasty or surgery), cerebrovascular events (transient ischaemic attack, ischaemic or haemorrhagic stroke), PAD (symptomatic intermittent claudication, distal ischaemia, revascularisation by angioplasty or surgery), and vascular death. Follow-up ended when the patient attended the 5-year follow-up visit or due to death. The cause of death was established for all patients who deceased during the follow-up period.

Statistical analysis

Continuous data were described using mean and standard deviation (SD) or median and range, if it does not present a normal distribution; categorical variables with relative frequencies and percentages. The normality of the continuous variables analysed was confirmed with the appropriate statistical studies.

To identify associations with AVE, the following independent variables were tested against the dependent variable "incidence of AVE", using chi-square with Yates' correction or Student *t*-test: age at SLE diagnosis, age at the time of ABI, disease duration, sex, age as a vascular risk factor, abdominal obesity, metabolic syndrome, DM, HTN, hypercholesterolaemia, smoking (current or past), any vascular risk factor (DM or HTN or hypercholesterolaemia or current/past smoking), exercise, alcohol consumption, family history of premature CV disease, BMI, menopause, previous subclinical organ damage (LVH and microalbuminuria), previous CV events [ischaemic heart disease and/or heart failure (IHD/HF), stroke, PAD], chronic kidney disease, previous arterial thrombosis (stroke or IHD/HF or PAD), uric acid levels, vitamin D levels, previous lupus nephritis, previous antiphospholipid syndrome (APS), previous neuropsychiatric lupus (NPSLE), lupus flares during follow-up, anti-DNA, anti-Ro, anti-La, anti-U1RNP, anti-Sm, and antiphospholipid antibodies (aPL; lupus anticoagulant and/or anticardiolipin antibodies at medium-high levels on at least 2 different determinations 12 weeks apart), SLEDAI, SDI value (categorised: 0 *vs.* ≥1), prednisone (cumulative dose in grams and maximum dose ever received), hydroxychloroquine (yes/no and total dose), cyclophosphamide (cumulative dose), low-dose aspirin (number of months on treatment), anticoagulants (number of months taking treatment), or statins (number of months taking treatment) and fibrinogen levels (continuous variable).

Given the fact that the probability of occurrence of the outcomes of interest

(AVE) was influenced by other alternative events (non-vascular death) a competing risk regression (CRR) approach was adopted to obtain more accurate estimates of the 5-year cumulative risk of AVE (21). The model proposed by Fine *et al*. (22) was implemented, as it does not depend upon the independence between both the competing event and the event of interest. Accordingly, subdistribution hazard ratios (SHR) were obtained as estimates of the relative effect of a putative risk factor on the occurrence of the AVE, and subdistribution cumulative hazard functions as estimates of the adjusted 5-year risks. Ninety five percent confidence intervals were also provided.

Those variables with a p-value <0.1 in the univariate analysis were subsequently included as potential predictors of AVE: sex, age at the time of ABI, disease duration in years, family history of premature CV disease, HTN, hypercholesterolemia, SDI value, APS, fibrinogen levels at the time of the ABI, previous arterial thrombosis, prednisone cumulative dose at baseline and abnormal ABI.

Regarding the model selection, we followed a manual backward procedure, starting with the full model and removing variables based on the lack of statistically significant association using likelihood ratio tests, until all the remaining variables were statistically significant. The proportionality of risks assumption was assessed through the introduction of time-dependent covariates and the use of graphical tools. As abnormal ABI was the factor of main interest, it was kept in all the models. Departures from linearity in the log-odds for continuous variables were assessed creating and statistically testing squared and cubic terms.

Stata 14.2 for Windows was used for all analyses (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP).

Ethics

The Ethics Committee for Clinical Research at Cruces University Hospital approved the study protocol in accordance with the Helsinki Declaration (CEIC E09/07). All patients signed an informed consent at the time of enrolment.

Table I. Baseline variables.

Female	200	(92%)
Race	Caucasian: 209	(96%)
Afro-Caribbeans:	3	(1.3%)
Hispanic:	2	(0.9%)
Arabic:	2	(0.9%)
Age at ABI	49	(15) years.
SLE duration at ABI	11	(0-37) years.
APS	21	(9.7%)
Lupus nephritis	60	(27.6%)
NPSLE	5	(2.3%)
Lupus flares	39	(18.3%)
SLEDAI at ABI	0: 104	(48.1%)
	1-5: 91	(42.2%)
	≥6: 21	(9.7%)
SDI at ABI	0: 98	(45.2%)
	1: 53	(24.4%)
	>1: 65	(30.4%)
Use of prednisone	191	(88.4%)
Maximum dose of prednisone	30.8	(25.9) mg
Average daily dose of prednisone	5.6	(8.2) mg
Cumulative dose of prednisone: mean (SD)	18.7	(57) g
Cumulative dose of prednisone: median (IQR)	7.32	(0-177.6) g
Hydroxychloroquine	193	(89.3%)
Cyclophosphamide	52	(24%)
Mycophenolate	34	(15.7%)
Azathioprine	64	(29.7%)
Family history of early vascular disease	25	(11.5%)
Current smoking at ABI	65	(30%)
Smoking (ever)	109	(50.2%)
Diabetes mellitus	7	(3.2%)
Hypertension	71	(32.7%)
Hypercholesterolaemia	74	(34.1%)
Statins	72	(33.3%)
Antiaggregants	103	(47.7%)
Anticoagulants	26	(12%)
Body mass index	Low-normal weight: 106	(49.1%)
	Overweight-obesity: 110	(50.9%)
SCORE	0-4: 205	(95%)
	≥5: 11	(5%)
Previous vascular disease	IHD: 6	(2.8%)
	CVD: 19	(8.8%)
	PAD: 3	(1.4%)

ABI: ankle-brachial index; SLE: systemic lupus erythematosus; APS: antiphospholipid syndrome; NPSLE: neuropsychiatric lupus; SDI: SLICC Damage Index; IHD: ischaemic heart disease; CVD: cerebrovascular disease; PAD: peripheral arterial disease.

Results

Baseline demographic variables

Two hundred sixteen patients started the follow-up. One hundred ninety-nine (92%) were women. Two hundred nine patients (96%) were white, with the remaining consisting of 3 Afro-Caribbeans, 2 Hispanics, and 2 Arabic. The age at baseline was 49 (15) years, and the follow-up after SLE diagnosis was 11 (0–37) years (Table I).

Cardiovascular risk factors

Traditional CV risk factors were frequent in our cohort, with 162 (74.7%) patients presenting at least one CVRF: HTN 32.7%, hypercholesterolaemia 34.1%, tobacco use 50.2%, overweight-obesity 50.9%, family history of premature CV disease 11.5%, DM 3.2%. 205 patients (95%) had a SCORE between 0 and 4 and 11 patients (5%) had a SCORE ≥5. Previous CV events were present in 26 (12%) patients: CVD in 19 (8.8%), IHD in 6 (2.8%) and PAD in 3 (1.4%). Two patients suffered two or more CV events: one with PAD and CVD and another with IHD and CVD; 72 (33.3%) patients had been treated with statins, 103 (47.7%) with antiaggregants and 26 (12%) with anticoagulants (Table I).

Baseline SLE-related variables and lupus flares

At baseline, 21 (9.7%) patients had an SLEDAI ≥6 and 104 (48.1%) were inactive with a SLEDAI score of 0. APS was diagnosed in 21 (9.7%) patients. 60 (27.6%) patients had been diagnosed of lupus nephritis (in 6 patients, lupus nephritis was active at the time of inclusion in the study). 5 (2.3%) patients had been previously diagnosed of NPSLE. The baseline SDI was 0 in 98 (45.2%) patients, 53 (24.4%) patients had a SDI index of 1 and 65 (30.4%) patients had a SDI >1. Thirty-nine patients suffered at least one lupus flare during follow-up (range 1 to 4 lupus flares).

Regarding SLE treatments, 191 (88.4%) patients had received prednisone with a mean maximum dose ever received 30.8 (25.9) mg/d, mean daily dose at baseline 5.6 (8.2) mg/d and median cumulative prednisone dose 7.32 (0–177.6) g. Hydroxychloroquine was used in 193 (89.3%), cyclophosphamide in 52 (24%), mycophenolate in 34 (15.7%) and azathioprine in 64 (29.7%) (Table I).

Cardiovascular events and mortality

Follow-up data were available for 212 (98.1%) patients, with 1016 patient/year observation; 4 patients discontinued follow-up. Among them, 186 (88%) patients survived during the whole follow-up period without suffering any AVE. 18 AVE were identified in 17 patients: 11 cerebrovascular events, 4 coronary events, 2 peripheral arterial disease events and 1 sudden death, with one patient presenting two angina pectoris episodes requiring percutaneous coronary interventions during follow-up. Fourteen patients died during the follow-up: 6 because of AVE or their sequelae, 4 due to cancer and 4 due to cardio-respiratory failure (Table II). The age at the time of death was 74 (14) years, and the age at the time of the AVE was 66 (16) years (Table II).

Ankle-brachial index

The baseline prevalence of abnormal ABI was 24.1%, being more prevalent in males (6/17, 35.3%) than females (46/199, 23.1%). In patients who suffered AVE during follow-up, 41.2% had a normal ABI while 58.8% had an abnormal ABI. In patients who remained free of AVE during follow-up, 79% had a normal ABI while 21% had an abnormal ABI. In the analysis structured by the type of AVE we observe the following findings: in patients with IHD and sudden death 100% had an abnormal ABI; in patients with CVD 54.5% had a normal ABI and 45.5% had an abnormal ABI; and in patients with PAD 50% had a normal ABI and 50% had an abnormal ABI (Table III).

Table II. Mortality causes.

Death causes	n (%)	Types
Arterial vascular events	6	4 cerebrovascular events 1 acute myocardial infarction 1 sudden death
Malignant neoplasm	4	2 lung cancer 1 gastrointestinal cancer 1 lymphoma
Other causes	4	1 interstitial lung disease 1 pulmonary hypertension 1 disseminated infection 1 multiple organ failure (at 90 years of age)

Table III. Arterial vascular events and ABI.

	Patients	Normal ABI	Abnormal ABI
All vascular events	17/212 (8.01%)	7/17 (41.2%)	10/17 (58.8%)
Cerebrovascular event: - Cerebrovascular accident (10) - Transient ischaemic attack (1)	11/212 (5.18%)	6/11 (54.5%)	5/11 (45.5%)
Coronary events (3 patients) - Acute myocardial infarction (2) - Angina pectoris with angioplasty (2)	4/212 (1.88%)	0/3 (0%)	3/3 (100%)
Peripheral arterial disease	2/212 (0.94%)	1/2 (50%)	1/2 (50%)
Sudden death	1/212 (0.47%)	0/1 (0%)	1/1 (100%)
No vascular event during follow-up	**195/212 (91.98%)**	**154/195 (79%)**	**41/195 (21%)**

Table IV. Competing risk regression: abnormal ABI.

Variable	SHR	*p*-value	95% CI
Female	0.22	0.017	0.07-0.77
Family history of early thrombosis	5.44	0.004	1.69-17.51
Previous thrombosis	5.01	0.007	1.55-16.19
Cumulative dose of prednisone	1.01	0.007	1.005-1.031
Abnormal ABI	2.65	0.089	0.86-8.14

SHR: subdistribution hazard ratio; ABI: ankle-brachial index.

Multivariate analysis

In the final model, the risk factors associated to cardiovascular events were family history of early thrombosis (SHR 5.44 [1.69-17.51]; p=0.004), personal history of previous arterial thrombosis (SHR 5.01 [1.55-16.19]; p=0.007) and cumulative dose of corticosteroids (in prednisone gram equivalents) (SHR 1.01 [1.005-1.031]; p=0.007). An abnormal baseline ABI showed a SHR 2.65 [95% confidence interval 0.86-8.14]; p=0.089. As a protective factor we identify the female sex (SHR 0.22 [0.07-0.77]; p=0.017) (Table IV).

Discussion

In the main objective of the study, we have found a clear statistical trend but not an association between abnormal ABI and risk of AVE. As secondary objectives of the study, we identified a set of risk factors to suffer AVE in SLE patients: family history of premature AVE, previous cardiovascular disease, male gender and higher cumulative glucocorticoids dose.

Although the results do not conclusively confirm the utility of the ABI as a predictor of AVE, we think that this

clear statistical trend observed should be taken into consideration, bearing in mind the relatively low power of the study, due to the small number of patients included in the study and the small number of events occurring during the 5-year follow-up time. In the studies that found association in the general population between the abnormal ABI and the risk of AVE, the number of participants was much higher, including thousands of patients, and with a longer follow-up, as can be seen in different cohorts or systematic reviews (23-26). For all these reasons we can neither confirm nor rule out a possible association between an abnormal ABI and a higher risk of AVE in SLE patients.

In the lupus population, only one study had, to our knowledge, a similar design. In a prospective cohort study, Kao *et al*. (15) investigated the association between the presence of carotid plaque, detected by using B-model ultrasound, and incident cardiovascular events: myocardial infarction, coronary angioplasty, coronary artery bypass graft, fatal cardiac arrest and cerebrovascular accident. All patients were women without previous cardiovascular disease, unlike our study cohort. The presence of carotid plaque (HR 4.67, 95% CI 1.41–15.53, p=0.01) and the duration of corticosteroid use (HR 1.08, 95% CI 1.03–1.13, p<0.01) were both associated with an increased risk for vascular events. The family history of AVE was analysed but was found non-significant.

In Schoenfeld's systematic review, only 9/20 of the studies took into account family history of premature AVE (1), and only in one of them a statistically significant association with IHD was shown in the multivariable analysis (26). In our cohort, family history of premature AVE was actually the predictor with the highest SHR. This is in keeping with large cohorts studies in the general population, in which this variable has been related to an increased risk of arterial events; indeed, family history of premature cardiovascular disease has been used for the stratification of total cardiovascular risk in the 2013 European Society of Hypertension (ESH) and the European Society of Cardiology (ESC) guidelines for the management of arterial hypertension (27).

In many studies designed to identify risk factors for AVE in SLE patients, patients with previous vascular disease have been excluded, whilst in the general population a history of arterial thrombosis conferred a very high cardiovascular risk (27). Patients with previous thrombosis had a 5-fold higher risk of AVE in the final model of our study.

Also, male gender was independently associated with an increased risk of arterial events. This finding is not reported in many of the studies of vascular disease in SLE because have been conducted in exclusively female populations (1), but is consistent with the results obtained in some SLE cohort and population-based studies (28-30), in the general population (31) and in other inflammatory rheumatic diseases (32).

The effect of glucocorticoids on the cardiovascular risk of SLE patients is complex. On the one hand, glucocorticoids can control lupus activity, which is a cause of premature atherosclerosis. On the other hand, the metabolic side effects of glucocorticoid can themselves increase cardiovascular risk (33), taking into account that the dose/toxicity gradient is not linear: damage risk increases with doses of prednisone over 7.5 mg/d, reaching maximum levels with doses over 30 mg/d (34). Thus, it is not surprising that studies analysing the relation of glucocorticoid therapy with cardiovascular disease have yielded heterogeneous results (1). In this study we built three different variables to model the effect of glucocorticoids on AVE: the maximum dose received during the follow-up, the average daily dose and the total cumulative dose. Only the cumulative total dose was identified as a risk factor, with each increase of 10 g over the mean of the whole cohort, 18.7g, resulting in an increased risk for AVE of around 2%. This is in keeping with a recent study from our cohort, in which a reduced dose glucocorticoid regime resulted in a significant decrease in cardiovascular damage after 5 years of follow-up (35). More recently, a longitudinal cohort study in Chinese SLE patients from Hong-Kong has shown that those receiving doses of prednisone ≥0.6 mg/kg/day for 4 weeks or longer were 14-fold more likely to die during the follow-up (36).

Our study has some limitations. When interpreting our results it must be taken into account the fact that our population was mainly constituted by Caucasians living in a country with a low general cardiovascular risk. Almost 90% of our patients received treatment with hydroxychloroquine, and the doses of prednisone were low compared with other cohorts (33). In probable relation with all this, the absolute number of AVE was low, a fact that could have reduced the study power to identify risk factors for arterial events. Another limitation is the number of patients included and the time of follow-up. Probably these two factors also limit the study power.

Among the strengths of our study, it should be emphasised the use of detailed information on clinical and immunological SLE variables, treatments administered and internationally agreed upon cardiovascular risk factors. Follow-up data were available for more than 98% of the 216 patients included in the original study. The statistical analysis was performed using the CRR approach, which substantially reduces bias associated with unreliable assumptions about the censoring profiles common in classical survival studies.

Of course, the findings obtained should be confirmed by other cohorts. A longer follow-up of this cohort can give us a future answer to the question of the prognostic utility of ABI for AVE in patients with SLE.

In summary, we have found that male gender, higher cumulative prednisone dose, family history of early vascular disease and personal history of arterial vascular disease are related to a higher risk for AVE in SLE patients. Regarding the ABI, we can consider carrying out this test, because could be useful to identify patients with SLE with a possible higher risk of AVE. In patients who present the previous factors, a more aggressive control of modifiable cardiovascular risk factors should be accomplished.

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