Review

A meta-analysis of avascular necrosis in systemic lupus erythematosus: prevalence and risk factors

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ABSTRACT

Objective. *To determine the prevalence of and risk factors for avascular necrosis (AVN) in systemic lupus erythematosus (SLE).*

Methods. *MEDLINE, CINAHL, Web of Science, EMBASE and Cochrane Library were searched from inception to July, 2015 and a random effects model was used to combine frequencies; study quality was assessed using STROBE.*

Results. *2,041 citations identified 62 articles. Many results had high heterogeneity. The prevalence of symptomatic AVN was 9% (range 0.8%–33%) in SLE and 29% for asymptomatic AVN; femoral head was the most common location (8.0%). High-dose corticosteroids (CS) any CS use, maximum and cumulative dose, pulse therapy, and CS side-effects (hypertension, Cushings, but not diabetes mellitus or hyperlipidaemia) were associated with AVN, as was active SLE (cutaneous vasculitis, renal and neuropsychiatric manifestations, serositis, cytopenias) and Sjögren's, Raynaud's phenomenon, arthritis, cyclophosphamide (but not azathioprine mycophenolate mofetil, or methotrexate) and more damage (excluding musculoskeletal system). Antimalarial drugs were not protective. Rashes and oral ulcers were not associated with AVN. Mean daily dose of CS and duration of CS use had no impact on AVN occurence. Autoantibodies and other immunological markers did not predispose to AVN, except IgM anticardiolipin antibodies which doubled the risk. African Americans experienced more AVN (OR 1.8, p=0.04).*

Conclusion. *AVN may occur in 1/3 of patients with SLE and 9% with symptoms. Features of active organ SLE (CNS, renal, cutaneous vasculitis, serositis, cytopenias) are associated with AVN as are CS, especially early in disease and at high doses. Those with early CS side-effects seem to have the highest risk of AVN.*

Introduction

As therapies for systemic lupus erythematosus (SLE) have improved (1), the challenge is to understand and prevent the long-term complications, whether they are due to the disease itself, treatment, and/or comorbidity.

Avascular necrosis (AVN) of bone is a well-recognised musculoskeletal complication of SLE, characterised by subchondral bone necrosis as a result of insufficient blood supply (2). Non-invasive diagnostic tests used to detect AVN include radiographs, skeletal scintigraphy, computed tomography, and magnetic resonance imaging (MRI); the latter is the most sensitive and specific (3). In SLE patients, AVN more frequently involves hips and knees but may contemporaneously affect multiple joints (4). Once x-ray changes occur, involved joints collapse within 6 to 24 months (5). The clinical course is typically progressive to end stage secondary osteoarthritis causing significant pain, limitation of movement, and poor quality of life (6). Most of SLE patients present late and arthroplasty is a common outcome.

Some of the largest studies indicate that the prevalence of AVN may be up to 44% in SLE (7). However, data are still contradictory with some studies showing the AVN rates as low as 1–3% (8-11). The ability to mitigate modifiable risk factors would be ideal. Steroid therapy has been reported as an important contributor to AVN; corticosteroids (CS) can directly inhibit osteoblasts and thus reduce the bone formation (12). Some studies also speculate the underlying systemic inflammation in SLE is involved (13). Increased TNF and homocysteine levels, production of oxidised LDLs were shown to

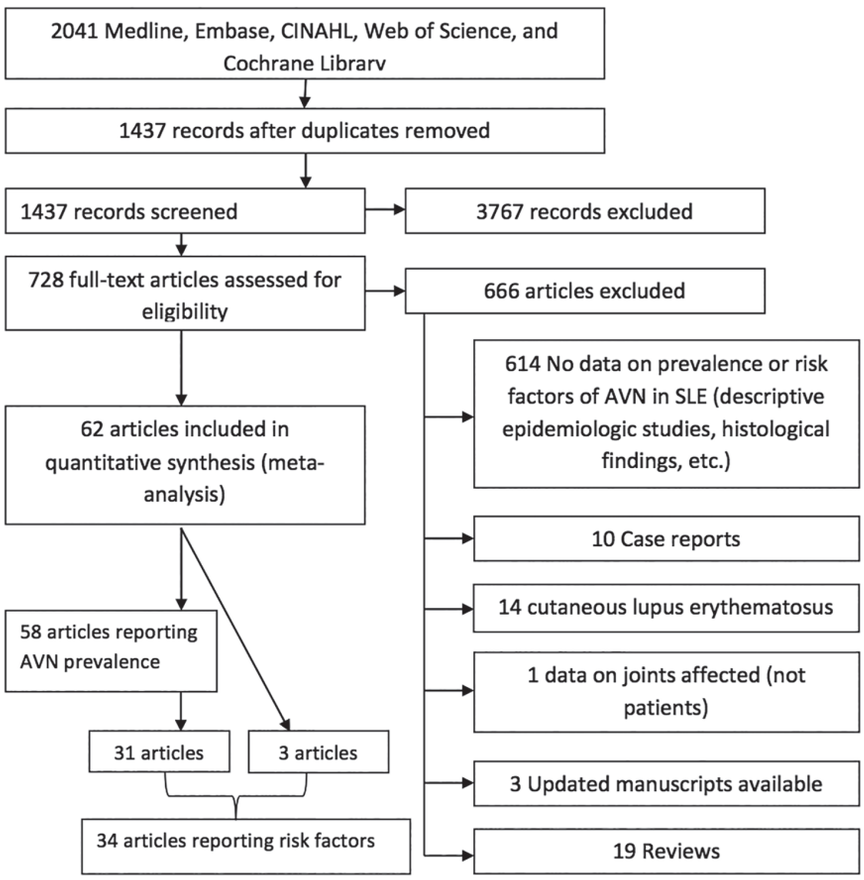

Fig. 1. Flow diagram of search results for avascular necrosis (AVN) in systemic lupus erythematosus (SLE)

reduce osteoblast maturation in favor of adipocytes, cause apoptosis of osteoblast-lineage cells and increase the development and activity of osteoclasts associated with accelerated bone loss (13). Inconclusive results were reported when analysing the association of AVN with some typical features of SLE like vasculitis (14-17), oral ulcers (18-20), serositis (14, 17, 20), Raynaud's phenomenon (20-23), antiphospholipid antibody positivity (20, 23-27), and with administration of antimalarial drugs (with a protective effect) (14, 28, 29). There is still conflicting literature with respect to the contribution of CS intake and AVN (18, 28-31). The role of age at disease onset is also unclear as most studies are exclusively adult-onset SLE (11, 25, 32-35).

A recent review of AVN risk factors in SLE showed the higher prevalence of arthritis, alopecia, oral ulcers, vasculitis, pleuritis, arterial hypertension, Cushingoid body habitus, as well as central nervous system (CNS), gastrointestinal and renal involvement in SLE patients with AVN compared to those without this complication (36). However, the total number of articles included was small (16) with insufficient studies available for a pooled analysis for alopecia, oral ulcers and serositis (4), anemia and pleuritic (3), and thrombophlebitis (2), that might affect conclusions. We have expanded our search to other databases (CINAHL, Cochrane library, Web of Science) that significantly increased the literature (69, 72, 73). Consequently, the aim of this study was to systematically review the prevalence of AVN in SLE including asymptomatic and symptomatic AVN, as well as of a site-specific (hip) AVN, and to study features in SLE that change the likelihood of AVN.

Methods

Search strategy

MEDLINE, MEDLINE In-Process & Other Non-Indexed Citations, EMBASE, CINAHL, Web of Science and the Cochrane Library were searched from the inception to July, 2015, using the terms "lupus", "bone loss", "bone mass", "osteonecrosis", "avascular necrosis", "risk", "aetiology", "prognosis", "aseptic necrosis", "hazard", "prevalence". All terms were searched as keywords, and when available MeSH, EMTREE and CINAHL, or other applicable subject terms were searched as well. Databases searched by keyword only included Cochrane Library, BIOSIS, and Web of Science. EndNoteX4 software was used to check for duplicate publications. Studies were limited to human with language restriction (English). Identified titles/abstracts were reviewed, and full reports were obtained if appropriate. Studies were considered if they provided original data on the prevalence or risk factors of AVN in patients with SLE. Studies were excluded if they 1) were case reports, editorials and review articles; 2) were studies for which updated manuscripts were available; 3) were duplicate populations. Searches were supplemented by hand-searching relevant articles (including citation searching), references of selected studies, guidelines and reviews. The systematic review and meta-analysis conform to the PRISMA statement (79).

Data collection

The search was performed by two reviewers (T.N. and M.P.G) and ambiguities were resolved with the other reviewer (JP) for inclusion into the systematic review. Data from each study were extracted including, but not limited to: year of publication, author, location of study, study design, patient population, ACR criteria met, sample size, ethnicity, mean age at diagnosis and disease onset, mean disease duration, proportion with AVN and its definition, disease activity and damage measures (SLEDAI, SLAM-R, SLICC/ACR damage index), medications used including steroids (mean, highest (maximum), and cumulative doses, and route), anticardiolipin antibodies and lupus anticoagulant, and biochemistry. If studies included patients with SLE and other rheumatic diseases, only data pertaining to the SLE cases were used.

Table I. Characteristics of the studies reporting frequency of avascular necrosis (AVN) in systemic lupus erythematosus (SLE).

Study	Country	Year	No. of SLE pts (% of females)	Method of AVN detection					No. (%) of pts with	AVN site	STROBE checklist
				Clinical symptoms	x-ray	radioisotope bone scan	MRI	other			
Watanabe, T *et al*. (32)	Japan	1997	113 (80)	S	Yes		Yes		7 (6.19)	MS	17/22
									6 (5.31)	hip	
Migliaresi, S *et al*. (33)	Italy	1994	69 (93)	S	yes	yes			1 (1.45)	MS	15/22
Massardo, L *et al*. (34)	Chile	1992	190 (87)	S	yes				17 (8.95)	MS	18/22
Lee, J *et al*. (25)	South Korea	2014	1051	S	yes		yes		73 (6.95)	MS	20/22
Koutsonikoli, A *et al*. (35)†	Greece	2015	43 (83)	S	Reported as part of SLICC/ACR				3 (6.98)	MS	19/22
Ruiz-Arruza, I *et al*. (11)	Spain	2014	230 (90)	S	Reported as part of SLICC/ACR				4 (1.74)	MS	20/22
Olsen, NJ *et al*. (44)	USA	2013	99 (88)	S	Reported as part of SLICC/ACR				6 (6.07)	MS	17/22
Swaak, AJ *et al*. (50)	Netherlands	1999	187 (89)	S		yes			15 (8.02)	MS	14/22
Pontikaki, I *et al*. (46)†	Italy	2014	104 (89)	S		Not indicated			7 (6.73)	MS	9/22
Mok, CC *et al*. (14)	Hong Kong	1998	320	S	yes	yes	yes		38 (11.99)	MS hip	17/22
									36 (11.25)		
To, CH *et al*. (63)	USA	2005	1357 (93)	S	Reported as part of SLICC/ACR				125 (9.21)	MS	20/22
Kunyakham, W *et al*. (15)	Thailand	2012	736 (94)	S	yes		yes		65 (8.83)	MS hip	15/22
									65 (8.83)		
Oinuma, K *et al*. (7)†††	Japan	2001	72 (94)	A			yes		32 (44.44)	MS	18/22
Mok, MY *et al*. (53)	UK	2000	265	S			yes		11 (4.15)	MS hip	16/22
									10 (3.77)		
Jaovisidha, S *et al*. (70)	Thailand	2007	11 (100)	A	yes		yes		2 (18.18)	hip	16/22
Houssiau, FA *et al*. (69)	Belgium	1998	40	A			yes		13 (32.5)	MS	17/22
Hamijoyo, L *et al*. (58)	Philippines	2008	540	S	yes		yes		43 (7.96)	MS	16/22
									40 (7.41)	hip	
Gurion, R *et al*. (51)†	Japan	2015	201 (83)	S	Reported as part of SLICC/ACR				9 (4.48)	MS	11/22
Griffiths, ID *et al*. (43)	USA	1979	68	S	yes				8 (11.76)	MS	13/22
									6 (8.82)	hip	
Gladman, D *et al*. (28)	Canada	2001	744	S	yes	yes	yes		95 (12.80)	MS	20/22
Ghaleb, R *et al*. (67)	Egypt	2010	100 (91)	S	yes		yes		15 (15.00)	hip	19/22
Fialho, S *et al*. (23)	Brazil	2006	46 (100)	A			yes		10 (21.74)	hip	14/22
Faezi, ST *et al*. (18)††	Iran	2015	665	S	yes	yes	yes		105 (15.79)	MS	19/22
									96 (14.43)	hip	
Dimant, J *et al*. (16)	USA	1978	234 (94)	S	yes	yes			22 (9.4)	MS	10/22
									18 (7.69)	hip	
Calvo-Alen, J *et al*. (59)	USA	2005	571	S	yes		yes		32 (5.6)	MS	22/22
Nagasawa, K *et al*. (72)†††	Japan	2004	45 (96)	A	Yes		Yes		15 (33.33)	MS	14/22
			45 (96)	S					5 (11.11)	MS	
Oh, SN *et al*. (55)††	South Korea	2004	415	S		yes	yes		37 (8.92)	MS	14/22
Ono, K *et al*. (68)	Japan	1996	62 (94)	S		yes			9 (14.52)	hip	16/22
Petri, M *et al*. (54)	USA	1995	407 (92)	S	Reported as part of SLICC/ACR				59 (14.5)	MS	10/22
Rascu, A *et al*. (8)	Germany	1996	280	S	yes				6 (2.14)	MS	14/22
									5 (1.79)	hip	
Saleh, JA *et al*. (20)	Arab Emirates	2010	126 (96)	S	yes		yes		11 (8.73)	MS	20/22
Sheikh, JS *et al*. (49)	USA	1998	175	S	yes	yes	yes		22 (12.57)	MS	19/22
Abeles, M *et al*. (65)††	USA	1977	365	S	yes				17 (4.66)	hip	15/22
Abid, N *et al*. (66)	Saudi Arabia	2013	46 (100)	S		Not indicated			7 (15.22)	hip	17/22
Dhillon, N *et al*. (64)	Canada	2014	1728	S	yes	yes	yes	CT	235 (13.59)	MS	13/22
Cozen, L *et al*. (56)	USA	1998	488 (93)	S					26 (5.33)	MS	14/22
Costallat, LTL *et al*. (57)	Brazil	2003	519	S	yes	yes	yes		42 (6.80)	MS	10/22
Chen, S *et al*. (41)	China	2006	50 (96)	S		Not indicated			8 (16.00)	MS	15/22
Cervera, R *et al*. (62)	USA	1999	1000 (91)	S		Not indicated			23 (2.3)	MS	21/22
Castro, TCM *et al*. (22)†,††	USA	2011	40 (83)	A			yes		7 (17.50)	MS	19/22
				S					1 (5.00)	hip	
Bogmat, L *et al*. (9)†	Ukraine	2014	44	S	Reported as part of SLICC/ACR				1 (3.10)	MS	11/22
Asherson, RA *et al*. (27)	France	1993	800	S	yes				37 (4.62)	MS	13/22
Artim-Esen, B *et al*. (61)	Turkey	2014	936	S	Reported as part of SLICC/ACR				119 (12.71)	MS	15/22
Aranow, C *et al*. (26)††	USA	1997	66 (92)	A			yes		8 (12.12)	hip	18/22
Gurion, R *et al*. (42)†	USA	2013	62* (86)	S			Not indicated		7 (11.29)	MS	12/22
			849** (82)	S					38 (4.48)	MS	
Mont, MA *et al*. (24)	USA	1997	103 (94)	S	yes		yes		31 (29.13)	MS	21/22
Weiner, ES *et al*. (48)	USA	1989	172	S	yes		bone biopsy		28 (16.28)	MS	20/22
Yang, Y *et al*. (60)†	Canada	2014	617	S	yes	yes	yes		37 (5.99)	MS	18/22
									26 (4.21)	hip	
Thilagavathi, N *et al*. (10)	India	2012	17 (0)	S			Not indicated		1 (5.88)	MS	9/22
Shaharir, SS *et al*. (47)	Malaysia	2014	150 (90)	S	Reported as part of SLICC/ACR				10 (6.67)	MS	20/22
Li, X *et al*. (52)	China	2013	219	S	yes		yes	CT	73 (33.33)	MS	10/22
Zizic, TM *et al*. (71)	USA	1985	54 (96)	A	yes	yes			28 (51.85)	MS	17/22
Smith, FE *et al*. (45)	USA	1976	99	S	yes				7 (7.07)	MS	11/22
									6 (6.06)	hip	
Nagasawa, K *et al*. (39)	Japan	1989	111 (96)	A	yes	yes			24 (21.62)	MS	16/22
Prasad, R *et al*. (31)	Canada	2007	570 (83)	S	yes	yes	yes	CT	65 (11.40)	MS	16/22
Sayarlioglu, M *et al*. (19)	Turkey	2012	868		yes	yes	yes		49 (5.65)	MS	16/22
Uea-areewongsa, P *et al*. (30)	Thailand	2009	186	S	yes		yes		41 (22.04)	MS	20/22
Murphy, NG *et al*. (40)	USA	1998	46	S	Reported as part of SLICC/ACR				4(8.69)	MS	15/22
									3 (6.52)	hip	

*: HUMS cohort, **: CARRA cohort, †: jSLE only, ††: all patients received corticosteroids, †††: all patients received high doses of corticosteroids (>40mg/day), A: asymptomatic AVN; S: symptomatic AVN; MRI: magnetic resonance tomography; MS: multiple sites assessed; CT: computed tomography; STROBE checklist: a 22-item Strengthening the Reporting of Observational Studies in Epidemiology checklist.

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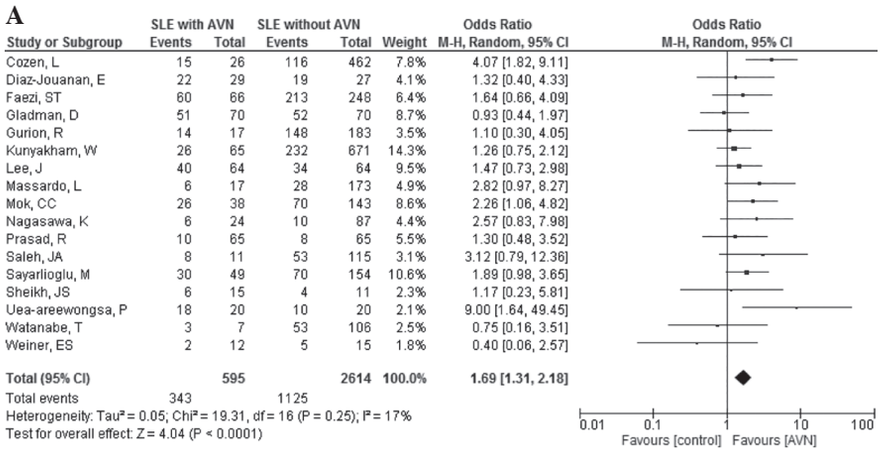

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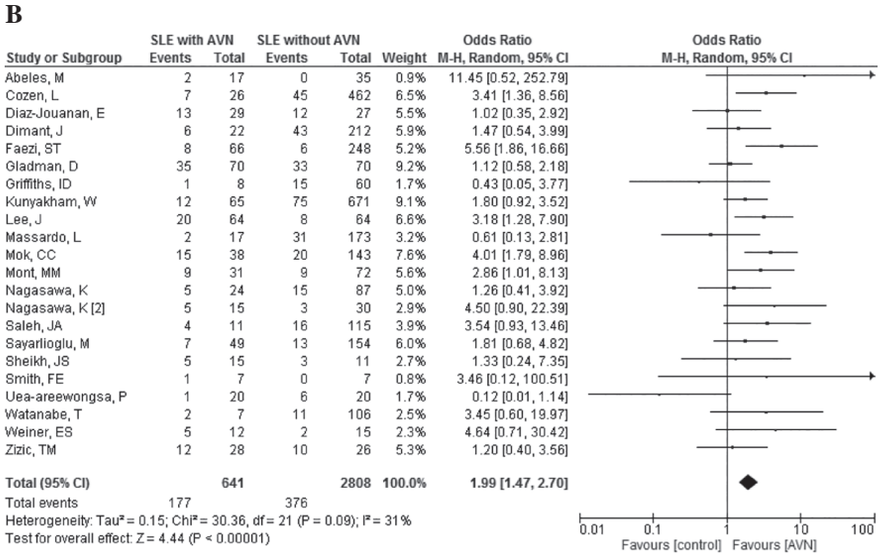

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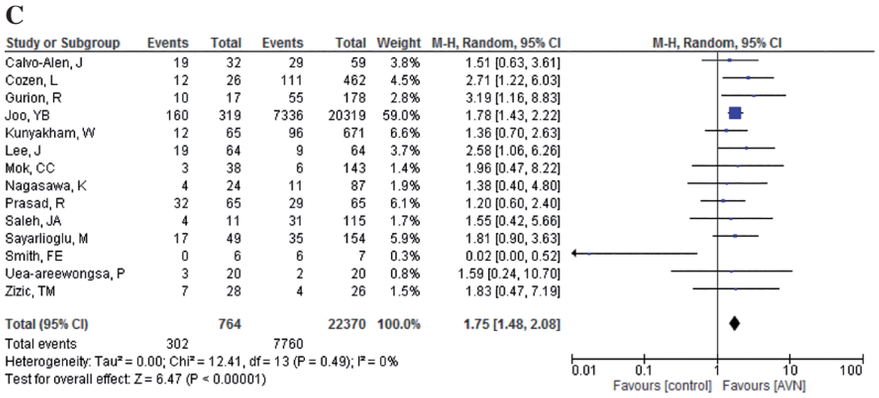


Quality assessment

To ensure accurate reporting, each study was assessed by using the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist (37), which is a 22-item checklist relating to the title and abstract of the article, background and objectives, methods, results, discussion and funding.

Statistical analysis

Descriptive statistics were used to summarise the data. Proportions were pooled using a random effects model. Forest plots were created to estimate prevalence of AVN with a 95% confidence interval (CI) and the I^2 statistic to explain the between-study heterogeneity (0–100%), with higher percentage variation suggesting more heterogeneity among studies. I^2 values of 25, 50, and 75% were nominally considered low, moderate, and high heterogeneity. Tau-squared was the square root of the between study variance, and *p*-value was for Cochrane's Q, the classic measure of heterogeneity. For certain risk factors that met meta-analysis eligibility criteria (Raynaud's phenomenon, antiphospholipid syndrome, renal disease, etc.), the random effects model was utilised to pool the effect sizes of the individual risk factors taking into account both the sampling error and between-study heterogeneity (Dersimonian and Laird inverse variance weighting random effect method). A $p<0.05$ was statistically significant. For the risk factors, such as cumulative CS dose, mean and maximum daily doses, duration of disease, duration of CS therapy, SLEDAI scores, age at diagnosis, the mean and standard deviation (SD) were used to pool data. When the published studies only reported the median, range and the sample size, for the samples of ≤25 patients we estimated the mean by using the formula $Mean = (a+2m+b)/4$ where m - the median, a and b - low and high end of the range, respectively), and n - the sample size, while we assumed that median was equal to mean when the sample size was larger than 25 SLE patients (38). For moderately sized samples ($15<n\leq70$), the formula range/4 was used to estimate the SD. For large samples (n >70), the formula range/6 gave the best estimator for the SD (39). Publication bias was assessed by visually inspecting a funnel plot. All analyses were conducted using SPSS v. 22, Comprehensive Meta-Analysis and RevMan 5.2 software.

Results

Description of included studies

2,041 citations were identified; 728 full-text articles were evaluated, and 62 met the inclusion criteria for AVN prevalence and/or risk factors in SLE patients. The most common reasons for exclusion were the absence of an appropriate data on AVN prevalence and/or risk factors, reviews and papers reporting cutaneous lupus (Fig. 1).

Fifty-eight studies representing 59 SLE case series (as two groups were includ-

ed in the study of Gurion *et al*. (42)) reported prevalence of AVN in SLE patients (7-11, 14-16, 18-20, 22-24, 26-35, 39-72), of these 31 also analysed risk factors for AVN (7, 14-16,18,20,22-26, 28,32-34,39,42,43,48,49,51,53,56,58-60,65,67-69,72). The characteristics of the studies reporting prevalence of AVN are presented in Table I. Fifty studies were longitudinal cohort (37 retrospective (8, 19. 24, 27,30, 31, 39, 42, 45,47-49,52, 54-56, 60-62,64-66,71), 13 prospective (7, 10,16, 22, 32, 33, 41, 43, 57, 63, 68, 70, 72)), and eight cross-sectional (9, 20, 23,26, 40, 51, 67,69).
Three studies directly addressed the risk factors for AVN in SLE (17, 29, 73). Forty-six studies reported prevalence of symptomatic AVN in 47 cases series (8-11, 14-16, 18-20, 24, 25, 28-35, 39-64) and nine studies included the data on asymptomatic AVN (7, 22, 23, 26, 39, 69-72).

Prevalence of AVN in SLE

The prevalence of symptomatic AVN (any location) ranged from 1.45% to 33% with wide variation in disease duration, follow-up time and different timeframes for the inclusion of AVN cases (Table I). The pooled prevalence of symptomatic AVN was 8.96% (95% CI 7.37-10.55; I^2 93%), and AVN of femoral head was the most common location (8.0%, 95%CI 5.88-10.12; I^2 84%).
The pooled prevalence of asymptomatic AVN was 28.52% (95% CI 19.46, 37.60, I^2 80%), when multiple localisations had been assessed by various imaging techniques. The frequency of AVN (overall, symptomatic and asymptomatic) had high heterogeneity. Three studies reported the prevalence of asymptomatic AVN of the femoral head at 12%, 18%, and 22% (23, 26, 70).

Risk factors for AVN in SLE patients

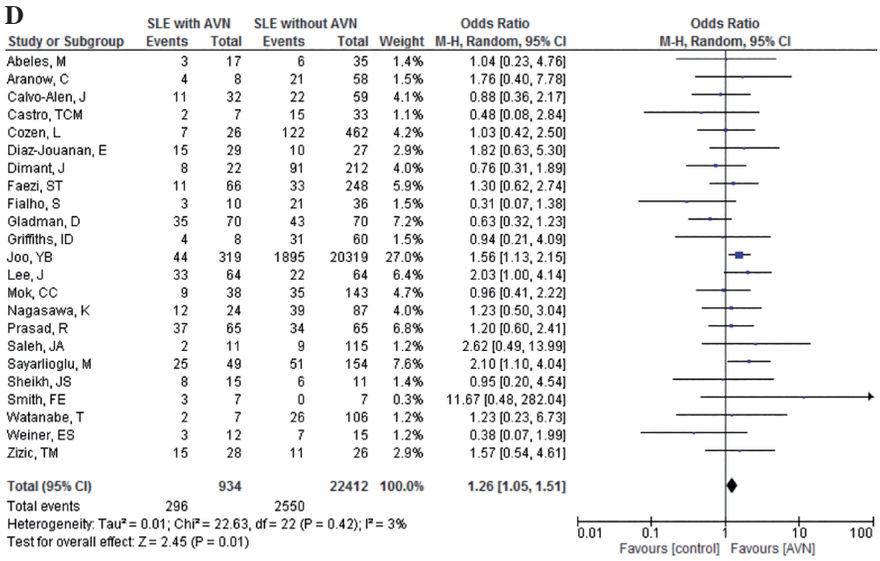
• *Ethnicity, clinical and laboratory manifestations, and disease activity*

The proportion of African-Americans was higher among patients with AVN (OR 1.79%, 95%CI 1.03-3.13, p=0.04; I^2 33%). Renal involvement was demonstrated as a risk factor across most of the studies where it was evaluated as seen in Figure 2. The summary odds ratio for renal involvement was 1.73, for proteinuria 1.84 and for impaired renal function 2.32 (all statistically significant) (Table II). Neuropsychiatric SLE manifestations (OR 1.99, p<0.00001), cutaneous vasculitis (OR 2.08, p=0.004), Raynaud's phenomenon (OR 1.26, p=0.01), Sjogren's syndrome (OR 3.09, p=0.04), arthritis (OR 1.69, p<0.0001), serositis (OR 1.80, p<0.001) were more common in AVN patients. Involvement of skin, alopecia and oral ulcers, livedo reticularis and lymphadenopathy were equally represented in both groups. Haematological disturbances overall were more often found in AVN cases (OR 1.92, p=0.02), particularly leukopenia and thrombocytopenia; while the frequency of haemolytic anaemia did not differ between AVN-positive and negative cases. IgM anticardiolipin antibodies (ACL) were more often detected in patients with AVN (OR 2.48, p=0.008), but the frequencies of IgG ACL and lupus anticoagulant were comparable in both groups. Antiphospholipid syndrome and the history of thrombosis were not associated with any additional AVN risk. Higher disease activity (measured by the SLEDAI) was not related to AVN. Organ damage measured with SLICC/ACR index (without the AVN item from the musculoskeletal component) was slightly increased in those with AVN. Arterial hypertension (OR 1.75, p<0.00001) and Cushingoid body habitus (OR 5.11, p<0.0001) and serum lipid levels were higher in AVN patients (Table II). Diabetes mellitus, osteoporosis and osteoporotic fractures did not show a significant association with AVN (Table II).
Autoantibodies (anti-Sm, anti-Ro, anti-La, anti-RNP, anti-dsDNA, ANA, rheumatoid factor), low complement, positive LE cell and VDRL tests and cryoglobulinaemia did not increase the risk of AVN development in patients with SLE.

• *Therapy*

The use of CS (OR 3.2, p=0.0002) and

D



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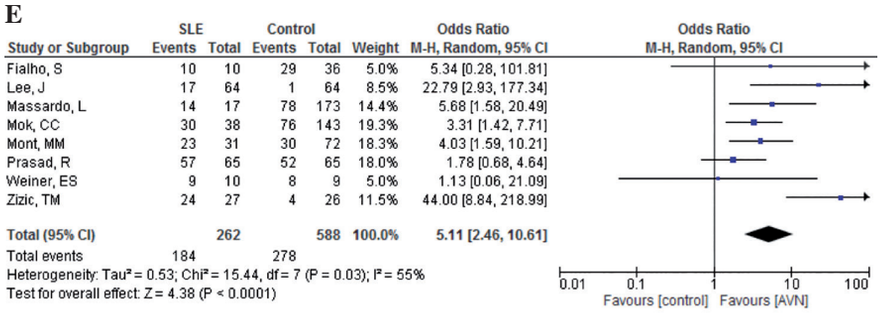

Fig. 2. Forest plot and summary odds ratio of the studies reporting the following clinical manifestations in SLE patients with and without avascular necrosis (AVN): **A**: renal involvement, **B**: central nervous system involvement, **C**: arterial hypertension, **D**: Raynaud's phenomenon. **E**: Cushingoid body habitus.

Table II. Meta-analysis of risk factors that may place patients with systemic lupus erythematosus at a higher risk for the development of avascular necrosis (AVN).

Study	Country	Year	No. of SLE pts (% of females)	Method of AVN detection					No. (%) of pts with	AVN site	STROBE checklist
				Clinical symptoms	x-ray	radioisotope bone scan	MRI	other			
Watanabe, T *et al*. (32)	Japan	1997	113 (80)	S	Yes		Yes		7 (6.19)	MS	17/22
									6 (5.31)	hip	
Migliaresi, S *et al*. (33)	Italy	1994	69 (93)	S	yes	yes			1 (1.45)	MS	15/22
Massardo, L *et al*. (34)	Chile	1992	190 (87)	S	yes				17 (8.95)	MS	18/22
Lee, J *et al*. (25	South Korea	2014	1051	S	yes		yes		73 (6.95)	MS	20/22
Koutsonikoli, A *et al*. (35)†	Greece	2015	43 (83)	S	Reported as part of SLICC/ACR				3 (6.98)	MS	19/22
Ruiz-Arruza, I *et al*. (11)	Spain	2014	230 (90)	S	Reported as part of SLICC/ACR				4 (1.74)	MS	20/22
Olsen, NJ *et al*. (44)	USA	2013	99 (88)	S	Reported as part of SLICC/ACR				6 (6.07)	MS	17/22
Swaak, AJ *et al*. (50)	Netherlands	1999	187 (89)	S		yes			15 (8.02)	MS	14/22
Pontikaki, I *et al*. (46)†	Italy	2014	104 (89)	S		Not indicated			7 (6.73)	MS	9/22
Mok, CC *et al*. (14)	Hong Kong	1998	320	S	yes	yes	yes		38 (11.99)	MS	17/22
									36 (11.25)	hip	
To, CH *et al*. (63)	USA	2005	1357 (93)	S	Reported as part of SLICC/ACR				125 (9.21)	MS	20/22
Kunyakham, W *et al*. (15)	Thailand	2012	736 (94)	S	yes		yes		65 (8.83)	MS	15/22
									65 (8.83)	hip	
Oinuma, K *et al*. (7)†††	Japan	2001	72 (94)	A			yes		32 (44.44)	MS	18/22
Mok, MY *et al*. (53)	UK	2000	265	S			yes		11 (4.15)	MS	16/22
									10 (3.77)	hip	
Jaovisidha, S *et al*. (70)	Thailand	2007	11 (100)	A	yes		yes		2 (18.18)	hip	16/22
Houssiau, FA *et al*. (69)	Belgium	1998	40	A			yes		13 (32.5)	MS	17/22
Hamijoyo, L *et al*. (58)	Philippines	2008	540	S	yes		yes		43 (7.96)	MS	16/22
									40 (7.41)	hip	
Gurion, R *et al*. (51)†	Japan	2015	201 (83)	S	Reported as part of SLICC/ACR				9 (4.48)	MS	11/22
Griffiths, ID *et al*. (43)	USA	1979	68	S	yes				8 (11.76)	MS	13/22
									6 (8.82)	hip	
Gladman, D *et al*. (28)	Canada	2001	744	S	yes	yes	yes		95 (12.80)	MS	20/22
Ghaleb, R *et al*. (67)	Egypt	2010	100 (91)	S	yes		yes		15 (15.00)	hip	19/22
Fialho, S *et al*. (23)	Brazil	2006	46 (100)	A			yes		10 (21.74)	hip	14/22
Faezi, ST *et al*. (18)† †	Iran	2015	665	S	yes	yes	yes		105 (15.79)	MS	19/22
									96 (14.43)	hip	
Dimant, J *et al*. (16)	USA	1978	234 (94)	S	yes	yes			22 (9.4)	MS	10/22
									18 (7.69)	hip	
Calvo-Alen, J *et al*. (59)	USA	2005	571	S	yes		yes		32 (5.6)	MS	22/22
Nagasawa, K *et al*. (72)†††	Japan	2004	45 (96)	A	Yes		Yes		15 (33.33)	MS	14/22
			45 (96)	S					5(11.11)	MS	
Oh, SN *et al*. (55)††	South Korea	2004	415	S		yes	yes		37 (8.92)	MS	14/22
Ono, K *et al*. (68)	Japan	1996	62 (94)	S		yes			9 (14.52)	hip	16/22
Petri, M *et al*. (54)	USA	1995	407 (92)	S	Reported as part of SLICC/ACR				59 (14.5)	MS	10/22
Rascu, A *et al*. (8)	Germany	1996	280	S	yes				6 (2.14)	MS	14/22
									5 (1.79)	hip	
Saleh, JA *et al*. (20)	Arab Emirates	2010	126 (96)	S	yes		yes		11 (8.73)	MS	20/22
Sheikh, JS *et al*. (49)	USA	1998	175	S	yes	yes	yes		22 (12.57)	MS	19/22
Abeles, M *et al*. (65)† †	USA	1977	365	S	yes				17 (4.66)	hip	15/22
Abid, N *et al*. (66)	Saudi Arabia	2013	46 (100)	S		Not indicated			7 (15.22)	hip	17/22
Dhillon, N *et al*. (64)	Canada	2014	1728	S	yes	yes	yes	CT	235 (13.59)	MS	13/22
Cozen, L *et al*. (56)	USA	1998	488 (93)	S					26 (5.33)	MS	14/22
Costallat, LTL *et al*. (57)	Brazil	2003	519	S	yes	yes	yes		42 (6.80)	MS	10/22
Chen, S *et al*. (41)	China	2006	50 (96)	S		Not indicated			8 (16.00)	MS	15/22
Cervera, R *et al*. (62)	USA	1999	1000 (91)	S		Not indicated			23 (2.3)	MS	21/22
Castro, TCM *et al*. (22)†, ††	USA	2011	40 (83)	A			yes		7 (17.50)	MS	19/22
				S					1 (5.00)	hip	
Bogmat, L *et al*. (9)†	Ukraine	2014	44	S	Reported as part of SLICC/ACR				1 (3.10)	MS	11/22
Asherson, RA *et al*. (27)	France	1993	800	S	yes				37 (4.62)	MS	13/22
Artim-Esen, B *et al*. (61)	Turkey	2014	936	S	Reported as part of SLICC/ACR				119 (12.71)	MS	15/22
Aranow, C *et al*. (26)† †	USA	1997	66 (92)	A			yes		8 (12.12)	hip	18/22
Gurion, R *et al*. (42)†	USA	2013	62* (86)	S		Not indicated			7 (11.29)	MS	12/22
			849** (82)	S					38 (4.48)	MS	
Mont, MA *et al*. (24)	USA	1997	103 (94)	S	yes		yes		31 (29.13)	MS	21/22
Weiner, ES *et al*. (48)	USA	1989	172	S	yes			bone biopsy	28 (16.28)	MS	20/22
Yang, Y *et al*. (60)†	Canada	2014	617	S	yes	yes	yes		37 (5.99)	MS	18/22
									26 (4.21)	hip	
Thilagavathi, N *et al*. (10)	India	2012	17 (0)	S		Not indicated			1 (5.88)	MS	9/22
Shaharir, SS *et al*. (47)	Malaysia	2014	150 (90)	S	Reported as part of SLICC/ACR				10 (6.67)	MS	20/22
Li, X *et al*. (52)	China	2013	219	S	yes		yes	CT	73 (33.33)	MS	10/22
Zizic, TM *et al*. (71)	USA	1985	54 (96)	A	yes	yes			28 (51.85)	MS	17/22
Smith, FE *et al*. (45)	USA	1976	99	S	yes				7 (7.07)	MS	11/22
									6 (6.06)	hip	
Nagasawa, K *et al*. (39)	Japan	1989	111 (96)	A	yes	yes			24 (21.62)	MS	16/22
Prasad, R *et al*. (31)	Canada	2007	570 (83)	S	yes	yes	yes	CT	65 (11.40)	MS	16/22
Sayarlioglu, M *et al*. (19)	Turkey	2012	868		yes	yes	yes		49 (5.65)	MS	16/22
Uea-areewongsa, P *et al*. (30)	Thailand	2009	186	S	yes		yes		41 (22.04)	MS	20/22
Murphy, NG *et al*. (40)	USA	1998	46	S	Reported as part of SLICC/ACR				4(8.69)	MS	15/22
									3 (6.52)	hip	

*: HUMS cohort, **: CARRA cohort, †: jSLE only; ††: all patients received corticosteroids; †††: all patients received high doses of corticosteroids (>40mg/day), A: asymptomatic AVN; S: symptomatic AVN; MRI: magnetic resonance tomography; MS: multiple sites assessed; CT: computed tomography; STROBE checklist: a 22-item Strengthening the Reporting of Observational Studies in Epidemiology checklist.

especially pulse therapy (OR 1.95, $p<0.00001$) were associated with AVN. Cumulative dose and maximum daily dose of CS were higher among patients who developed AVN (mean difference 7.18 g, $p<0.00001$, and 10.3 mg/day, $p=0.002$, respectively) (Fig. 3); however, the mean daily dose and duration of CS use were similar. Rarely AVN occurred without CS exposure (3 to 15% of AVN cases) (16, 28, 29, 42, 43, 56). Immunosupressive drugs were more often used in AVN patients but heterogeneity among the reported data was high. When the drugs within the group of immunosupressants were analysed separately, cyclophosphamide was the only one associated with AVN (OR 2.79, $p=0.03$) (Table I). The proportion of SLE patients receiving the lipid-lowering drugs was comparable among those with and without AVN.

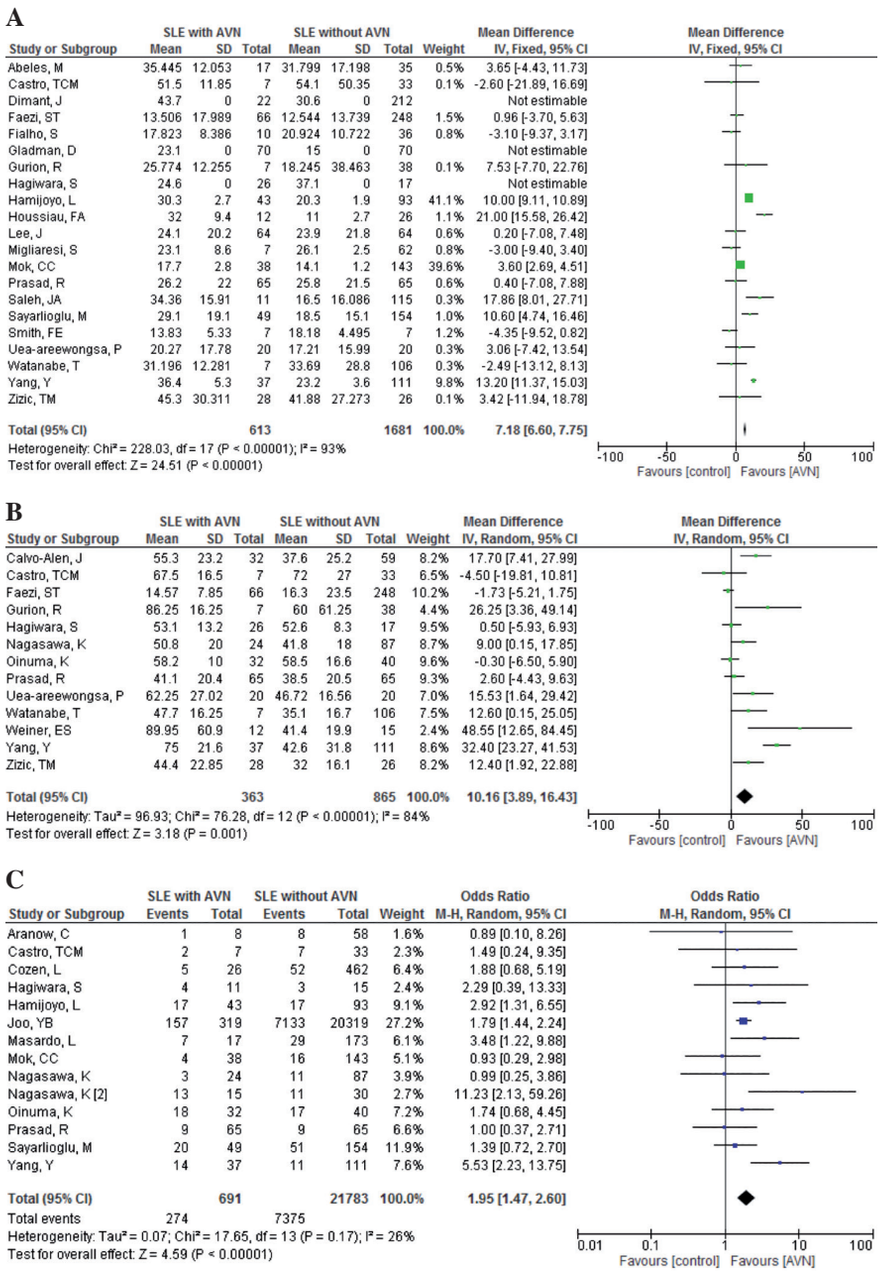

Fig. 3. Forest plot analysis. The mean difference in cumulative (**A**) and maximum (**B**) corticosteroid doses, and summary odds ratio of pulse therapy (**C**) in SLE patients with and without avascular necrosis (AVN).

Discussion

The literature suggests the average prevalence of symptomatic AVN is 9% in SLE population (mostly the femoral head in 8% overall), and nearly 30% if screening for asymptomatic AVN, ranging from 2% to 15% for symptomatic hip AVN, and 12% to 52% for asymptomatic AVN. Such variability may be due to differences in patient selection (*i.e.* patients receiving high-dose CS therapy (7, 72); case definition including various imaging techniques and even self-report (42)), and different follow-up and disease duration. Conventional x-ray and bone scan were used in most studies (8, 14-16, 18-20, 23, 24, 28, 30-34, 45, 48, 49, 50, 55, 57, 58, 60, 64, 65, 67, 68, 70-72) which are less sensitive than MRI (7, 22, 26, 53, 69) and might have underestimated the true occurrence of AVN. MRI is the most sensitive method to diagnose AVN that remains clinically and radiologically occult (3, 74), but the clinical relevance of asymptomatic AVN is unknown as the natural history could be different without consequences of joint damage. The potentially higher use of steroids in older studies may have increased the overall prevalence of AVN. The studies reporting the lowest frequency of asymptomatic AVN (12% (26), 18% (70) and 21.7% (23)) examined only femoral head. The highest prevalence of symptomatic AVN (>20%) has been noted in two large cohorts (219 and 186 patients, respectively) followed for years (19 and 16 years, respectively) (30, 52). That might account for a larger proportion of SLE patients who developed AVN during the time of follow-up. Our meta-analysis showed that duration of CS therapy and the mean daily dose did not increase the risk of AVN in SLE but cumulative corticosteroids are a risk, as well as high doses (such as maximum daily dose, and pulse therapy). Cumulative dose of CS which included both pulse and oral CS showed a stronger association with AVN than oral cumulative doses (69) suggesting that pulses of CS significantly increase the risk of AVN. These findings are in contrast with the data published by Felson and Anderson who did not find a correlation between a bolus dose and AVN rate (as opposed to steroid oral dose) in their meta-analysis of 22 studies (75). There is obvious confounding

between significant organ activity and high-dose CS as pulse CS is usually reserved for severe organ involvement. In one study, both disease activities measured with SLEDAI and high cumulative CS dose in the previous year of AVN diagnosis were significantly associated with AVN in SLE patients (23). However, only SLEDAI remained an independent risk factor in a multivariate analysis (23). CS downregulate blood flow in bone arteries by modulating vasoactive agents such as endothelin-1 or bradykinin and thus may worsen the pathogenetic mechanisms associated with high disease activity which are responsible for development of AVN: vasculopathy and vascular occlusion, abnormal endothelial function, abnormal lipid metabolism, fat emboli, and microfracture (13). The importance of CS-independent factors in AVN pathology is supported by the fact that some of the patients who underwent high-dosage corticosteroid treatment, did not develop AVN in the course of disease (7), and some SLE patients with AVN have never received CS (14).

Timing of steroids may be important. A prospective study of 72 patients with active SLE revealed that the time of AVN onset (evaluated by repeated MRI) was within the first months (from 1 to 5 months; mean 3 months) after starting high-dose CS (7); whereas, the maximum CS doses at 24-36 months had no effect on AVN (32, 33). In one study, SLE patients who did not develop AVN after an initial course of high-dose steroid therapy, were unlikely to develop AVN later (75). In patients undergoing organ transplantation the total amount of prednisone administered during the first months after transplantation correlated positively with the incidence of AVN (76). This is in accordance with the experimental findings that CS stimulated osteoclastic activity predominantly within the first 6–12 months after initiation of steroid therapy (77). It was noted that minimal or moderate corticosteroid preloading lessened the risk of AVN (68). Thus, the dose-escalation later in the disease course may be considered as a "high dosage regimen with preloading" which does not have a significant effect on AVN development. Perhaps, lower dose CS preloading for both oral and intravenous CS use may reduce the risk of AVN. Petri *et al*. reported a dose-dependent effect of CS on AVN development especially 60mg/d and no cases in her series at less than 29mg/d (54). The duration of high-dose CS of ≥140mg/d was strongly linked to AVN (69). Another study suggested the daily dose of CS is important only at time of AVN onset (60) and this is in accordance with a rapid development of AVN after initiation of high-dosage CS (68). There was an absence of AVN if the dose of prednisone was less than 30 mg/d in one report (75). The actual time of AVN onset was often unknown causing difficulty when analysing CS doses in relation to AVN. The studies reporting the proportion of SLE patients who received high doses of CS (≥30–40mg/day) in groups with and without AVN also showed inconsistent results (2 of 4 studies were positive) (26, 34, 15, 56).

Potential CS side-effects were associated with AVN (systemic arterial hypertension, higher serum levels of cholesterol and triglycerides and Cushingoid body habitus), but, osteoporosis, fractures and diabetes mellitus did not increase the risk of AVN. Other complications of CS treatment were also reported in association with AVN in single studies: elevation of serum levels of albumin and leukocyte count (68, 72) and more frequent infectious complications in AVN cases (major infections (34) and septic arthritis (15)).

Cutaneous vasculitis, renal and CNS involvement, serositis, Sjögren's syndrome and some cytopenias doubled the risk of AVN in SLE patients. Data are contradictory with respect to disease activity and AVN. Disease activity was assessed at different time points in studies: at disease onset (28, 67), at study entry (18, 20), at the highest steroid dose (14, 30), or the mean adjusted SLEDAI was calculated over the observation period (60). It would be more important to analyse the effect of flares in close temporal relationship with the onset of AVN. One study published a high SLEDAI score (≥8) in the year prior to AVN was a significant risk factor of AVN, while more remote disease activity (SLEDAI scores at SLE diagnosis and during 13–24 months preceding AVN) had no association with AVN (23).

Raynaud' s phenomenon (RP) and cutaneous vasculitis were significant risk factors for AVN in our meta-analysis potentially supporting the role of vasculopathy in the pathogenesis of AVN. Recently a pathogenetic role for antiphospholipid antibodies in AVN has been hypothesised since these antibodies promote coagulation and could induce thromboses in the end arteries of bone. AVN has been reported in patients with primary antiphospholipid syndrome (78) and in patients with SLE who did not receive corticosteroids (14). Our meta-analysis did not reveal an association between IgG ACL, lupus anticoagulant and AVN, but IgM ACL doubled the risk of AVN. Interestingly, AVN does not seem to be associated with systemic sclerosis (SSc) which is accompanied by severe RP and vasculopathy, but SSc also has low rates of steroid use. Rashes and oral ulcers were not associated with AVN. Among CNS manifestations psychosis and brain infarction had a significant association with AVN, while seizures did not (18, 20).

Unexpectedly, our results did not find antimalarial drugs protective. Perhaps there is confounding where the majority of patients received antimalarial treatment. Cytotoxic therapy with cyclophosphamide slightly increased AVN. Cyclophospamide use is associated with more severe disease.

We expanded our search to other databases (CINAHL, Cochrane library, Web of Science) that yielded an additional 25 articles examining AVN risk factors (7, 16-18, 20, 22, 23, 25, 26, 29, 33, 42, 43, 48, 49, 51, 53, 56, 60, 65, 67-69, 72, 73) compared to a recent review (36). With an increased number of studies included in our meta-analysis we could establish a significant association between AVN and cerebrovascular involvement, RP, serositis, haematological manifestations, and IgM ACL, which had not been detected previously in a meta-analysis (36), while we did not confirm that oral ulcers, alopecia and the mean CS dose were associated with AVN in SLE.

The study has some limitations. We

used a broad strategy to capture evidence from many different settings, and the patient cohorts in some of the studies were relatively small. The heterogeneity among studies is also related to the methodology of case ascertainment, the data sources, the lack of uniformity in how outcomes are measured, and the wide variation in follow-up. It is difficult to separate the underlying risk associated with a certain disease characteristic from confounders: potential treatment effects, trauma, alcohol consumption, comorbidities (*i.e.* diabetes), as well as other disease manifestations. It is more plausible that the impact of the covariates captures some of the true variation among effects, but the meta-analysis cannot test relations such as causality. Testing the impact of covariates for statistical significance is important and for this purpose the use of meta-regression under the random-effects model may be an option when the number of studies is enough for a ratio of at least ten studies for each risk factor (*i.e.* for disease activity, cumulative dose of CS, etc.). On the other hand, our meta-analysis can provide useful insights by revealing potential risk factors to be further tested by meta-regression and highlighting a deficiency in a particular topic that deserves further attention – MRI screening for AVN at high-risk SLE populations.

Conclusion

AVN frequently complicates SLE particularly active organ SLE (CNS, renal, cutaneous vasculitis, serositis), and usually occurs soon after the initiation of corticosteroid therapy at high doses. Those patients with early side-effects of CS therapy (systemic arterial hypertension, elevated cholesterol serum levels and Cushingoid body habitus) are at the highest risk of AVN. Avoiding high-dose steroids or preloading with lower doses of steroids first may be a strategy to reduce AVN.

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