Microvascular findings in patients with systemic lupus erythematosus assessed by fundus photography with fluorescein angiography

J.-H. Lee[1], S.-S. Kim[2], G.-T. Kim[3]

[1]Division of Rheumatology, Department of Internal Medicine; and [2]Department of Opthalmology, Maryknoll Medical Centre, Busan, Republic of Korea; [3]Division of Rheumatology, Department of Internal Medicine, Kosin University College of Medicine, Busan, Republic of Korea.

Abstract

Objective

Although a series of trials support systemic lupus erythematosus (SLE) is associated with increased atherosclerosis and cardiovascular events, the link between microvascular structural change and the disease activity of SLE is not defined. We measured retinal microvasculature change by fundus photography with fluorescein angiography (FAG) and investigated the association between retinal vasculature and clinical parameters of SLE.

Methods

Fifty SLE patients and fifty healthy controls were included. Morphometric and quantitative features of the capillary image including retinal vascular sign and vessel diameters were measured with fundus photography and FAG. Information concerning SLE duration, cumulative dose of steroids and/or immunosuppressive drug intake was recorded, and autoantibodies were checked. SLE activity was assessed by SLE disease activity index (SLEDAI).

Results

The mean central retinal arteriolar equivalent (CRAE) was 89.7±14.5 µm in SLE patients, showing narrower arteriole than that of controls (102.2±11.3 µm). The mean central retinal venular equivalents (CRVE) was 127.7±14.8 µm in SLE patients, also, narrower than that of controls (144.1±14.2 µm), but both reached no statistical significance (p=0.154, p=0.609, respectively). Retinopathy was found in 26% of SLE patients. SLE patients with retinopathy were older than those without it, but reached no statistical significance. Disease duration, antidsDNA, and complement levels had no effect on the presence of retinopathy. SLE patients with retinopathy had a tendency to have higher cumulative steroid doses, hsCRP and IgG aCL levels than those without retinopathy. With multiple regression analysis, hsCRP and IgG aCL were identified as contributing factors to the decreased CRAE, whereas no contributing factor was found to CRVE.

Conclusion

Retinopathy and retinal arteriolar narrowing were more common in SLE patients, and retinal arteriolar diameter had significant correlation with hsCRP and IgG aCL levels. Retinal imaging is a comparative method for the assessment of microvascular findings of SLE patients.

Key words

systemic lupus erythematosus, fundus photography, fluorescein angiography

Ji-Hyun Lee, MD
Sang-Soo Kim, MD
Geun-Tae Kim, MD

Please address correspondence and reprint requests to:
Geun-Tae Kim, MD,
Division of Rheumatology,
Department of Internal Medicine,
Kosin University College of Medicine,
34, Amnam-dong, Seo-gu,
602-703 Busan, Republic of Korea.
E-mail: gtah311@gmail.com

Received on February 18, 2013; accepted in revised form on April 19, 2013.

Funding: this work was supported by a grant from Kosin University College of Medicine (2012).

Competing interests: none declared.

Introduction

In patients with systemic lupus erythematosus (SLE), atherosclerosis is reported to occur prematurely, and to be independent of traditional risk factors for cardiovascular disease (1). Furthermore, in the context of inflammation and higher prevalence of conventional risk factors, lupus patients are expected to have poorer endothelial functions compared with their age and sex-matched healthy controls, even before they develop clinical atherosclerosis. Atherosclerosis in SLE is believed to be a multifactorial process, involving immune system activation, chronic inflammation, and oxidative stress (2). Before atherosclerotic lesions arise, vascular wall permeability, elasticity and thickness are deranged due to increased endothelial dysfunction and inflammation (3).

An intact vascular endothelium is essential in maintaining control of arterial tone and coagulation status, and it is postulated that endothelial dysfunction is a precursor to frank atherosclerosis (4). There are several methodologies that are currently being used for *in vivo* endothelial function assessment, including venous occlusion plethysmography, flow-mediated dilatation (FMD), laser Doppler iontophoresis, pulse wave analysis and retinal vascular imaging (5). The retina has long been provided a convenient arterial bed in which it is possible to make non-invasive, *in vivo* assessments of arterial architecture. Retinal vascular imaging has been studied as a possible tool for cardiovascular prediction in healthy older populations, particularly in individuals who may be more susceptible to microvascular disease, such as women and diabetic individuals (6, 7).

Previous studies in patients with SLE pointed out the importance of early detection and intervention during the very early stage of atherosclerosis to prevent clinical vascular events, because cardiovascular disease has become a major cause of death in patients with SLE (8-11). Observational studies investigating endothelial dysfunctions in lupus patients revealed that subclinical features of atherosclerosis such as carotid intima-media thickness and carotid plaque detected by computed tomography are increased in lupus patients compared with healthy subjects (12). Also, Mak *et al*. reported that endothelium-dependent, but not endothelium-independent FMD is significantly impaired in lupus patients who are naïve for vascular events (13).

There are, however, no sufficient data about the retinal vascular findings in lupus patients, and it is still unknown that endothelial dysfunction appears earlier than controls in SLE patients without conventional cardiovascular risk factors. Furthermore, the pathophysiological link between the presence of the retinal microvascular changes and the role of concomitant autoantibodies is yet to be discovered. We evaluated whether more retinal microvascular changes are observed in lupus patients without conventional cardiovascular risk factors, compared to the controls. We also investigated the association between retinal microvascular signs and clinical, laboratory parameters of SLE patients.

Patients and methods

Study Population

Fifty SLE patients (47.06±14.7 years, 45 women) according to the ACR criteria (14) from the outpatient clinic of the Rheumatology Division were consecutively included. Fifty healthy volunteers (47.1±12.0 years) from the health screening centre were selected as control group. Exclusion criteria for both groups were smoking (in the last 5 years), hypercholesterolaemia, diabetes mellitus (DM), hypertension, pregnancy, renal failure, chronic hepatopathy, and hypothyroidism. All subjects using any lipid-lowering drugs such as statins or fibrates (in the last 3 months) were also excluded. Information concerning SLE duration, cumulative dose of steroids and/or immunosuppressive drug intake was recorded. The study was approved by the Institutional Review Board and informed consent was obtained from all participants.

Fundus photography with fluorescein angiography (FFA)

Fundus photography was conducted according to a standardised protocol, using a 45° digital fundus camera (Canon

CF-1). Participants were seated in a room with dim light. Both eyes were photographed after pupil dilatation by 0.5% tropicamide eye drops. Two photographic fields were taken for each eye: the first centred on the optic disc and the second centred on the fovea. Retinal vascular caliber was measured with a computer-based programme (IVAN, University of Wisconsin, Madison, USA). For each photograph, arterioles and venules coursing through an area of 0.5–1 disc diameter from the optic disc margin were measured and summarised at the average central arteriolar (CRAE) and venular equivalents (CRVE) (15). These equivalents are projected calibers for the central retinal vessels, measured away from optic disc. The arteriole-to-venule ratio (AVR), which gives the relative caliber of arterioles and venules, was also calculated. The photographs were evaluated by an ophthalmologist for retinopathy signs and the diameters of the individual retinal vessels were measured.

Also, we assessed retinal photographs for the presence and severity of arteriovenous nicking (AVN), focal arteriolar narrowing (FAN), and opacification of the arteriolar wall (OAW). FAN was defined as localised narrowing along an arteriole, AVN as a narrowing on both sides of a venule when crossed by an arteriole, and OAW as enhanced central light reflex from the arteriolar wall. These qualitative retinal signs were compared with standard images and graded as absent, mild or severe (16). Retinopathy was defined as the presence of any of the following lesions: haemorrhages, vascular tortoisity, cotton wool spots, papilloedema, optic atrophy and retinal detachment. Retinal capillary images obtained from SLE patients using high-resolution FFA were compared with those derived from age matched controls.

Two trained examiners (SJ Seo, SS Kim) separately performed the assessments, masked to the clinical characteristics of the participants. Intraclass correlation coefficients for intra-examiner agreement were 0.88 (arteriolar calibers) and 0.90 (venular calibers), and for inter-examiner agreement were 0.80 (arteriolar calibers) and 0.91 (venular calibers)

Disease-specific evaluation

Disease activity was assessed by the SLE disease activity index (SLEDAI) (17). All SLE patients and controls were fasting for at least 12 hours at the beginning of the study before blood tests. Peripheral blood cell counts were determined using an automated haematology analyser (SE-9000, Sysmax). In terms of immunological parameters, we measured anti-double stranded DNA antibodies (anti-dsDNA Ab) by enzyme immunoassay (EIA) with the Bio-Flex DNA ds test, which do not react with single-stranded DNA (reference; IgG ≤4 IU/mL, IgM ≤20 IU/mL), and antinuclear antibody (ANA), complement concentrations on an autoanalyser (ADIVA 1800) by turbid immunometry (reference; C3 50-90 mg/dl, C4 10-40 mg/dl). The β2 glycoprotein I (GPI)-dependent anti-cardiolipin antibody (aCL) titers and lupus anticoagulant (LAC) were determined using EIA assay (DRVVT; Diluted-Russell, S-Viper-Venom Test) (reference; IgG ≤12 U/mL, IgM ≤12 U/mL). Anti-Ro antibody (reference; ≤1.0 AI), anti-La antibody (reference; ≤1.0 AI), anti-Smith (Sm) antibody (reference; ≤1.0 AI), and antiRNP antibody (reference; ≤1.0 AI) were also checked using EIA assay (Bioplex 2200). The plasma concentrations of high sensitivity C-reactive protein (hsCRP) was measured by performing fully automated turbid immunometry (Advia 1800, Siemens). ANA were also determined in controls to exclude the presence of autoimmune diseases.

Statistical analysis

Statistical analysis was performed with the statistical programme SPSS for Windows version 12.0 (Chicago, IL, USA). Results are presented as mean±standard deviation (SD) or percentage. Comparisons were performed between SLE and control groups using Student *t*-test for quantitative variables and chi-square or the exact Fisher test for qualitative variables. Correlations between variables were made by calculating the correlation coefficient through Pearson correlation tests. Statistical significance was set as below 0.05.

Results

Clinical characteristics of subjects

There were no significant differences between SLE and control groups in terms of age and the other clinical parameters that are known to affect the retinal vascular changes (Table I). At the time of the study, 46 SLE patients (92%) were taking prednisolone, 30 patients (60%) non-steroidal anti-inflammatory drugs (NSAID), and 30 patients (60%) hydroxychlorquine. The mean cumulative dose was steroid treatment 4513±5404 mg (as prednisolone). Eight patients (16%) have taken immunosuppressant drugs, including cyclophosphamide and azathioprine. Thirty nine patients (78%) have no proteinuria, and 4 patients (8%) have ne-

Table I. Clinical characteristics and parameters of the retinal vascular changes of the study population.

	SLE patients (n=50)	Controls (n=50)	*p*-value
Age, yrs	47.06 ± 14.7	47.1 ± 12.0	0.932
Female, n (%)	45 (90%)	45 (90%)	0.99
BMI, kg/m	22.6 ± 6.4	22.5 ± 8.5	0.87
Systolic blood pressure, mmHg	125.3 ± 11.9	122.3 ± 8.9	0.18
Diastolic blood pressure, mmHg	81.6 ± 11.3	80.4 ± 7.8	0.25
Total cholesterol, mg/dl	198.2 ± 29.7	186.7 ± 22.3	0.23
CRAE, μm	89.7 ± 14.5	102.2 ± 11.3	0.154
CRVE, μm	127.7 ± 14.8	144.1 ± 14.2	0.609
AVR	0.69 ± 0.54	0.71 ± 0.66	0.223
AVN, n (mild/severe)	22 (17/5)	8 (7/1)	0.017
FAN, n (mild/severe)	25 (20/5)	9 (8/1)	0.528
OAW, n (mild/severe)	38 (35/3)	19 (19/0)	0.307

All values are presented as mean±SD.
CRAE: central retinal arteriolar equivalents; CRVE: central retinal venular equivalents; AVN: arteriovenous nicking; FAN: focal arteriolar narrowing; OAW: opacification of the arteriolar wall.

phrotic range proteinuria. The parameters of atherosclerosis of SLE patients and controls are shown in Table I.

Retinal findings

The parameters of retinal microvascular changes of SLE patients and controls are shown in Table I. The mean central retinal arteriolar equivalent (CRAE) was 89.7±14.5 μm in SLE patients, showing narrower arteriole than that of controls. The mean central retinal venular equivalents (CRVE) was also narrower than that of controls, but both reached no statistical significance (p=0.154, p=0.609, respectively). The mean AVR showed no significant differences between two groups.

The prevalence of AVN was 44% (77.2% mild and 22.8% severe), and significantly higher in SLE group. The prevalence of FAN was 50% (80% mild and 20% severe), of OAW was 76% (92.1% mild and 7.9% severe), and showed no significant differences between the two groups (Table I). We divided SLE patients into two groups: patients with and without retinopathy for further analysis (Table II). SLE patients with retinopathy were older than those without AVN, but reached no statistical significance. Disease duration, anti-dsDNA, and complement levels had no effect on the presence of retino-pathy. Also, no correlation was found between the proteinuria level and retinopathy (p=0.129). SLE patients with retinopathy had a tendency to have higher cumulative steroid doses, hsCRP and IgG aCL levels than those without retinopathy.

Correlation between the retinal vascular diameters and the disease activity of SLE group

Age, disease duration, SLEDAI and cumulative steroid dose had no effect on CRAE and CRVE. Only hsCRP and IgG aCL were related to CRAE (R=0.532, p=<0.001, R=0.448, p=0.001, respectively). IgG and IgM aCL were also related to CRVE (Table III). With multiple regression analysis, hsCRP and IgG aCL were identified as ca ontributing factor to the decreased CRAE, whereas no contributing factor was found to CRVE (Tables IV and V).

Table II. Characteristics of SLE patients with and without retinopathy.

	SLE without retinopathy (n=37)	SLE with retinopathy (n=13)	p-value
Age, yrs	46.6 ± 14.6	48.8 ± 15.7	0.50
Disease duration, yrs	6.28 ± 5.09	4.96 ± 4.16	0.26
Cumulative steroid dose	3823 ± 4345	6478 ± 7544	0.004
hsCRP mmol/L	0.91 ± 3.00	3.00 ± 5.02	0.003
antidsDNA, IgG	24.05 ± 44.07	26.76 ± 67.37	0.42
antidsDNA, IgM	23.06 ± 27.80	23.84 ± 37.99	0.07
antiSm	0.21 ± 0.42	0.07 ± 0.28	0.13
antiRo	0.51 ± 0.50	0.38 ± 0.50	0.18
antiLa	0.35 ± 0.48	0.30 ± 0.63	0.82
antiRNP	0.24 ± 0.43	0.15 ± 0.37	0.16
aCL, IgG	6.95 ± 14.66	21.90 ± 58.52	0.002
aCL, IgM	5.07 ± 14.51	4.53 ± 7.67	0.81
C3	99.92 ± 37.96	112.08 ± 35.28	0.59
C4	23.22 ± 11.45	25.16 ± 13.81	0.74
SLEDAI	4.72 ± 5.10	5.76 ± 6.67	0.09

All values are presented as mean±SD.
SLE: systemic lupus erythematosus; hsCRP: high sensitivity C-reactive protein; anti-dsDNA: anti-double stranded DNA antibodies; aCL: anti-cardiolipin antibody; C: complement; SLEDAI SLE: disease activity index.

Table III. Correlation coefficients between the parameters of retinal vascular diameter and clinical parameters of SLE group (n=50).

	CRAE	CRVE
Age, yrs	-0.113 (0.434)	-0.201 (0.162)
Disease duration, yrs	0.172 (0.231)	0.080 (0.582)
Cumulative steroid dose	0.166 (0.250)	0.074 (0.611)
hsCRP mmol/L	0.532 (< 0.001) *	0.180 (0.211)
antidsDNA, IgG	0.040 (0.784)	0.074 (0.609)
antidsDNA, IgM	0.043 (0.768)	0.060 (0.680)
antiSm	-0.042 (0.772))	0.010 (0.944)
antiRo	0.198 (0.167)	0.256 (0.072)
antiLa	0.075 (0.604)	0.181 (0.208)
antiRNP	0.007 (0.960)	0.017 (0.905)
aCL, IgG	0.448 (0.001) *	0.336 (0.017) *
aCL, IgM	0.253 (0.077)	0.313 (0.027) *
C3	0.068 (0.680)	0.046 (0.783)
C4	0.136 (0.410)	0.062 (0.710)
SLEDAI	0.135 (0.351)	0.033 (0.822)

All values are presented as mean±SD.
SLE: systemic lupus erythematosus; hsCRP: high sensitivity C-reactive protein; anti-dsDNA: anti-double stranded DNA antibodies; aCL: anti-cardiolipin antibody; C: complement; SLEDAI: SLE disease activity index.

Discussion

In this study, we estimated retinal microvascular changes by fundus photography and fluorescent angiography and retinal microvascular changes are shown to be increased in SLE patients. The addressed issue is of clinical importance, since several studies conducted in recent years have identified retinal microvascular signs as an early manifestation of atherosclerotic cardiovascular disease (18-20), and showed that arteriolar narrowing as well as a reduced AVR have been associated with an increased risk of hypertension, risk of stroke and a higher cardiovascular mortality rate (21). There is, therefore, a growing need for new, sensitive, and accurate non-invasive methods for the evaluation of microvascular signs that would provide an efficient identification of individuals at the early stage of atherosclerotic disease.

The retina has long provided a convenient arterial bed in which it is possible to make non-invasive, *in vivo* assessments of arterial architecture. The presence of abnormalities, such as focal and gener-

Table IV. Multiple linear regression analysis of CRAE and clinical parameters of SLE group (n=50).

CRAE (R^2=0.529 adjusted R^2=-0.222 multivariate analysis)							
	Univariate analysis				Multivariate analysis		
	Coefficient (β)	95%CI	*p*-value	R^2	Coefficient (β)	95%CI	*p*-value
Age, yrs	-0.113	-0.396–0.173	0.434	-0.008	-0.210	-0.757–0.312	0.399
Disease duration, yrs	0.172	-0.339–1.369	0.231	0.010	0.225	-0.631–2.028	0.289
Cumulative steroid dose	0.166	0.000–0.001	0.250	0.027	0.067	-0.001–0.001	0.754
hsCRP mmol/L	0.532	1.244–3.378	0.000	0.283	0.548	0.544–3.858	0.011
antidsDNA, IgG	0.040	-0.072–0.095	0.784	0.002	0.093	-0.116–0.166	0.717
antidsDNA, IgM	0.043	-0.118–0.159	0.297	0.002	-0.116	-0.274–0.166	0.617
antiSm	-0.042	-12.435–9.285	0.772	0.002	-0.339	-31.341–9.396	0.259
antiRo	0.198	-2.476–13.909	0.167	0.039	0.427	-3.685–29.195	0.122
antiLa	0.075	-5.994–10.203	0.604	0.006	-0.179	-19.867–9.792	0.490
antiRNP	0.007	-9.830–10.331	0.960	0.000	0.196	-9.818–23.20	0.411
aCL, IgG	0.448	0.085–0.319	0.001	0.200	0.611	0.044–0.485	0.021
aCL, IgM	0.253	-0.031–0.596	0.077	0.604	0.135	-0.258–0.539	0.475
C3	0.068	-0.107–0.162	0.680	0.005	0.259	-0.173–0.383	0.443
C4	0.136	-0.246–0.588	0.410	0.018	-0.157	-1.104–0.707	0.654
SLEDAI	0.135	-0.404–1.115	0.351	0.018	-0.128	-1.570–0.916	0.592

Table V. Multiple linear regression analysis of CRVE and clinical parameters of SLE group (n=50).

CRVE (R^2=0.397 adjusted R^2=-0.003 multivariate analysis)							
	Univariate analysis				Multivariate analysis		
	Coefficient (β)	95%CI	*p*-value	R^2	Coefficient (β)	95%CI	*p*-value
Age, yrs	-0.201	-0.487–0.084	0.162	0.040	-0.410	-0.979–0.104	0.108
Disease duration, yrs	0.006	-0.638–1.123	0.582	0.006	0.165	-0.873–1.902	0.451
Cumulative steroid dose	0.074	-0.001–0.001	0.611	0.005	0.057	-0.001–0.001	0.789
hsCRP mmol/L	0.180	-0.467–2.508	0.211	0.032	0.065	-1.625–2.150	0.776
antidsDNA, IgG	0.074	-0.063–0.107	0.609	0.006	0.110	-0.117–0.177	0.677
antidsDNA, IgM	0.060	-0.112–0.170	0.680	0.004	-0.170	-0.303–0.143	0.466
antiSm	0.010	-10.682–11.456	0.944	0.000	-0.215q	-29.258–13.978	0.472
antiRo	0.256	-0.707–15.749	0.072	0.066	0.282	-8.351–25.308	0.308
antiLa	0.181	-2.976–13.292	0.208	0.033	0.059	-13.415–16.727	0.822
antiRNP	0.017	-9.650–10.880	0.905	0.000	0.326	-5.571–27.931	0.181
aCL, IgG	0.336	0.029–0.280	0.017	0.113	0.554	-0.016–0.500	0.065
aCL, IgM	0.313	0.043–0.670	0.027	0.604	0.214	-0.181–0.629	0.264
C3	0.046	-0.117–0.154	0.783	0.002	0.418	-0.111–0.452	0.223
C4	0.062	-0.344–0.501	0.710	0.004	-0.192	-1.159–0.673	0.588
SLEDAI	0.033	-0.693–0.868	0.822	0.001	0.165	-2.049–0.466	0.206

alised narrowing, AVN, altered AVR, and suboptimal arterial diameter at bifurcations, can be suggestive of a more generalised circulatory disorder (22, 23). It has been reported that abnormalities in retinal arterioles are related to the presence of carotid plaque, hypertension, and serum markers of inflammation and endothelial function such as von Willebrand factor (24). Also, a correlation has been made between the presence of peripheral vascular disease and retinal arteriolar abnormalities (23).

Retinopathy in SLE patients develops with an incidence of 7–26% (26, 27), and it is generally understood that the causes of retinopathy of SLE include active lupus, antiphospholipid antibody syndrome, and drugs used to treat SLE (28). In this study, retinopathy was found in 26% of the patients with SLE, comparable with previous studies. We found that SLE patients with retinopathy had a tendency to have higher cumulative steroid doses, hsCRP and IgG aCL levels than those without retinopathy. There were some reports which showed increased prevalence of cataracts and glaucoma in SLE patients (29, 30), and Ushiyama *et al*. suggested that the retinopathy in patients with SLE was associated with renal dysfunction, CNS lupus, and aCL (27). In this study, no correlation was found between the proteinuria level and retinopathy, and we excluded the case of renal failure and CNS lupus. However, though it did not reach a statistical significance, SLE patients with retinopathy had a higher SLEDAI score than those without it, suggesting that retinopathy may develop in SLE with high disease activity. There are several studies which showed retinal vascular calibers were consistently associated with higher levels of inflammation markers, cholesterol, and both subclinical and clinical atherosclerosis (31-33). We checked hsCRP in our study population, and with multiple regression analysis, hsCRP and IgG aCL were identified as a contributing factor to the decreased CRAE, whereas no contributing factor was found to CRVE. Considering the fact that CRP only goes up if there is infection in addition to lupus, it seems to be difficult to see the precise correlation between hsCRP and retinal finding in SLE. However, an interrelation was found between CRAE and hsCRP, and we can sustain that the presence of systemic inflammation is a promoter for early vascular damage through endothelial dysfunction.

This study has some limitations that should be considered, which are related to the small number of patients and selection of study population. Further studies with a larger population should be undertaken to overcome this limitation. Also, we evaluated hsCRP levels only once at baseline and did not evaluate the effects of changes in the levels of these markers over time. Variation over time in the levels of inflammatory markers would lead to a false estimation, so follow-up studies which evaluate the effects of changes in inflammation have to be undertaken. We also did not consider the early retinal impairment which could be observed in patients with antimalarial agents, and did not measure the retinal functional

changes. Recently, there has been a report of early retinal impairment in patients treated with hydroxychloroquine using frequency doubling perimetry (34). It would be interesting to correlate the retinal functional changes with retinal microvascular changes. Finally, we did not check the disease damage index of SLE patients, which could be a predicting factor for retinal vascular change.

Conclusion

In summary, measurement of retinal vessel diameters can be a sensitive method for the assessment of microvascular changes in patients with SLE. Retinal arteriolar narrowing is more frequently detected in SLE, and its prevalence was correlated with inflammatory markers. The results suggest that the patients with higher cumulative steroid doses, antiphospholipid antibody and persistent inflammation will be prone to the development of arterial stiffening, which will be a marker of end-organ damage. These findings reinforce the need to evaluate subclinical atherosclerosis in SLE patients, and to find predictors of atherosclerotic lesions.

Acknowledgements

The authors thank Sang-Jin Seo for help with accessing fundus photography with fluorescein angiography.

References

1. ZELLER CB, APPENZELLER S: Cardiovascular disease in systemic lupus erythematosys: The role of traditional and lupus related risk factors. *Curr Cardiol Rev* 2008; 4: 116-22.
2. RHEW EY, RAMSEY-GOLDMAN R: Premature atherosclerotic disease in systemic lupus erythematosus-role of inflammatory mechanisms. *Autoimmun Rev* 2006; 5: 101-5.
3. WESTERWEEL PE, LUYTEN HA, KOOMANS HA, DERKSEN RH, VERHAAR MC: Premature atherosclerotic cardiovascular disease in systemic lupus erythematosus. *Arthritis Rheum* 2007; 56: 1384-96.
4. CELERMAJER DS, SORENSEN KE, GOOCH VM *et al*.: Non-invasive detection of endothelial dysfunction in children and adults at risk of atherosclerosis. *Lancet* 1992; 340: 1111-5.
5. ALAM TA, SEIFALIAN AM, BAKER D: A review of methods currently used for assessment of in vivo endothelial function. *Eur J Vasc Endovasc Surg* 2005; 29: 269-76.
6. WONG TY, KLEIN R, SHARRETT AR *et al*.: Retinal arteriolar narrowing and risk of diabetes mellitus in middle-aged persons. *JAMA* 2002; 287: 2528-33.
7. CHEUNG N, WANG JJ, KLEIN R, COUPER DJ, SHARRETT AR, WONG TY: Diabetic retinopathy and the risk of coronary heart disease: the Atherosclerosis Risk in Communities Study. *Diabetes Care* 2007; 30: 1742-6.
8. UROWITZ MB, GLADMAN DD, TOM BD, IBANEZ D, FAREWELL V: Changing patterns in mortality and disease outcomes for patients with systemic lupus erythematosus. *J Rheumatol* 2008; 35: 2152-8.
9. BERNATSKY S, BOIBIN JF, JOSEPH L *et al*.: Mortality in systemic lupus erythematosus. *Arthritis Rheum* 2006; 54: 2550-7.
10. CHIN CWL, TAN RS, THUMBOO J: Endothelial function and arterial stiffness assessment as early surrogate markers of vascular risk in patients with systemic lupus erythematosus. *Clin Exp Rheumatol* 2013; 31: 295-301.
11. GHIADONI L, MOSCA M, TANI C, VIRDIS A, TADDEI S, BOMBARDIERI S: Clinical and methodological aspects of endothelial function in patients with systemic lupus erythematosus. *Clin Exp Rheumatol* 2008; 26: 680-7.
12. KIANI AN, POST WS, MAGDER LS, PETRI M: Predictors of progression in atherosclerosis over 2 years in systemic lupus erythematosus. *Rheumatology* (Oxford) 2011; 50: 2071-9.
13. MAK A, LIU Y, HO RC: Endothelium-dependent but not endothelium-independent flow-mediated dilation is significantly reduced in patients with systemic lupus erythematosus without vascular events: a metaanalysis and metaregression. *J Rheumatol* 2011; 38: 1296-303.
14. HOCHBERG M: Updating American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1997; 40: 1725-34.
15. WONG TY, KNUDTSON MD, KLEIN R, KLEIN BE, MEUER SM, HUBBARD LD: Computer-assisted measurement of retinal vessel diameters in the Beaver Dam Study: Methodology, correlation between eyes and effect of refractive errors. *Ophthalmology* 2004; 111: 1183-90.
16. LINDLEY RI: Retinal microvascular signs: a key to understanding the underlying pathophysiology of different stroke subtypes? *Int J Stroke* 2008; 3: 297-305.
17. BOMBARDIER C, GLADMAN DD, UROWITZ MB, CARON D, CHANG CH: Derivation of the SLEDAI. A disease activity index for lupus patients. The Committee on Prognosis Studies in SLE. *Arthritis Rheum* 1992; 35: 630-40.
18. WANG JJ, MITCHELL P, LEUNG H, TOCHTCHINA E, WONG TY, KLEIN R: Hypertensive retinal vessel wall signs in a general older population: The Blue Mountains Eye study. *Hypertension* 2003; 42: 534-41.
19. IKRAM MK, WITTEMAN JCM, VINGERLING JR, BRETELER MMB, HOFMAN A, DE PONG PT: Retinal vessel diameters and risk of hypertension: the Rotterdam Study. *Hypertension* 2006; 47: 189-94.
20. WONG TY, KLEIN R, SHARRETT AR *et al*.: Retinal arteriolar diameter and risk for hypertension. *Ann Intern Med* 2004; 140: 248-55.
21. WANG JJ, LIEW R, KLEIN R *et al*.: Retinal vessel diameter and cardiovascular mortality: pooled data analysis from two older populations. *Eur Heart J* 2007; 28: 1984-992.
22. CHAPMAN N, DELL'OMO G, SARTINI MS *et al*.: Peripheral vascular disease is associated with abnormal arteriolar diameter relationships at bifurcations in the human retina. *Clin Sci* (Lond) 2002; 103: 111-6.
23. WONG TY, KLEIN R, COUPER LS *et al*.: Retinal microvascular abnormalities and incident stroke: the Atherosclerosis Risk in Communities Study. *Lancet* 2001; 358: 1134-40.
24. KLEIN R, SHARRETT AT, KLEIN BE *et al*.: Are retinal arteriolar abnormalities related to atherosclerosis? The atherosclerosis risk in communities study. *Arterioscler Thromb Vasc Biol* 2000; 20: 1644-50.
25. LIEW G, SHARRETT AR, WANG JJ *et al*.: Relative importance of systemic determinants of retinal arteriolar and venular caliber. The Atherosclerosis Risk in Communities Study. *Arch Opthalmol* 2008; 126: 1404-10.
26. STAFFORD-BRADY FJ, UROWITZ MB, GLADMAN DD, EASTERBROOK M: Lupus retinopathy. *Arthritis Rheum* 1988; 31: 1105-10.
27. USHIYAMA O, USHIYAMA K, KOARADA S *et al*.: Retinal disease in patients with systemic lupus erythematosus. *Ann Rheum Dis* 2000; 59: 705-8.
28. WALLACE DJ, HAHN BH, ANAYA J-M, TALAL N: Head and neck findings in SLE: Sjögren's syndrome and the eye, ear, and lalynx. *In* Dubois' Lupus Erythematosus. 5th ed. pp. 783-91.
29. MOSCA M, TANI C, CARLI L, BOMBARDIERI S: Glucocorticoids in systemic lupus erythematosus. *Clin Exp Rheumatol* 2011; 29 (Suppl. 68): S126-9.
30. GHIADONI L, MOSCA M, TANI C, VIRDIS A, TADDEI S, BOMBARDIERI S: Clinical and methodological aspects of endothelial function in patients with systemic lupus erythematosus. *Clin Exp Rheumatol* 2008; 26: 680-7.
31. DE JONG FJ, IKRAM MK, WITTEMAN JC, HOFMAN A, DE JONG PT, BRETELER MM: Retinal vessel diameters and the role of inflammation in cerebrovascular disease. *Ann Neurol* 2007; 61: 491-5.
32. KLEIN R, KLEIN BE, KNUDTSON MD, WONG TY, TSAI MY: Are inflammatory factors related to retinal vessel caliber? The Beaver Dam Eye Study. *Arch Ophthalmol* 2006; 124: 87-94.
33. VAN DOORNUM S, STRICKLAND G, KAWASAKI R *et al*.: Retinal vascular caliber is altered in patients with rheumatoid arthritis: a biomarker of disease activity and cardiovascular risk? *Rheumatology* 2011; 50: 939-43.
34. TANGA L, CENTOFANTI M, ODDONE F *et al*.: Retinal functional changes measured by frequency-doubling technology in patients treated with hydroxychloroquine. *Graefes Arch Clin Exp Ophthalmol* 2011; 249: 715-21.