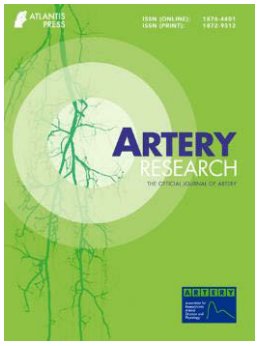

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Retinal vascular calibers in contemporary patients with chronic systemic inflammatory diseases: The Greek REtinal Microcirculation (GREM) study

Evaggelia K. Aissopou [a,*], Athanase D. Protogerou [a,b,c], Theodore G. Papaioannou [d], Maria Tektonidou [a,b], Nikolaos Tentolouris [a], Panagiotis G. Theodossiadis [e], Coen D.A. Stehouwer [f,g], George D. Kitas [b,h], Petros P. Sfikakis [a,b]

[a] *Cardiovascular Research Laboratory and Rheumatology Unit, 1st Department of Propaedeutic and Internal Medicine & Cardiovascular Unit, "Laiko" Hospital, Medical School, National and Kapodistrian University of Athens, Greece*
[b] *Joint Academic Rheumatology Program of the National and Kapodistrian University of Athens Medical School, Greece*
[c] *Cardiovascular Prevention & Research Unit, Department of Pathophysiology, Medical School, National and Kapodistrian University of Athens, Greece*
[d] *Biomedical Engineering Unit, 1st Department of Cardiology, Hippokration Hospital, Medical School, National and Kapodistrian University of Athens, Greece*
[e] *2nd Department of Ophthalmology, Attikon University Hospital, Greece*
[f] *Department of Medicine, Maastricht University Medical Centre, Maastricht, The Netherlands*
[g] *Cardiovascular Research Institute Maastricht (CARIM), Maastricht University Medical Centre, Maastricht, The Netherlands*
[h] *Arthritis Research UK Epidemiology Unit, University of Manchester, Manchester, UK*

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Abstract *Background:* Chronic systemic inflammatory diseases (CSID) are associated with increased cardiovascular morbidity and mortality. Widening of retinal venular calibers has been independently associated with systemic inflammation and cardiovascular risk in the general population. We aimed to test the hypothesis that retinal vessel calibers are altered in a population with rheumatoid arthritis (RA), systemic lupus erythematosus (SLE) and

* Corresponding author. 75, Mikras Asias Street, (Building 16—basement), 115 27 Athens, Greece. Fax: +30 213 2061755.
E-mail address: eaiswpou@yahoo.gr (E.K. Aissopou).

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spondyloarthropathies (SpA) compared to a reference group (RG).
Methods: Between 2012 and 2014 digital retinal images were obtained from consecutive individuals and retinal vessel calibers were measured with validated software to determine central retinal arteriolar and venular equivalents.
Results: One hundred eighty-eight patients with CSID [(74 RA, 75 SLE, 39 SpA), (70.2% females, mean age 50.4 ± 12.5 years)] and 512 non-CSID individuals [(187 normotensives and 325 hypertensives, 90 of whom untreated; RG), (43.7% females, mean age 52.3 ± 11.7)] were recruited. Logistic regression analysis after adjustment for all factors associated with retinal vessel calibers in univariate analysis (age, sex, body mass index, blood pressure, anti-hypertensive/lipid modifying drugs and disease duration), showed that both arteriolar and venular retinal vessel calibers were comparable between CSID patients and the RG. No significant differences were found regarding retinal vessel calibers between each patient subgroup and the RG.
Conclusions: Retinal vessel calibers were not significantly altered in patients with CSID. Well-controlled disease, as indicated by inflammatory indices, may be an explanation of our results suggesting that sufficient control of inflammation could improve microvascular abnormalities in these populations.

Introduction

Chronic systemic inflammatory diseases (CSID) are associated with high risk of cardiovascular morbidity and mortality.[1,2] Inflammation and endothelial dysfunction play a key role in the pathogenesis of atherosclerosis and previous studies have shown that chronic systemic inflammation could partly explain the increased cardiovascular risk in patients with CSID.[3] Microvascular damage has been implicated in cardiac or renal failure, vascular dementia and stroke.[4,5]

The retina is a unique site where the in vivo microvasculature can be directly visualized and monitored repeatedly over time. Retinal vessel caliber measurement is a precise, reproducible and non-invasive method for assessing the systemic microvasculature through semiautomated image analysis software.[6] Several large population-based studies (e.g. MESA, Rotterdam study) showed that systemic inflammatory markers (e.g. C-reactive protein, white blood cells, interleukin 6, erythrocyte sedimentation rate) are associated with larger retinal venules.[7–9] In contrast, increasing age and hypertension are associated with retinal arteriolar narrowing.[10]

The effect of inflammation on retinal microcirculation in patients with CSID has been poorly investigated. Van Doornum et al. demonstrated that 51 patients with rheumatoid arthritis (RA) had wider retinal venules compared with 51 age and sex matched controls.[11] Okada et al. concluded that 124 patients with autoimmune rheumatic diseases had larger retinal venules than in-hospital patients.[12] However, in a cross-sectional study by our group concerning 93 patients with systemic sclerosis (SSc) found no differences regarding retinal vessel calibers between SSc and 29 age, sex matched controls.[13] Recently, a prospective clinical study by Moi et al. was conducted investigating the effect of suppressing inflammation on retinal microcirculation in 53 patients with RA and found significant association between suppression of inflammation and reduction of retinal venular diameter.[14]

The aim of our study was to investigate whether retinal vessel calibers are different in 188 treated patients with CSID such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE) and spondyloarthropathies (SpA) compared with 512 non-hospitalized individuals free of any CSID. We also intended to study the role of systemic inflammatory markers in this context.

Methods

Study design-population

The Greek REtinal Microcirculation (GREM) Study is a cross-sectional observational study carried out from August 2012 to September 2014 at the Cardiovascular Research Laboratory and Rheumatology Unit of the 1st Department of Propaedeutic and Internal Medicine of "Laiko" Hospital in Athens (Greece). The objective of GREM Study is to evaluate retinal vessel calibers in patients with different chronic inflammatory diseases using as reference group individuals free of any CSID. Seven hundred and eighty-five consecutive individuals were recruited from the outpatient Hypertension and Rheumatology clinics for global non-invasive cardiovascular risk assessment and retinal photography. Forty-seven patients were excluded because of ungradable photos from both eyes due to inadequate pupil dilation (n = 43) and cataract (n = 4). We also excluded 38 diabetic patients since our control group aimed to be consisted of healthy or hypertensives free of diabetic retinopathy.

The final population of our analysis consisted of 188 patients with CSID [74 patients with rheumatoid arthritis (RA), 75 with systemic lupus erythematosus (SLE) and 39 with spondyloarthropathies (SpA); 26 with ankylosing spondylitis and 13 with psoriatic arthritis]. The reference group (RG) consisted of 512 individuals without any history of CSID (325 individuals with hypertension - of whom 235 treated with antihypertensive drugs and 90 untreated - and 187

individuals without hypertension). The hospital's ethical committee approved the study protocol and all participants provided informed consent.

All participants were asked to refrain from food and any vasoactive substance or medication the morning of the examination. Data on medical and family history was obtained using a structured questionnaire. A recent biochemical profile (last 2–3 months) was retracted from patients' medical records. Anthropometric measurements, including weight and height were estimated using standard techniques; body mass index was calculated as weight (kg)/height $(m)^2$.

Retinal microvascular analysis

Both eyes of each participant were photographed with a 45° digital non-mydriatic retinal camera (Topcon TRC-NW8, Tokyo, Japan) after 5 min of adaptation in the dark. Retinal images were centered on the optic disc, followed by quantitative retinal grading, conducted by a well-trained physician (EKA) blinded to clinical data. Measurements from the right eye were used in the analysis; the left eye was chosen if measurements could not be performed in the right eye. For each photograph, the calibers of the six largest retinal arterioles and venules passing through a zone between 0.5 and 1.0 disc diameters from the optic disc margin were measured and analyzed using a Static Retinal Vessel Analyzer (SVA-T and Vesselmap 2 software,[15] Visualis, Imedos Systems UG, Jena, Germany). These measurements were then summarized using formulas described by Knudtson and Hubbard[16] to compute the central retinal arteriolar equivalent (CRAE) and the central retinal venular equivalent (CRVE), representing the average internal caliber of retinal arterioles and venules, respectively. The intra-observer reproducibility of retinal vascular measurements was excellent as indicated by the intraclass correlation coefficient (>0.9).

Statistical analysis

Statistical analysis was performed using the SPSS statistical package (IBM Corp., version 21.0, Armonk, NY, USA). Normality of the variables distribution was tested using the Kolmogorov–Smirnov test and histograms. Normally distributed variables are presented as mean values ± standard deviation, non-parametric variables as median (interquartile range) and categorical variables as frequencies. Binary Logistic regression analysis (enter method) was performed to evaluate the alterations of retinal vessel calibers (CRAE, CRVE) between patients with CSID and controls, as well as among each inflammatory group separately (RA, SLE, SpA) and controls. CRAE and CRVE transformed into categorical variables according to their median (171.3 μm for CRAE and 209.6 μm for CRVE). The potential confounders were selected among those variables which had univariate analysis association ($p < 0.10$) with retinal vessel calibers in the present study. The models testing CRAE and CRVE were additionally adjusted for fellow caliber to provide unbiased and biologically plausible results as suggested by Liew et al.[17] The results are presented as exp(B) [95% confidence intervals]. The level of statistical significance was set at $p < 0.05$.

Results

Characteristics of the 188 patients with CSID [74 RA (39.4%), 75 SLE (39.9%) and 39 SpA (20.7%) (70.2% females, mean age 50.4 ± 12.5 years)] are presented in Table 1, as well as of each subpopulation. Their median disease duration was 9 years (range 3.0–15.8). All patients with CSID were treated with immunosuppressive drugs (Table 1). The levels of systemic inflammatory markers are also presented [CRP: 3.3 mg/L (interquartile (IQ) range 1.9–7.0), ESR: 15.0 mm/h (IQ range 8.0–27.5) and WBC: 6.760 10^9/L (IQ range 5.370–8.585)].

Binary logistic regression models for CRAE and CRVE were constructed to assess the differences of retinal vessel calibers between patients with CSID and the RG, as well as between each subgroup and RG (Table 2). After adjustment for potential confounders (age, sex, BMI, MAP, BP lowering drugs, lipid modifying drugs, disease duration and CRVE) retinal arterioles had no significant differences between the RG and patients with CSID. Similarly, after adjustments for age, mean arterial pressure (MAP), lipid modifying drugs, disease duration, white blood cells (WBC) and CRAE, retinal venules were not different between patients with CSID and controls. P value of the comparison between overall population with CSID and controls was 0.283 (when CRAE was the dependent variable) and 0.339 (when CRVE was the dependent variable) respectively. The same results for both retinal vessel calibers were found when each subgroup (RA, SLE, SpA) was compared with RG (Table 2). In a subanalysis where we excluded patients with hypertension from both CSID and RG groups (120 CSID versus 187 RG), similar results were found (data not shown).

Discussion

In the present study we investigated the differences of retinal vessel calibers in 188 patients with CSID compared to 512 individuals without any history of CSID. Two are the main findings: (i) no differences regarding retinal venules were found between treated patients with CSID and healthy non-hospitalized (mainly hypertensive) individuals and (ii) these results remained the same when we compared separately each subgroup with controls. Moreover, these associations were not affected by most systemic inflammatory markers (CRP, ESR and WBC) which were however within normal ranges or only modestly elevated; only WBC showed significant association with CRVE in the univariate analysis.

At first glance our results are not consistent with the previous limited studies conducted in patients with rheumatoid arthritis[11] or other autoimmune rheumatic diseases jointly (RA, SLE, PsA).[12] However it should be mentioned that both studies[11,12] have not reported the percentage of patients treated with anti-inflammatory drugs while in one of them the control group included hospitalized patients.[12] The disease activity has been evaluated using a clinical score (DAS-28) in the first study[11] and CRP levels in the second one.[12] In our study the 188 patients with CSID were well–controlled at the time of retinal vessel calibers' evaluation as this may be indicated by the levels of systemic inflammatory markers (CRP, ESR and WBC) which are reported in Table 1.

Table 1 Characteristics of the overall population and the subpopulations (RG, RA, SLE, SpA).

	RG (n = 512)	RA (n = 74)	SLE (n = 75)	SpA (n = 39)
Age, years	52.3 ± 11.7	56.3 ± 10.6***	44.6 ± 11.9***	50.1 ± 12.0***
Males, %	56.3	23.0***	10.7***	79.5***
CVD, %	4.1	5.4*	13.3*	0.0*
Smoking (%)				
never-	44.5	44.6*	42.7*	7.7*
current-	29.9	32.4*	33.3*	69.2*
ex-	25.6	23.0	24.0	23.1
Hypertension[a], %	63.5	35.1	37.3	35.9
Dyslipidemia (%)	37.0	43.8**	18.7**	23.1**
Family history of CAD, %	13.7	19.2	8.0	17.9
Body Mass Index (kg/m^2)	28.2 ± 5.2	26.8 ± 4.8	25.5 ± 5.3	27.1 ± 3.4
Systolic BP, mmHg	130.7 ± 15.8	124.4 ± 18.5	122.0 ± 16.6	124.9 ± 15.1
Diastolic BP, mmHg	80.7 ± 9.9	76.4 ± 12.8	74.2 ± 10.1	78.0 ± 10.2
Mean BP, mmHg	92.2 ± 11.9	89.4 ± 13.6	85.4 ± 11.3	89.0 ± 11.0
Heart rate, bpm	67.8 ± 11.1	70.2 ± 10.1	69.4 ± 9.9	68.8 ± 12.1
Disease characteristics				
Disease duration, years	–	10.0 (5.0–19.0)*	9.0 (1.0–15.0)*	10.0 (4.0–15.0)*
ESR (mm/h)[b]	10.0 (5.0–18.0)	16.50 (7.5–28.5)	17.0 (9.0–32.0)	11.0 (8.0–20.3)
CRP (mg/L)[b]	3.2 (1.4–3.4)	3.3 (3.2–7.7)	2.6 (0.9–4.8)	4.3 (2.7–8.7)
WBC (10^9/L)[b]	6.525 (5.526–7.790)	6.700 (5.538–8.163)**	5.900 (4.470–7.760)**	7.890 (6.300–9.800)**
Drugs				
BP lowering drugs, %	46.9	28.4	40.5	25.6
Lipid modifying drugs (%)	24.2	25.7	13.5	17.9
Cortisone	–	68.9***	41.9***	7.7***
Methotrexate	–	52.7***	5.3***	12.8***
Leflunomide	–	10.8**	–	2.6**
Plaquenil	–	9.5***	55.4***	–
Biologics	–	45.9***	–	59.0***
Azathiorpine	–	–	8.1**	–
NSAIDS	–	9.5*	–	5.1*
Retinal vessels				
CRAE, μm	170.0 ± 17.1	173.8 ± 18.6	179.3 ± 16.1	172.9 ± 15.5
CRVE, μm	207.8 ± 18.8	209.7 ± 19.5	212.5 ± 16.7	210.0 ± 19.3

RG: reference group, CSID: chronic Systemic inflammatory disease; RA: rheumatoid arthritis; SLE: systemic lupus erythematosus; SpA: spondyloarthropathies; CVD: cardiovascular disease; CAD: coronary artery disease; BP: blood pressure; ESR: erythrocyte sedimentation rate; CRP: C - reactive protein; WBC: white blood cells; NSAIDS: non-steroid anti-inflammatory drugs; CRAE: central retinal arteriolar equivalent; CRVE: central retinal venular equivalent, ***$p < 0.001$, **$p < 0.01$, *$p < 0.05$.

[a] Hypertension was defined as office systolic and/or diastolic BP > 139/89 mmHg or use of BP lowering drugs.

[b] Reference group data was missing in 279 patients for ESR, 360 for CRP and 126 for WBC respectively.

The evidence regarding the effect of inflammation on retinal microcirculation is limited to two cross-sectional[11,12] and one prospective clinical studies.[14] The first one[11] compares 51 RA patients with 51 age and gender matched controls and found dilated retinal venules in RA patients versus controls, especially in those with high disease activity. The second one[12] conducted in 76 RA patients, 17 SLE, 11 PsA and 20 with another rheumatological disease as well as in 124 age and gender matched hospitalized controls, concluded that patients with autoimmune rheumatic diseases had wider retinal venules than controls and this increase remained in the subgroup with RA. It is important to mention that the patients of both studies had similar disease duration with our patients (10 years). However, neither of two studies report whether patients are treated with immunosuppressive agents or not.

This is an important limitation as the impact of therapy on retinal vessel calibers is fundamental but not well studied. Only one, recently published study,[14] investigated the effect of disease suppression on retinal microvascular caliber in patients with active RA and demonstrated that venular diameter decreases in parallel with improvements in disease activity. Moreover under conditions of stable, low-level inflammation and maintenance immunosuppression, retinal venular caliber remains unchanged during short-term follow-up. Notably, these results support the hypothesis that systemic inflammation promotes venular widening in RA, but its effects may be reversible with effective control of disease activity. The later might have potential implications in the management of patients with inflammatory diseases. Future comparative clinical studies need to confirm these findings.

Table 2 Logistic regression analysis [exp(B) (95% confidence intervals)] of CRAE, CRVE in patients with CSID versus RG.

	CRAE*	CRVE**
RA versus RG	1.158 (0.476, 2.816)	1.534 (0.601, 3.914)
SLE versus RG	0.596 (0.228, 1.561)	1.167 (0.445, 3.063)
SpA versus RG	0.673 (0.251, 1.803)	2.355 (0.844, 6.575)

CRAE: central retinal arteriolar equivalent; CRVE: central retinal venular equivalent; RG: reference group; RA: rheumatoid arthritis; SLE: systemic lupus erythematosus; SpA: spondyloarthropathies.
*Model testing CRAE was adjusted for age, sex, body mass index, mean arterial pressure, disease duration, blood pressure lowering drugs, lipid modifying drugs and CRVE.
**Model testing CRVE was adjusted for age; mean arterial pressure, disease duration, white blood cells, blood pressure lowering drugs, lipid modifying drugs and CRAE.

To our knowledge, this is the first cross-sectional study regarding the effect of inflammation on retinal vessel calibers in a large population (N = 188) with autoimmune rheumatic diseases and treated with immunosuppressive agents compared to healthy mainly hypertensives controls (N = 512). Our results might be explained by the recently published prospective clinical study that showed significant association between suppression of inflammation and the reduction of retinal venular diameter.[14] The improvement of retinal venular calibers using therapies targeting inflammation could be an explanation why retinal vessel caliber did not differ between the CSID patients studied, who had explicitly well-controlled systemic inflammation at the time of the examination, and the reference group. However, further prospective studies should be conducted to validate our findings and confirm the important role of anti-inflammatory/immunosupressive therapies on the retinal microcirculation in patients with CSID.

The strengths of our study were that a large number of well-characterized patients has been included and that a highly reproducible and validated method was used to measure retinal vessel calibers. The limitations of our study are mainly: (i) the cross-sectional design of the study; (ii) each of the three inflammatory markers that we studied (CRP, ESR, WBC) do not behave similarly in each inflammatory disease (RA, SLE SpA); (iii) our control group included mainly individuals with hypertension (63.5%). The last limitation could be responsible for a widening of retinal venular caliber[18] and therefore the lack of significant differences between patients with CSID and RG. However, the role of hypertension on widening of retinal venular caliber has not been consistently confirmed[10,19] and a subanalysis excluding patients with hypertension from both CSID and RG groups gave similar results.

In conclusion, in a well-controlled population - as depicted by inflammatory indices - with CISD no differences regarding retinal venular calibers were found when compared to a reference group with cardiovascular risk factors free of any CSID. Moreover, the same results remained when studying each disease group separately. The suppression of inflammation is pivotal in the management of patients with CSID and may be associated with improved retinal microcirculation. Future prospective clinical studies should be conducted to further investigate this association and validate our results.

Conflicts of interest

The authors declare no conflicts of interest.

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