Retinal microvascular abnormalities in major depression

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Background. The aim of our study was to find a possible association between retinal microvascular abnormality and major depression in a non-geriatric population.
Method. The participants with major depression were hospitalised at the University Hospital in Hradec Kralove, Department of Psychiatry. Retinal images were obtained using a stationary Fundus camera FF450 by Zeiss and a hand-held camera by oDocs.
Results. Fifty patients (men n=18, women n=32) aged 16 to 55 (men's average age 33.7±9.9 years, women's average age 37.9±11.5 years) were compared with fifty mentally healthy subjects (men n=28, women n=22) aged 18 to 61 (men's average age 35.3±9.2 years, women's average age 36.6±10.6 years) in a cross-sectional design. The patients were diagnosed with a single depressive episode (n=26) or a recurrent depressive disorder (n=24) according to the ICD-10 classification. Our results confirmed significant microvascular changes in the retina in patients with depressive disorder in comparison to the control group of mentally healthy subjects, with significantly larger arteriolar (P<0.0001) as well as venular (P<0.001–0.0001) calibres in major depression.
Conclusion. According to the literature, acute and chronic neuroinflammation is associated with changes in microvascular form and function. The endothelium becomes a major participant in the inflammatory response damaging the surrounding tissue and its function. Because the retina and brain tissue share a common embryonic origin, we suspect similar microvascular pathology in the retina and in the brain in major depression. Our results may contribute to a better understanding of depression etiopathogenesis and to its personalized treatment.

Key words: depression, retinal microvascular abnormality, biomarker, neuroinflammation

Received: February 11, 2023; Revised: May 25, 2023; Accepted: June 8, 2023; Available oline: July 17, 2023
https://doi.org/10.5507/bp.2023.026

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INTRODUCTION

Major depressive disorder (MDD) is a debilitating condition and the most common mental illness, affecting more than 300 million people worldwide[1]. It may manifest as a single episode or as recurrent episodes. Depression is approximately twofold more common in women than in men. This may be explained by the imbalance of hormones during menstruation and pregnancy, increased stress sensitivity in women, maladaptive coping strategies, or multiple social roles[2].

Various theories have been postulated to clarify the pathophysiology of depressive disorder. One of the first and major theory of depression is the monoamine-deficiency hypothesis which claims that depletion in monoamine neurotransmitters serotonin and norepinephrine in the central nervous system is an etiologic factor[3]. A recent hypothesis considers the interaction of genetic background with deleterious environmental factors, especially stressful life events, including epigenetic mechanisms[4,5]. The hypothalamic-pituitary-adrenal (HPA) axis hypothesis proposes that dysregulation of the HPA axis and the alteration in glucocorticoid response to stress are implicated in depression prior to monoamine abnormalities[6]. Other hypotheses are represented by the macrophage theory and cytokine hypothesis, which postulate a critical role of excessive function of macrophages and cytokines, with an elevated level of proinflammatory cytokines acting as neuromodulators in major depression[7,8]. Yet another theory considers stress-induced reductions in neurogenesis[9]. The inflammatory and neurodegeneration hypothesis suggests that inflammatory processes lead to decreased neurogenesis and increased neurodegeneration in the central nervous system[10].

Another hypothesis supported by a growing body of evidence indicates that inflammation accompanied by an increased oxidative and nitrosative stress may play a crucial role in major depression[11,12]. This stress is manifested as an increased peroxidation of lipids and an elevated production of mitochondrial reactive oxygen species (mtROS) (ref.[13,14]). The latter may indicate the presence of mitochondrial dysfunction. Moreover, ROS can inflict damage on biomolecules, including DNA. An increased concentration of 8-oxoguanine which is a marker of oxidative DNA damage was found in patients suffering from depression[15-23].

The vascular inflammatory response in major depression involves a complex interaction between endothelial cells, inflammatory cells (neutrophils, lymphocytes, monocytes, and macrophages), vascular smooth muscle cells, and extracellular matrix. Vascular injury is associated with an increased excretion of adhesion molecules by endothelial cells and recruitment of inflammatory cells, growth factors, and cytokines, with consequent effects on vascular smooth muscle cells, extracellular matrix, and endothelial cells[24]. Cytokines include monokines, synthesized by macrophages, and lymphokines, produced by activated T-lymphocytes and natural killer cells. Monokines include interleukin-1, tumour necrosis factor, α and β interferons, and colony stimulating factors. Lymphokines include interleukins-2-6, γ interferon, granulocyte-macrophage colony-stimulating factor, and lymphotoxin. Endothelial cells, fibroblasts and other selected cells may also synthesize cytokines[25]. Circulating cytokines interact with specific receptors on various cell types and activate the JAK-STAT, nuclear factor -κB, and the Smad signalling pathways, leading to an inflammatory response involving cell adhesion, permeability, and apoptosis. Cytokine-induced activation of these pathways in endothelial cells modifies the production and/or activity of vasodilatory mediators (nitric oxide, prostacyclin, endothelium-derived hyperpolarising factor, and bradykinin), as well as of vasoconstrictive mediators (endothelin and angiotensin II) (ref.[24]). Acute and chronic inflammation is associated with changes in microvascular forms and functions. On activation by proinflammatory mediators, the endothelium becomes a major participant in the generation of the inflammatory response[26]. High plasma levels of homocysteine are associated with atherosclerosis[27] and with male major depressive disorders[28]. Microvascular changes can be easily evaluated in vivo in the retina of the eye in a non-invasive manner, the retina being part of the central nervous system and thus a suitable substitute for brain tissue in neuropsychiatric research.

AIM

The main aim of our study was to find out possible retinal microvascular abnormalities in patients with major depressive disorder compared with healthy controls. We also looked for possible associations of retinal microvascular diameters with various demographic, genetic, biochemical, clinical, or therapeutic variables.

MATERIAL AND METHODS

Study subjects

The participants with depressive disorder were hospitalised at the Department of Psychiatry, University Hospital in Hradec Kralove (UHHK). Healthy volunteers were age-matched hospital employees (nurses and hospital attendants). They were recruited via advertisement at the UHHK.

The patients' inclusion criteria were age under 55 years, single or recurrent major depression according to the 10th revision of the International Classification of Mental Disorders (ICD-10), and an absence of eye disorders related to retinal microvasculature. The type of depression was determined by the prevalence of clinical symptoms (anxious or (an-) hypohedonia), which with low mood led to hospitalization. The healthy volunteers' inclusion criteria were age under 65 years and the absence of mental disorders or eye disorders, influencing retinal microvasculature.

Procedures

We obtained information on age, employment and marital status, duration of education, body mass index (BMI), and somatic comorbidities (arterial hypertension, AH; diabetes mellitus, DM; myocardial infarction, MI; history of stroke; lower leg varicose veins) as well as on cigarette smoking. In the participants with depressive disorder, we also evaluated possible drug resistance, stressful life events in recent history, and the type of depression (anxious or inhibited). We also collected information about the age at the first episode of depression and about the total duration of the mood disorder. We measured levels of blood C-reactive protein (CRP), interleukin-6 (IL-6), and dyslipidaemia. We applied the Montgomery-Asberg Depression Rating Scale (MADRS) (ref.[29]). The apolipoprotein E (ApoE) genotype was also detected in major depression.

Measurement of retinal vasculature

Retinal images were obtained using a stationary Fundus camera FF450 by Zeiss and a hand-held camera by oDocs. Retinal images were quantified using the semi-automated software VAMPIRE (Vessel Assessment and Measurement Platform for Images of the REtina) (ref.[30]).

We computed the vessel diameter as the cross-sectional span of the vessel mask perpendicular to the vessel's estimated axis. The arteriolar and venular diameters passing through the extended zone between 0.5 and 2 disc diameters from the optic disc were measured[31]. Based on the revised Knudtson-Parr-Hubbard formula, the six largest arterioles and the six largest venules present in this extended zone were chosen for calculations[32]. The Central Retinal Artery Equivalent (CRAE) for arterioles and the Central Retinal Vein Equivalent (CRVE) for venules were calculated using an iterative process by progressively replacing the largest and smallest vessel diameters until a single number was reached. To convert the obtained values from pixels to micrometres (μm), we used a calibration factor[31,33] of 3.5 (for stationary fundus camera) and 3.4 (for hand-held camera).

Statistical analysis

IBM SPSS Statistics version 23 statistical software (Armonk, NY: IBM Corp.) was used to analyse the data. Groups were compared on quantitative parameters using the Student's t-test, Mann-Whitney U test, or Kruskal-Wallis test. The chi-square test or Fisher's exact test were

applied to compare qualitative parameters. The relationships between the vessel width and quantitative parameters were assessed using the Spearman's correlation analysis. Data normality was verified using the Shapiro-Wilk test. All tests were performed at the significance level of 0.05.

Ethical issues

Our study was approved by the Ethics Committee of the University Hospital in Hradec Kralove, Czech Republic on May 5th, 2016 (Reference number 201605 S12P). The Ethics Committee composition meets the requirements of ICH GCP (the International Conference on Harmonisation-Good Clinical Practice) standards and the Ethics Committee works according to its written procedure in compliance with the standard (ICH E6). All study participants signed voluntarily the Informed consent. The study was performed in accordance with the Declaration of Helsinki ethical principles for medical research[34].

RESULTS

The study involved 50 patients with a diagnosis of depression in the diagnostic categories F32 (depressive episode, n=26) and F33 (recurrent depressive disorder, n=24) according to the ICD-10 classification of mental disorders. There were 11 (61.1%) patients with an anxious type of depression in the group of men and 19 (59.4%) patients in the group of women. The participants with depressive disorder were aged 16 to 55 (men n=18, women n=32), and were compared with mentally healthy subjects in the age range from 18 to 61 (men n=28, women n=22). Patients with major depressive disorder were treated with antidepressants. There were 22 (44%) patients who used monotherapy, 25 (50%) subjects who used a combination of two antidepressants and 3 (6%) patients who used a combination of three antidepressants. Among them, there were 22 cases using selective serotonin reuptake inhibitors (SSRIs), 17 cases treated with serotonin antagonists and reuptake inhibitors (SARIs), 14 cases with serotonin-noradrenaline reuptake inhibitors (SNRIs), 13 cases using noradrenaline and specific serotonergic antidepressants (NASSAs), 7 cases treated with tricyclic antidepressants (TCAs), 5 cases using melatonin receptor agonist (MASSA), 2 cases with multimodal antidepressants (MMA) and 1 case using norepinephrine-dopamine reuptake inhibitors (NDRIs). The most frequent was the monotherapy with SSRIs – 9 patients, followed by the combination of SSRIs and SARIs – 8 patients, the combination of SNRIs and NASSAs – 5 patients, the monotherapy with SNRIs, the monotherapy with NASSAs and the combination of SNRIs and SARIs – 3 patients. Among all patients, 13 patients didn't use any psychopharmacotherapy before the hospitalization.

The demographic and clinical parameters of the study subjects are presented in Tables 1 and 2.

We found significant microvascular changes in the retina in the group of depressive patients in comparison to the control group of mentally healthy subjects, i.e. larger arteriolar and venular calibres in the group of men

Table 1. Demographic and clinical data in men and women – quantitative parameters.

Variable	Major depression men n=18 women n=32 (mean ± SD)	Healthy controls men n=28 women n=22 (mean ± SD)	*P*
Age (years)	men 33.7±9.9 women 37.9±11.5	men 35.3±9.2 women 36.6±10.6	men 0.444 women 0.555
Education (years)	men 13.2±2.0 women 13.4±2.1	men 14.0±2.3 women 14.5±2.5	men 0.195 women 0.049
Body mass index (kg/m^2)	men 25.6±5.4 women 24.9±4.1	men 25.9±3.8 women 22.4±3.1	men 0.431 women 0.019
Age at the onset of depression (years)	men 28.6±10.0 women 30.5±12.4	NA	NA
Total duration of the mood disorder (years)	men 5.1±5.3 women 7.3±8.0	NA	NA
MADRS (score)	men 20.7±6.0 women 18.6±5.2	NA	NA
Cholesterol blood level (mmol/L)	men 4.85±0.99 women 5.06±0.86	NA	NA
CRP blood level (mg/L)	men 3.59±2.93 women 2.15±2.08	NA	NA
IL-6 serum level (ng/L)	men 2.65±1.21 women 3.01±1.73	NA	NA

MADRS, the Montgomery-Asberg Depression Rating Scale; CRP, C-Reactive Protein; IL-6, Interleukin-6; NA, not applicable; SD, standard deviation.

Physiological levels according to the Institute of Clinical Biochemistry and Diagnostics, UHHK:

Cholesterol blood level: 0–5.2 mmol/L; CRP blood level: 0–5 mg/L; IL-6 serum level: 0–43.5 ng/L.

Table 2. Demographic and clinical data in men and women – qualitative parameters.

Variable	Major depression men n=18 women n=32 Number (percent)	Healthy controls men n=28 women n=22 Number (percent)	*P*
Employment			
Yes	men 14 (77.8) women 21 (65.6)	men 25 (89.3) women 15 (68.2)	men 0.407
No (over one year)	men 4 (22.2) women 11 (34.4)	men 3 (10.7) women 7 (31.8)	women 1.000
Marital status			
Single	men 6 (33.3) women 10 (32.3)	men 15 (53.6) women 8 (36.4)	men 0.285
Married/with a partner	men 10 (55.6) women 20 (62.5)	men 12 (42.9) women 9 (40.9)	women 0.164
Divorced	men 2 (11.1) women 2 (6.5)	men 1 (3.6) women 5 (22.7)	
Stressful life events in the history			
Yes	men 14 (77.8) women 21 (65.6)	NA	NA
No	men 4 (22.2) women 11 (34.4)	NA	
Type of depression			
Anxious	men 11 (61.1) women 19 (59.4)	NA	NA
Inhibited	men 7 (38.9) women 13 (40.6)	NA	
Drug resistance			
Yes	men 2 (11.1) women 2 (6.3)	NA	NA
No	men 16 (88.9) women 30 (93.8)	NA	
Smoking			
Yes	men 6 (33.3) women 9 (28.1)	men 8 (28.6) women 3 (13.6)	men 0.753
No	men 12 (66.7) women 23 (71.9)	men 20 (71.4) women 19 (86.4)	women 0.320
Arterial hypertension			
Yes	men 2 (11.1) women 4 (12.5)	men 3 (10.7) women 1 (4.5)	men 1.000
No	men 16 (88.9) women 28 (87.5)	men 25 (89.3) women 21 (95.5)	women 0.638
History of myocardial infarction			
Yes	men 0 (0) women 0 (0)	men 0 (0) women 0 (0)	men 1.000
No	men 18 (100) women 32 (100)	men 28 (100) women 22 (100)	women 1.000
History of stroke			
Yes	men 0 (0) women 0 (0)	men 0 (0) women 0 (0)	men 1.000
No	men 18 (100) women 32 (100)	men 28 (100) women 22 (100)	women 1.000
Diabetes mellitus			
Yes	men 0 (0) women 1 (3.1)	men 0 (0) women 0 (0)	men 1.000
No	men 18 (100) women 31 (96.9)	men 28 (100) women 22 (100)	women 1.000

Table 2. *(Continued)*

Variable	Major depression men n=18 women n=32 Number (percent)	Healthy controls men n=28 women n=22 Number (percent)	*P*
Lower leg varicose veins Yes			
	men 0 (0)	men 1 (3.6)	men 1.000
No	women 3 (9.4)	women 3 (13.6)	
	men 18 (100)	men 27 (96.4)	women 0.678
	women 29 (90.6)	women 19 (86.4)	
Apolipoprotein E gene polymorphism			
2/3	men 2 (18.2)	NA	
	women 4 (17.4)		
2/4	men 1 (9.1)	NA	NA
	women 0 (0)		
3/3	men 6 (54.5)	NA	
	women 14 (60.9)		
3/4	men 2 (18.2)	NA	
	women 5 (21.7)		

NA, not applicable.

(*P*≤0.0001) as well as in the group of women (*P*≤0.001–0.0001) (Table 3 and 4).

A moderate negative correlation between age and VRM (CRVE in the right eye in μm) (CC -0.449, *P*=0.010) and a weak negative correlation between age and ALM (CRAE in the left eye in μm) (CC -0.356, *P*=0.0496) were demonstrated in the group of women, but not in the group of men with major depressive disorder. A moderate positive correlation between ARM (CRAE in the right eye in μm) and cholesterol level (CC 0.476, *P*=0.046) was demonstrated in the group of men, but not in the group of women with major depressive disorder. A moderate negative correlation between MADRS score and VRM (CC -0.478, *P*=0.007) and a weak negative correlation between MADRS score and ALM (CRAE in the left eye in μm) (CC -0.395, *P*=0.031), and ARM (CC -0.389, *P*=0.031) were demonstrated in the group of women, but not in the group of men with MDD. There was no correlation of CRAE or CRVE with the duration of education, age at the first episode of major depression, the duration of illness, or BMI, nor of serum/blood levels of CRP or IL-6 in either gender group of patients.

A significantly greater width of ALM was found in the drug resistant group of men (*P*=0.049) as compared with the healthy males. There was no significant association of CRAE or CRVE with marital status, smoking, DM, or blood pressure in either gender group of patients, or in the healthy unrelated volunteers, or with the ApoE genotype in major depression. We also found no significant association of CRAE or CRVE with the type of prescribed antidepressant in major depression.

DISCUSSION

A significant difference in BMI and the duration of education was found in women with major depression as compared with the control group. Women with depression were less educated and had higher BMI values than women in the control group. This may be explained by the fact that depression affects women more than males[2]. We did not find any significant difference between depression and healthy controls in other demographic parameters in either gender. Similarly, no significant differences were detected in the incidence of smoking, arterial hypertension, diabetes mellitus, or lower leg varices, nor in the history of myocardial infarction or stroke, between major depression subjects and controls in either gender group. In the participants with depression, blood markers of inflammation (CRP, IL-6) and blood cholesterol levels were within the physiological range, which may be due to the fact that the intensity of microvascular inflammation is not so striking as to affect whole body markers.

The key finding of our study is the presence of statistically significant microvascular changes in the retina of the eye in the group of patients with depressive disorder compared with mentally healthy participants, i.e. the greater width of arterioles and venules in both depressed gender groups. This may be explained by microvascular inflammation and will be discussed below. Our results concerning a possible association of age, blood cholesterol level, or drug resistance with retinal microvascular changes in major depression were inconclusive. Neither did we find any association of retinal microvascular changes with other demographic or clinical variables.

Other studies also evaluated retinal vascular abnormalities in patients with major depression.

Table 3. Comparison of retinal arteriolar and venular equivalents in the groups of men.

Men		Depression n=18	Healthy unrelated volunteers n=28	*P*
ALM	Mean	158.2	112.8	< 0.0001
	SD	16.8	13.2	
	Median	157.4	111.3	
	Minimum	134.3	90.0	
	Maximum	189.7	137.6	
ARM	Mean	158.2	114.1	< 0.0001
	SD	16.9	12.8	
	Median	163.1	112.7	
	Minimum	126.8	93.5	
	Maximum	186.7	141.8	
VLM	Mean	233.6	199.7	< 0.0001
	SD	17.4	18.1	
	Median	229.6	202.7	
	Minimum	203.3	163.1	
	Maximum	266.2	240.5	
VRM	Mean	228.3	201.1	0.0001
	SD	20.2	19.3	
	Median	225.6	199.9	
	Minimum	184.3	168.0	
	Maximum	262.8	238.7	

CRAE, central retinal artery equivalent; CRVE, central retinal vein equivalent;
ALM, CRAE in the left eye (μm); ARM, CRAE in the right eye (μm); VLM, CRVE in the left eye (μm); VRM, CRVE in the right eye (μm).

Table 4. Comparison of retinal arteriolar and venular equivalents in the groups of women.

Women		Depression n=32	Healthy unrelated volunteers n=22	*P*
ALM	Mean	156.6	121.3	< 0.0001
	SD	14.5	16.6	
	Median	155.1	117.8	
	Minimum	128.9	94.5	
	Maximum	194.6	152.3	
ARM	Mean	158.1	124.2	< 0.0001
	SD	14.2	15.1	
	Median	155.6	122.3	
	Minimum	134.6	102.9	
	Maximum	188.4	153.3	
VLM	Mean	227.9	205.1	0.001
	SD	19.6	25.4	
	Median	230.5	201.4	
	Minimum	180.2	172.6	
	Maximum	272.3	266.0	
VRM	Mean	231.0	199.5	< 0.0001
	SD	15.4	17.6	
	Median	229.7	200.9	
	Minimum	195.2	175.4	
	Maximum	260.4	233.8	

CRAE, central retinal artery equivalent; CRVE, central retinal vein equivalent;
ALM, CRAE in the left eye (μm); ARM, CRAE in the right eye (μm); VLM, CRVE in the left eye (μm); VRM, CRVE in the right eye (μm).

Sun et al. (2007) (ref.[35]) performed a large population-based cohort study on 2,420 subjects in order to examine the association between the manifestations of depression and microvascular abnormalities of the retina such as retinopathy, focal arteriolar narrowing, arteriovenous nicking, generalised retinal arteriolar narrowing, and generalised retinal venular dilatation. Data provided from digital retinal photographs, as well as from the short-item Centers for Epidemiologic Studies Depression Scale (CES-D) were analysed. Overall, no association was found between retinal microvascular abnormalities and the symptoms of depression.

Cheung et al. (2009) (ref.[36]) investigated 10,364 Caucasian and African Americans aged 48–73 years to establish a possible association between microvascular changes in the retina with vital exhaustion, including depressive symptoms. Vital exhaustion was modestly associated with the presence of retinopathy (OR 1.27; 95% CI 1.01–1.59), particularly retinal haemorrhages and generalised retinal venular widening.

In the study by Ikram et al. (2010) (ref.[37]), the authors tested whether smaller retinal arteriolar or larger venular calibres were associated with incident late-life depression. Among the total number of 3,605 participants, those with incident depression symptoms during follow-up visits and monitoring were identified. After the mean follow-up of 9.0 years, 555 patients (15.4%) developed late-life depression. There was no correlation between retinal vascular calibres and incident late-life depression, either in smaller arteriolar or larger venular calibres.

Li et al. (2013) (ref.[38]) measured symptoms of antenatal depression, anxiety, sleep quality, and retinal vascular calibre of 952 Asian pregnant women aged 18 to 46 years. Li applied retinal photography and the assessments of the Edinburgh Postnatal Depression Scale (EPDS), State-Trait Anxiety Inventory (STAI), and Pittsburg Sleeping Quality Index (PSQI). In multiple linear regression models, each standard deviation (SD) increase in the Edinburgh Postnatal Depression Scale and the Pittsburgh Sleep Quality Index was significantly associated with a 0.80 μm (P=0.03) and a 1.22 μm (P=0.01) widening in the retinal arteriolar calibre, respectively. The authors conclude that their study demonstrates relationships between antenatal depressive symptoms and poor sleep quality with retinal arteriolar widening in pregnant women.

Meier et al. (2014) (ref.[39]) investigated whether the link between depression and retinal vessel calibre was already apparent in otherwise healthy young adults and adolescents. The tests were applied in 865 participants in the years 2000–2013. They included the SPHERE (Somatic and Psychological Health Report) questionnaire which contains subscale scores related to depression, anxiety and overall mental health. For the measurement of retinal vessel calibre, stereoscopic optic disc-centred photographs

were taken. The results were summarised as CRAE and CRVE. The results revealed that depression and anxiety symptoms were positively associated with wider retinal arteriolar calibre (P=0.016) even after adjusting for other cardiovascular risk factors (P=0.025), but not with CRVE. It means that pathological microvascular mechanisms associated with depression/anxiety may be operative already from a young age.

In the Multi-Ethnic Study of Atherosclerosis (MESA), Gennip et al. (2022) (ref.[40]) investigated the associations between the baseline retinal arteriolar and venular calibres (CRAE and CRVE) and incident depressive symptoms. The authors used longitudinal data on 4,366 participants (mean age = 63.2 years; 48.5% women; ethnicity – 38% White, 28% African, 23% Hispanic, and 11% Chinese-Americans), recruited from 6 US communities, without any baseline depressive symptoms. Depressive symptoms, defined as the 20-item Center for Epidemiologic Studies Depression Scale score ≥16 and/or use of antidepressant medication, were determined between 2002 and 2004 and at 3 follow-up examinations conducted every 1.5–2 years thereafter. Fundus photography was performed at baseline according to a standardized protocol with the use of a 45-degree digital non-mydriatic camera. The authors found that after a mean follow-up period of 6.1 years, 21.9% (n=958), participants had developed incident depressive symptoms. After adjustment for sociodemographic, lifestyle, and cardiovascular factors, a 1-standard-deviation larger baseline CRVE was associated with a higher risk of depressive symptoms (HR=1.10, 95% CI: 1.02–1.17), but a 1-standard-deviation larger baseline CRAE was not statistically significantly associated with incident depressive symptoms (HR = 1.04, 95% CI: 0.97–1.11).

Another possible method of retinal diagnostic in major depressive disorder is optical coherence tomography (OCT). Kalenderoglu A. et al. (2016) (ref.[49]) compared ganglion cell layer (GCL), and inner plexiform layer (IPL) volumes and retinal nerve fibre layer (RNFL) thickness between first episode and recurrent MDD patients and healthy controls using optic coherence tomography in order to detect findings supporting a degenerative process. Their study included 50 patients with first episode MDD (men n=16, women n=34), 50 patients with recurrent MDD (men n=15, women n=35) and 50 controls. Sociodemographic data form was filled for all study group, and Hamilton Depression Rating Scale (Ham-D), and Clinical Global Impression Scale (CGI) were applied to depressive patients. The results showed that GCL and IPL volumes were significantly smaller in recurrent depression patients than first episode patients (P<0.001) and in all MDD patients than controls (P<0.001). There were significant negative correlations between their volumes and disease severity parameters such as Ham-D (GCL: CC -0.200, P=0.005; IPL: CC -0.221, P=0.002) and CGI scores (GCL: CC -0.248, P<0.001; IPL: CC -0.268, P<0.001), and disease duration (GCL: CC -0.247, P<0.001; IPL: CC -0.252, P<0.001). Mean choroid thickness was higher in MDD patients than controls (P<0.001) and in first episode MDD than in recurrent MDD patients (P<0.001).

Another recent research was performed by Liu X. et al. (2022) (ref.[50]). The authors measured 78 patients (aged 17 to 55 years, men n=27) with newly diagnosed and unmedicated MDD and compared them with 47 sex- and age- matched healthy controls. They underwent retinal vessel density and structure examination using OCT and visual field examination using perimetry. All participants were assessed for their clinical status using the Young Mania Scale and 24-item Hamilton Depression Rating Scale. The results showed that patients with MDD had lower retinal vessel density (including radial peripapillary capillary vessel density, superficial and deep capillary plexus vessel density), thinner subfoveal choroidal thickness, and poorer visual fields compared to healthy control group (all P<0.05).

As this brief literature review shows, the results in this field of knowledge are not unambiguous, and in some cases they are even contradictory. Nevertheless, the preponderance of literature data points to the fact that the retinal vascular abnormalities are associated with symptoms of depression. This may be based on the imbalance of mediators of the immune response system (cytokines) in favour of proinflammatory processes. The effects of proinflammatory cytokines on the hypothalamus-pituitary-adrenal axis result in the release of glucocorticoid hormones[41]. Also, OCT examinations showed structural changes in retinal layers and vessel density in patients with MDD.

Our study was limited by the small number of study subjects; nevertheless, the key results are statistically significant. As markers of inflammation, we studied CRP and IL-6 blood levels only. However, they are not sensitive enough to indicate microinflammation in retinal vessels. We examined one ethnicity only (Caucasians), and so our results may not be relevant for countries with a different ethnic composition. We did not collect any information regarding the lifestyle of the participants, which may influence the possible incidence of microinflammation. A general weakness of cross-sectional studies, like the present one, is that it does not elucidate whether inflammation induces depression or vice versa.

The advantages of our study are based on the fact that retinal vascular measurements were carried out precisely, using computer software. Our patient group was homogeneous – only hospitalized patients of a relatively young age with a small number of associated somatic diseases were investigated.

In future research, a more comprehensive examination of inflammatory markers, including other cytokines, in patients and healthy volunteers would be appropriate. CRP is an acute-phase reactant that serves as a pattern-recognition molecule in the innate immune system[42]. CRP has been traditionally thought of as a bystander marker of vascular inflammation, without playing a direct role in the inflammatory process. However, recent evidence suggests that CRP may contribute directly to the proinflammatory state. CRP stimulates monocyte release of inflammatory cytokines such as IL-1b, IL-6, and tumor necrosis factor-α (TNF-α) (ref.[43]) and may also directly act as a proinflammatory stimulus to phagocytic cells by binding to the FcγRII receptor[44]. It has also been recently

revealed that CRP causes expression of intercellular adhesion molecule 1 and vascular cell adhesion protein 1 by endothelial cells[45], and mediates monocyte chemoattractant protein-1 induction also in endothelial cells, an effect that is inhibited by simvastatin and fenofibrate[46]. The CRP opsonization of low-density lipoprotein (LDL) also mediates LDL uptake by macrophages[47,48].

In addition to this, longitudinal control examinations of all study participants during the following years would provide a more accurate assessment of the inflammation/microvascular state and its dynamics. This would contribute to a better understanding of the etiopathogenesis of depression, with a possible therapeutic potential.

CONCLUSION

The results of our study show a significant association of depressive disorder with the enlargement of retinal vessel calibres in a non-geriatric study population. The mechanisms underlying these retinal venular and arteriolar abnormalities are not entirely known. We can assume that they are caused by cytokines that act during a neurogenic inflammation. However, we cannot say for sure what is primary – the development of depression with the resulting cascade of inflammatory processes, or neurogenic inflammation with subsequent development of depressive symptoms; or as some epidemiological studies have shown, that changes in retinal arteriolar and venular diameters are reflective of a wide range of genetic, epigenetic, and environmental factors. More research is needed in this area. Retinal microvascular examination could be a potential screening tool to identify individuals at risk for depression, because retina and brain tissue have the same embryonic origin, and microvascular inflammation may participate in the etiopathogenesis of major depression in the brain. This examination could possibly be used in the early diagnostics and prevention of depressive disorder. In this way, the suffering of affected subjects may be decreased, as well as the negative socioeconomic effect of depression. Future longitudinal studies with a precise laboratory assessment may shed light on this issue.

Acknowledgements: This work was supported by the MH CZ – DRO (UHHK, 00179906).
The authors are grateful to Ian McColl MD, PhD for assistance with the manuscript.
Author contributions: ES: principal investigator, study design, data processing, preparation of the manuscript; LH: study design, data processing, preparation of the manuscript; AS: data processing, preparation of the manuscript; JZ: statistical analysis, preparation of the manuscript; JS: study design, data processing, preparation of the manuscript.
Conflict of interest statement: The authors state that there are no conflicts of interest regarding the publication of this article.

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