• Clinical Research •

Dry eye rate and its relationship with disease stage in patients with primary hypertension: a cross-sectional study in Vietnam

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Abstract

● **AIM:** To determine the dry eye (DE) rate and its relationship with disease stage in patients with primary hypertension.

● **METHODS:** A cross-sectional study included 432 patients with primary hypertension (with an equal number of patients in each group: 144 in stage I, II, and III hypertension) and 144 healthy subjects as a control group. The Ocular Surface Disease Index (OSDI) and Schirmer I test without anesthetics were conducted on all 576 subjects. Subjects with OSDI scores <13 and Schirmer I values equal to or under 10 mm were diagnosed with DE.

● **RESULTS:** The ratio of DE in hypertension patients was higher than in the control group (41.7% versus 18.8%; *P*<0.001). The proportion of patients with DE increased gradually according to the hypertension stage: 27.1% in stage I, 40.3% in stage II, and 57.6% in stage III, *P*<0.001. Age, duration of hypertension, plasma urea, creatinine, and high-sensitivity C-reactive protein (CRP-hs) levels in hypertension patients with DE were higher than those without DE, *P*<0.001. Advanced age, a long duration of hypertension, diabetes mellitus, elevated plasma creatinine, and CRP-hs levels were independent factors associated with DE in primary hypertension patients, *P*<0.001.

● **CONCLUSION:** DE is a common disorder associated with advanced age, a long duration of hypertension, diabetes mellitus, elevated plasma CRP-hs, and creatinine levels in patients with primary hypertension.

● **KEYWORDS:** primary hypertension; dry eye; stage of hypertension; plasma creatinine

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INTRODUCTION

Systemic arterial hypertension, is characterized by the continuous elevation of blood pressure within the systemic arteries. This condition is categorized into two types: primary and secondary hypertension[1-2]. The intricate pathophysiological mechanisms behind primary hypertension involve genetics, environmental influences, and the intricate interplay of the integrated nervous system. This includes components such as the renin-angiotensin-aldosterone system, the role of natriuretic peptides and the endothelium, the sympathetic nervous system, and the immune system[2-4].

Primary hypertension is a risk factor for and a contributor to various diseases. These include cardiovascular ailments like stroke, coronary artery disease, heart failure, peripheral vascular disease, and conditions like renal disease and hypertensive retinopathy[1,5-7]. Hypertensive retinopathy typically advances subtly, often devoid of symptoms, but in severe cases, it can lead to reduced vision, eye swelling, and even double vision[7].

Apart from the aforementioned clinical manifestations, hypertensive patients have also exhibited dry eye (DE), tied to inflammatory immune responses, oxidative stress, retinal impairment, and antihypertensive medications[1,8-10].

The implications of DE encompass diminished visual functionality[11], a negative impact on contrast sensitivity[12], the amplification of stray light due to an unstable tear film, and a decrease in contrast sensitivity[13]. Nevertheless, research is scarce exploring DE and its related factors in individuals afflicted with primary hypertension. For these reasons, we hypothesized a correlation exists between DE, disease stage, and other factors among primary hypertensive patients.

SUBJECTS AND METHODS

Ethical Approval The study was approved by the Ethics Committee of Nghe An Eye Hospital, approved under decision No.0678/QD-BVMNA. Informed consent was obtained from all the participants.

Patients A total of 432 patients diagnosed with primary hypertension (144 individuals within each stage) and receiving treatment at Nghe An General Friendship Hospital in Nghe An Province, Vietnam, were enrolled in this study, spanning from January 2021 to January 2023. The classification of hypertensive stages was established based on target organ complications, as defined by World Health Organization criteria[14]. Exclusion criteria encompassed patients with inflammatory eye complications, users of contact lenses, and those with a history of eye surgery. Additionally, individuals with acute infections, suspected surgical conditions, and pregnant or lactating women were omitted from the study. A control group of 144 individuals of similar age and sex and confirmed good health through regular health check-ups was also included. Clinical characteristics and laboratory data were gathered at the study's outset. Expert medical practitioners verified the identification of target organ complications.

Five hundred and seventy-six participants were referred to ophthalmologists to evaluate the occurrence of DE. These individuals underwent the Ocular Surface Disease Index (OSDI) questionnaire and the Schirmer I test (without anesthetics) following standard protocols[15-16]. The OSDI questionnaire consists of 12 items, with scores ranging from 0 to 100. Scores of 0-12 indicate the absence of DE, while scores of 13 or higher signify the presence of DE. For scores between 13-22, the condition is categorized as mild DE; 23-32 indicates moderate DE; and 33-100 reflects severe DE [15]. DE is established if Schirmer I values are equal to or below 10 mm in at least one eye. The lowest value between both eyes was used for statistical analysis.

Data on the duration of hypertension, treatment specifics (particularly the use of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers), and biochemical markers such as urea, creatinine, albumin, protein, and high-sensitivity C-reactive protein (CRP-hs) were concurrently collected alongside the Schirmer I test.

Table 1 Comparison of some characteristics and ratio of DE in hypertension group and control group *n* (%)

Parameters	Hypertension group (*n*=432)	Control group (*n*=144)	*P*
Ages (y), mean±SD	61.26±11.31	62.03±10.54	0.473
Gender			0.130
Male	170 (39.4)	67 (46.5)	
Female	262 (60.6)	77 (53.5)	
Lipid disorder	350 (81.0)	89 (61.8)	<0.01
OSDI (scale)			<0.001
Normal	252 (58.3)	117 (81.2)	
Mild	29 (6.7)	24 (16.7)	
Moderate	115 (26.6)	3 (2.1)	
Severe	36 (8.3)	0	
Median (IQR)	11 (9-27)	7 (5-10)	<0.001
Schirmer I (mm), median (IQR)	12 (7-13)	13 (11-14)	<0.001
DE	180 (41.7)	27 (18.8)	<0.001

DE: Dry eye; SD: Standard deviation; IQR: Interquartile range; OSDI: Ocular Surface Disease Index.

Statistical Analysis The continuous data from normally distributed sources were characterized using the mean and standard deviation, and they underwent analysis through the Student *t*-test. Conversely, data with skewed distributions were described using the median (25^{th} percentile-75^{th} percentile) and were subject to analysis through the Mann-Whitney *U* test and the Kruskal Wallis test. Categorical data were displayed in terms of frequency and percentage, and their analysis was carried out using the Chi-square test. We conducted a multivariable-adjusted regression analysis to identify factors independently associated with DE. Statistical analysis was performed using Statistical Package for Social Science (SPSS) version 20.0 (Chicago, IL, USA) with a *P*-value <0.05 was considered significant.

RESULTS

The results in Table 1 indicate that the patient cohort exhibited a notably higher OSDI score and significantly lower Schirmer I value than the control group, with *P*<0.001. The prevalence of DE among hypertensive patients surpassed that of the control group (*P*<0.001). Table 2 shows that parameters such as age, hypertension duration, plasma urea, creatinine, CRP-hs, and DE incidence gradually increased in alignment with the severity of the hypertensive stage, *P*<0.001. Conversely, the utilization rate of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers displayed a progressive decrease with escalating hypertensive stages, *P*<0.05.

Table 3 underscores that patients afflicted with DE manifested higher levels of age, hypertension duration, diabetic mellitus ratio, plasma urea, creatinine, and CRP-hs when contrasted with those without DE, *P*<0.05. Interestingly, the study did not identify a significant connection between using angiotensin-converting enzyme inhibitors/angiotensin receptor blockers medications and DE.

Table 2 Comparison of demographic and laboratory characteristics according to patients with different stages of hypertension *n* (%)

Parameters	Total (*n*=432)	Stage 1 (*n*=144)	Stage 2 (*n*=144)	Stage 3 (*n*=144)	*P*
Ages (y), mean±SD	61.26±11.31	56.79±12.4	60.3±10.65	66.69±8.22	<0.001
Gender					0.698
Male	170 (39.4)	60 (41.7)	53 (36.8)	57 (39.6)	
Female	262 (60.6)	84 (58.3)	91 (63.2)	87 (60.4)	
Duration of hypertension, median (IQR), y	7 (5-10)	5.5 (4.5-7)	6.8 (5-9.8)	9.8 (6.8-12)	<0.001
Systolic BP, mean±SD	133.48±18.42	131.24±19.31	133.74±16.73	135.46±19.0	0.148
Diastolic BP, mean±SD	80.81±9.39	79.38±8.75	80.02±8.65	83.04±10.34	0.002
ACEi/ARB	275 (63.7)	103 (71.5)	92 (63.9)	80 (55.6)	0.019
BMI (kg/m^2)					<0.001
<18.5	17 (3.9)	7 (4.9)	8 (5.6)	2 (1.4)	
18.5-22.9	209 (48.4)	92 (63.9)	54 (37.5)	63 (43.8)	
≥23.0	206 (47.7)	45 (31.3)	82 (56.9)	79 (54.9)	
Mean±SD	22.75±2.53	22.17±2.5	23.03±2.69	23.03±2.3	0.004
Lipid disorder	350 (81)	102 (70.8)	123 (85.4)	125 (86.8)	0.001
Diabetic mellitus	123 (28.5)	35 (24.3)	41 (28.5)	47 (32.6)	0.293
Cholesterol (mmol/L), mean±SD	5.15±1.17	4.89±1.2	5.35±1.17	5.23±1.09	0.003
Triglycerid (mmol/L), median (IQR)	1.49 (1.06-2.09)	1.36 (0.98-1.93)	1.5 (1.07-2.33)	1.55 (1.12-2.15)	0.022
LDL-C (mmol/L), mean±SD	3.09±0.85	2.82±0.87	3.23±0.84	3.22±0.76	<0.001
HDL-C (mmol/L), mean±SD	1.33±0.32	1.3±0.32	1.36±0.31	1.34±0.33	0.301
URE (mmol/L), median (IQR)	5.8 (4.9-7.27)	5.35 (4.33-6.29)	5.6 (4.69-6.89)	7.27 (5.43-9.0)	<0.001
Creatinine (μmol/L), median (IQR)	80.9 (71.4-96.7)	77.2 (68.3-84.22)	80.75 (71.4-96)	89.1 (74.8-103.6)	<0.001
CRP-hs (mg/L), median (IQR)	1.4 (0.9-2.1)	1.2 (07-2.1)	1.5 (0.9-2.1)	2.1 (0.9-3.1)	<0.001
OSDI (scale)					<0.001
Normal	252 (58.3)	105 (72.9)	86 (59.7)	61 (42.4)	
Mild	29 (6.7)	27 (18.8)	2 (1.4)	0	
Moderate	115 (26.6)	12 (8.3)	56 (38.9)	47 (32.6)	
Severe	36 (8.3)	0	0	36 (25)	
Median (IQR)	11 (9-27)	8 (6-14)	10.5 (9-26)	27 (10-32.75)	<0.001
Schirmer I (mm), median (IQR)	12 (7-13)	13 (9-14)	12 (7-14)	7 (5.25-12)	<0.001
DE	180 (41.7)	39 (27.1)	58 (40.3)	83 (57.6)	<0.001

SD: Standard deviation; IQR: Interquartile range; BP: Blood pressure; ACEi: Angiotensin converting enzyme inhibitors; ARB: Angiotensin receptor blockers; BMI: Body mass index; LDL-C: Low-density lipoprotein cholesterol; HDL-C: High-density lipoprotein cholesterol; CRP-hs: High sensitive C-reactive protein; OSDI: Ocular Surface Disease Index; DE: Dry eye; URE: Plasma urea.

Upon analysis, advanced age, prolonged hypertension duration, presence of diabetes mellitus, elevated plasma creatinine, and increased CRP-hs levels independently emerged as factors associated with DE in primary hypertension patients, *P*<0.01.

DISCUSSION

Ratio of Dry Eye in Primary Hypertension Patients Our study showed up to 41.7% of patients were diagnosed with DE (180/432 patients; Table 1). There are not many studies on DE in primary hypertension patients, but many studies have shown that DE is associated with hypertension in healthy people as well as in people with chronic disease. Marculino *et al*[17] studied the rate of DEs and the risk factors in 582 adults. The results showed that the rate of DEs accounted for 24.4%. DEs were more common in the hypertensive group (OR=1.98; 95%CI: 1.14-3.43, *P*=0.015). Ferrero *et al*[18] found that 34.4% of older people (≥65y) had DEs in a study of 1045 people, and hypertension was an independent factor related, *P*=0.014. The etiology of DE can vary among individual patients, potentially stemming from factors such as escalated permeability of the tear film and inflammation affecting both the ocular surface and lacrimal gland, as highlighted in reference[19]. The role of the inflammatory immune response in the development of DE has more recently been substantiated. This process initiates with the involvement of natural killer cells, which secrete interferon-gamma alongside other proinflammatory cytokines like interleukin-1, interleukin -6, and tumor necrosis factor-alpha. These factors prompt the upregulation of antigen-presenting cells at the ocular surface, consequently initiating an adaptive immune response. This response facilitates the infiltration of more inflammatory cells into the ocular surface,

Table 3 Comparison of demographic and laboratory characteristics in primary hypertension patients with and without DE *n* (%)

Parameters	Total (*n*=432)	With DE (*n*=180)	Without DE (*n*=252)	*P*
Ages (y), mean±SD	61.26±11.31	68.84±10.01	55.85±8.8	<0.001
Gender				0.816
Male	170 (39.4)	72 (40)	98 (38.9)	
Female	262 (60.6)	108 (60)	154 (61.1)	
Duration of hypertension, median (IQR), y	7 (5-10)	10 (9.05-12.07)	5.5 (4.5-6.7)	<0.001
ACEi/ARB	275 (63.7)	117 (65.0)	158 (62.7)	0.624
BMI (kg/m^2)				0.300
<18.5	17 (3.9)	9 (5)	8 (3.2)	
18.5-22.9	209 (48.4)	80 (44.4)	129 (51.2)	
≥23.0	206 (47.7)	91 (50.6)	115 (45.6)	
Mean±SD	22.75±2.53	22.69±2.58	22.79±2.49	0.680
Lipid disorder	350 (81.0)	154 (85.6)	196 (77.8)	0.042
Diabetic mellitus	123 (28.5)	91 (50.6)	32 (12.7)	<0.001
Cholesterol (mmol/L), mean±SD	5.15±1.17	5.24±1.13	5.09±1.19	0.208
Triglycerid (mmol/L), median (IQR)	1.49 (1.06-2.09)	1.57 (1.1-2.26)	1.4 (1.05-2.01)	0.102
LDL-C (mmol/L), mean±SD	3,09±0.85	3.18±0.82	3.02±0.86	0.047
HDL-C (mmol/L), mean±SD	1.33±0.32	1.31±0.33	1.35±0.31	0.297
URE (mmol/L), median (IQR)	5.8 (4.9-7.27)	7.27 (5.61-8.9)	5.37 (4.68-6.2)	<0.001
Creatinine (μmol/L), median (IQR)	80.9 (71.4-96.7)	99.1 (79.57-104.27)	75.7 (68.5-83.9)	<0.001
CRP-hs (mg/L), median (IQR)	1.4 (0.9-2.1)	2.1 (1.2-3.2)	1.1 (0.5-1.9)	<0.001
OSDI, median (IQR)	11 (9-27)	28 (26-31)	9 (7-10)	<0.001
Schirmer I (mm), median (IQR)	12 (7-13)	6 (5-7)	13 (12-14)	<0.001

DE: Dry eye; SD: Standard deviation; IQR: Interquartile range; ACEi: Angiotensin converting enzyme inhibitors; ARB: Angiotensin receptor blockers; BMI: Body mass index; LDL-C: Low-density lipoprotein cholesterol; HDL-C: High-density lipoprotein cholesterol; CRP-hs: High sensitive C-reactive protein; OSDI: Ocular Surface Disease Index; URE: Plasma urea.

damaging its integrity[20]. The mechanism underlying ocular damage in hypertensive patients exhibits a connection to ocular hypertension and glaucoma. This linkage arises due to the shared mechanisms and co-occurrence of hypertension and glaucoma[21]. Additionally, damage to the retina caused by hypertension and systemic inflammation in hypertensive patients contribute to ocular impairment, ultimately contributing to DE[7,22]. Consequently, our study's findings offer a more lucid depiction of the association between hypertension and DE.

Relation Dry Eye and Disease Stage, Some Factors in Primary Hypertension Patients Our results show that DE was elevated together with the hypertension stage at 27.1%, 40.3%, and 57.6%, respectively, for stages I, II, and III, *P*<0.001. Significantly, the OSDI score gradually increased, and the Schirmer value gradually decreased from the group of hypertensive patients stage I to III, *P*<0.001 (Table 2). We found that there were some factors related to this result because age, plasma creatinine, and CRP-hs levels increased gradually from the group of patients with stage I to stage III hypertension, *P*<0.001 (Table 2), that the factors have all been confirmed by previous studies to be related to DEs[20-23]. In multivariate analysis, we found that advanced age, long duration of hypertension, diabetes mellitus, elevated plasma creatinine, and CRP-hs are independent factors associated with DE in patients with primary hypertension, *P*<0.01 (Table 4). Several factors have been established to cause DE in the elderly, including lack of tears due to low production and evaporation and many abnormalities in the position of the eyelids, causing the tear

Table 4 Multivariate logistic regression analysis of some clinical variables related to DE in primary hypertension patients

Variable	OR	95%CI	*P*
Age	1.172	1.103-1.244	<0.001
Male	1.097	0.445-2.706	0.84
Duration of hypertension	2.273	1.805-2.862	<0.001
Diabetic mellitus	4.288	1.639-11.218	0.003
Lipid disorder	1.397	0.482-4.05	0.538
Plasma creatinine	1.091	1.053-1.131	<0.001
Plasma CRP-hs	1.998	1.201-3.323	0.008

OR: Odds ratio; CI: Confidence interval; CRP-hs: High sensitive C-reactive protein; DE: Dry eye.

film to break down more quickly[24-25]. DEs, lacrimation, photophobia, burning sensation, and visual dysfunction are common manifestations in diabetic patients[26]. CRP-hs is an inflammatory marker, a risk factor, and a predictor for various non-infectious diseases, including cardiovascular diseases such as coronary artery disease, peripheral vascular disease, and atherosclerosis[27]. Recently, under the illumination of molecular biology, the primary mechanism of inflammation-related DE has been confirmed[28-30]. Our results demonstrate that inflammation plays a role in the pathogenesis of DE in patients with primary hypertension.

Although the research goal has been achieved, the topic is still limited in some points. First, due to the lack of fluorescence, we could not perform tear film break up time to diagnose DE instead of OSDI and Schirmer test. Second, we could not analyze the relationship between hypertensive retina with DEs and related factors in primary hypertension patients, such as smoking, duration of diabetes, and lifestyle. Finally, the relationship between DEs and some characteristics of patients with primary hypertension had only been described through cross-sectional observations and had not been followed over a long period.

In conclusion, DE is a common disorder in primary hypertension patients, accounting for 41.7% (180/432 patients). Factors associated with DE include advanced age, prolonged disease duration, stage disease, diabetic mellitus, and increased plasma creatinine and CRP-hs levels.

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