Risk factors for hypertensive retinopathy in a Chinese population with hypertension: The Beijing Eye study

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Abstract. Hypertensive retinopathy (HRP) is a clinical feature and systemic manifestation of hypertension. There have been few reports on the risk factors for hypertensive retinopathy in China. The aim of the present study was to describe risk factors associated with HRP in a population-based sample of Chinese patients with hypertension in Beijing. The clinical data of 228 hypertensive patients was retrospectively studied, including 112 patients with retinopathy for the HRP group and 116 patients without retinopathy for the NO-HRP group. Basic clinical data and plasma clinical indicators of the two groups were compared. Logistic regression models were used to assess risk factors associated with HRP. Duration of hypertension, smoking habits, family history of hypertension, plasma level of endothelin-1 (ET-1) and systolic and diastolic blood pressure were significantly increased in the HRP group compared with the NO-HRP group (P<0.05). No significant differences were identified between the two groups for other factors. Logistic regression models indicated that hypertension duration (P<0.001, 95% CI: 0.962-0.988) and ET-1 level (P<0.001, 95% CI: 1.144-1.278) were significantly associated with HRP. The diagnostic threshold of ET-1 to diagnosis HRP was 43.5 ng/l. Of the factors studied, longer hypertension duration and elevated ET-1 level were identified to be risk factors for HRP in patients with hypertension from Beijing. Detecting the plasma level of ET-1 in patients with hypertension may be a useful diagnostic indicator for HRP.

Introduction

Hypertensive retinopathy (HRP) is a clinical feature and systemic manifestation of hypertension and one of the leading causes of visual impairment among adult patients with hypertension (1,2). The visual impairment is devastating in people of working age in industrialized countries and affects the daily lives of millions of people. Epidemiological studies, conducted in Chinese patients with hypertension, have indicated that 67-73% of patients have fundus lesions and 12-15% have retinopathy (3,4). Hypertensive retinopathy is a risk factor for stroke (5), cardiovascular disease (6,7) and cerebrovascular disease (8). Therefore, it is important to study the risk factors of retinopathy in hypertensive patients, in order to reduce the incidence of hypertensive retinopathy and associated cardiovascular and cerebrovascular diseases (9,10).

In recent decades, the prevalence of hypertension in China has increased substantially due to the ageing population and changes in diet, particularly in eastern populations that account for 60% of China's total population (11,12). There have been few reports on the risk factors for hypertensive retinopathy in China. However, a report on diabetic retinopathy indicated that longer diabetes duration and elevated blood pressure are risk factors for diabetic retinopathy in Chinese patients with diabetes (13).

In the present study, the clinical data of 228 hypertensive patients were retrospectively studied in order to identify any associations between HRP and basic clinical data or plasma parameters, with the aim of revealing risk factors for HRP.

Patients and methods

Ethics statement. The present study was performed with the approval of the Ethics Committee of Beijing Friendship Hospital Affiliated to Capital Medical University (Beijing, China). All aspects of the study complied with the Declaration of Helsinki (14). In addition, all participants provided written informed consent for the use of their data in the present study.

Patients. A total of 228 patients with essential hypertension were recruited from Beijing Friendship Hospital from August 2016 to June 2017. Patients with essential hypertension were diagnosed according to WHO/1SH1999 guidelines (15). All patients underwent retinal photography to diagnose whether retinopathy was present (5), then they were divided into a retinopathy group (HRP) and a non-retinopathy group (NO-HRP). Exclusion criteria for the study included the presence of secondary hypertension, diabetes, pregnancy,

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hepatic failure, heart failure, goiter, malignant neoplasms or nephropathy (creatinine, ≥120 mol/l), or the patient having received blood products within the previous 15 days.

Clinical parameters. The sex and age of each patient was recorded. In addition, the patients were asked whether they smoked and whether they had a family history of hypertension (a parent or grandparent with hypertension was considered to indicate a family history of hypertension). The height and weight of all participants was measured and body mass index was calculated as follows: Body mass index (kg/m^2) = weight (kg)/height^2 (m).

The patients were allowed to rest for ≥10 min before systolic blood pressure (mmHg) and diastolic blood pressure (mmHg) were measured using an automated blood pressure monitor (EW3106; Panasonic, Osaka, Japan). A repeated measurement was performed on a different day (with an interval of ≥2 weeks) and the mean average of the two measurements was calculated (16).

Ophthalmologic examination. A 45˚ non-mydriatic retinal photograph centered on the region of the optic disc and macula was taken from one randomly selected eye following 5 min of dark adaption. Three professional ophthalmologists evaluated the images for signs of retinopathy. If ambiguity was observed, the majority of votes were taken into account. Macular field: Where the exact center of the optic disc is laid at the nasal end of the horizontal meridian of the field view. Disc/nasal field: Where the optic disc is positioned one disc-diameter in from the temporal edge of the field on the horizontal meridian. The details of the macular and disc/nasal field, and the method of ophthalmologic examination were as described previously (17). Keithy-Wagener grading standards (18) was used for fundus grading: Level I was defined as retinal artery thinning with reflective enhancement; Level II demonstrated retinal artery stenosis and arteriovenous cross oppression; Level III was based on the vascular lesions of level I and II, with cotton-like exudate; and Level IV was allocated on the basis of optic disc edema.

Blood samples. Peripheral blood (5-10 ml) was collected and EDTA was added, then the sample was centrifuged (1,000 x g, at room temperature) for 10 min (5810R; Eppendorf, Hamburg, Germany) to collect plasma. The plasma levels of total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-chol), low-density lipoprotein cholesterol (LDL-chol), apolipoprotein A (ApoA) and apolipoprotein B (ApoB) were measured using an automatic biochemical analyzer (AU680; Beckman Coulter, Inc., Brea, CA, USA) (19).

The plasma level of endothelin-1 (ET-1) was measured as previously described (20). Briefly, a C18 sep-column (Thermo Fisher Scientific, Inc., Waltham, MA, USA) was used to extract ET-1 from plasma. A radioimmunoassay kit (cat. no. JK0088; Peninsula Laboratories International, Inc., San Carlos, CA, USA) was used to detect the concentration of ET-1 (21,22).

Statistical analysis. SPSS 20.0 (IBM Corp., Armonk, NY, USA) was used for data analysis. Measurement data are expressed as the mean ± SD. Comparisons between two groups were performed using Student's t-test or χ^2 tests. One-way ANOVA with Duncan's post hoc test was used for comparing multiple groups. The correlation between plasma level of ET-1 and hypertension duration in patients with hypertensive retinopathy was analyzed by Pearson's correlation coefficient. Logistic regression models were constructed to determine the odds ratio (OR) and 95% confidence interval (CI) for putative risk factors associated with HRP. Receiver operating characteristic curve (ROC) was used for to analyze the diagnostic value of ET-1 in HRP. P<0.05 was considered to indicate a statistically significant difference.

Results

Basic clinical data. The basic clinical data of the HRP group (n=112) and the NO-HRP group (n=116) are presented in Table I. There was no significant difference in age (P=0.924), sex (P=0.372) or body mass index (P=0.933) between the two groups. However, the hypertension duration (P=0.001), systolic blood pressure (P=0.003) and diastolic blood pressure (P=0.004) were significantly higher in the HRP group compared with the NO-HRP group.

Of the 112 patients in the HRP group, 79 (70.53%) had a family history of hypertension, which was significantly higher compared with the NO-HRP group (67/116; 57.76%; P=0.044). Furthermore, 69/112 (61.61%) patients in the HRP group smoked, which was significantly higher compared with the NO-HRP group 50/116 (43.10%; P=0.005).

Plasma index. Blood samples were taken from patients in each group and centrifuged to separate the plasma. Then, plasma levels of TC, TG, HDL-chol, LDL-chol, ApoA, ApoB and ET-1 were detected. The results are presented in Table II. No significant differences in TC (P=0.824), TG (P=0.751), HDL-chol (P=0.724), LDL-chol (P=0.129), ApoA (P=0.521) or ApoB (P=0.804) were observed between the HRP group and the NO-HRP group. However, the plasma levels of ET-1 were significantly higher in the HRP group compared with the NO-HRP group (P<0.001).

Logistic regression. To identify risk factors for HRP, logistic regression analysis was performed with HRP as the dependent variable and age, sex, hypertension duration, body mass index, family history of hypertension, smoking habit, systolic blood pressure, diastolic blood pressure, TC, TG, HDL-chol, LDL-chol, ApoA, ApoB and ET-1 levels as independent variables. The results indicated that hypertension duration (P<0.001, 95% CI: 0.962-0.988) and ET-1 level (P<0.001, 95% CI: 1.144-1.278) were significantly associated with the presence of HRP (Table III).

Diagnostic significance of plasma levels of ET-1. Of the 112 patients in the HRP group, 40 were stage I, 33 were stage II, 23 were stage III and 16 were stage IV, which was based on Keithy-Wagener grading standards. The mean ET-1 level of stage I, stage II, stage III and stage IV patients was 50.33±17.20, 61.97±14.51, 84.52±11.37 and 104.06±15.76, respectively, and the level of ET-1 significantly increased with each increase in disease stage (P<0.01; Fig. 1A). In addition, the plasma level of ET-1 was positively correlated with hypertension duration (r=0.842, P<0.01; Fig. 1B).

Table I. Basic clinical data of the HRP and NO-HRP groups.

Variables	HRP (n=112)	NO-HRP (n=116)	t or χ^2	P-value
Age (years)	58.10±9.67	58.23±11.36	0.096	0.924
Sex				
Male	48	43	0.796	0.372
Female	64	73		
Hypertension duration (months)	121.16±85.35	83.16±82.11	3.426	0.001
Body mass index (kg/m^2)	25.08±3.01	25.11±3.12	0.085	0.933
Family history of hypertension				
Yes	79	67	4.039	0.044
No	33	49		
Smoking				
Yes	69	50	7.819	0.005
No	43	66		
Systolic blood pressure (mmHg)	156.00±19.01	149.19±14.34	3.057	0.003
Diastolic blood pressure (mmHg)	98.54±11.89	94.67±7.77	2.921	0.004

HRP, hypertensive retinopathy; NO-HRP, no hypertensive retinopathy.

Table II. Plasma levels of TC, TG, HDL-chol, LDL-chol, ApoA, ApoB and ET-1 in the HRP and NO-HRP groups.

Variable	HRP (n=112)	NO-HRP (n=116)	t	P-value
TC (mmol/l)	5.29±0.88	5.26±1.07	0.233	0.824
TG (mmol/l)	1.94±0.45	1.92±0.52	0.318	0.751
HDL-chol (mmol/l)	1.33±0.24	1.31±0.30	0.353	0.724
LDL-chol (mmol/l)	3.48±0.24	3.42±0.29	1.523	0.129
ApoA (g/l)	1.11±0.17	1.13±0.21	0.643	0.521
ApoB (g/l)	0.91±0.14	0.90±0.16	0.248	0.804
ET-1 (ng/l)	68.46±24.31	29.44±14.46	14.738	<0.001

TC, total cholesterol; TG, triglycerides; HDL-chol, high-density lipoprotein cholesterol; LDL-chol, low-density lipoprotein cholesterol; ApoA, apolipoprotein A; ApoB, apolipoprotein B; ET-1, endothelin-1; HRP, hypertensive retinopathy; NO-HRP, no hypertensive retinopathy.

As indicated in Fig. 1C, the receiver operating characteristic (ROC) curve of ET-1 for HRP exhibited an area under the curve (AUC) of 0.918. The Youden index was largest when plasma level of ET-1 was 43.5 ng/l, suggesting a diagnostic threshold of 43.5 ng/l for ET-1 (sensitivity 85.7%, specificity 86.2%).

Discussion

Hypertension, one of the most common chronic diseases in middle-aged and elderly people, is a primary risk factor for the occurrence of cardiovascular and cerebrovascular diseases (23). Recently, hypertension has increasingly gained the attention of researchers (24,25). The retina is the only place in the body where it is possible to see small blood vessels and their changes, using an eye mirror (26,27). Since retinal arteriolar stenosis is considered to be a typical sign of HRP and a sign of target organ damage, retinopathy is of great importance in estimating the duration, severity and prognosis of hypertension. In the early stages of hypertension, most of the fundus blood vessels are normal. However, with the development of the disease, the formation of atherosclerotic plaques gradually increases the thickness and decreases the diameter of blood vessels, followed by the development of arteriosclerosis and the corresponding retinopathy. Eventually, this results in decreased vision for patients and in severe cases, blindness (28,29).

In the present study on adults from Beijing, it was demonstrated that the duration of hypertension, family history of hypertension, percentage of smokers, blood pressure and plasma level of ET-1 were significantly increased in the HRP group compared with the NO-HRP group. Previous research reported a positive correlation between retinopathy and blood pressure in patients with hypertension (30). Following an increase in blood pressure, the microcirculation of the retina will be damaged to varying degrees (30). However, the

Table III. Logistic regression analysis with hypertensive retinopathy as the dependent variable.

Variable	B	S.E.	Wald	Sig.	Exp(B)	95% CI
Age	-0.049	0.030	2.675	0.102	0.953	0.899-1.010
Sex	0.891	0.670	1.767	0.184	2.437	0.655-9.063
Hypertension duration	-0.025	0.007	13.540	<0.001	0.975	0.962-0.988
Body mass index	-0.106	0.102	1.074	0.300	0.900	0.736-1.099
Family history of hypertension	-0.351	0.641	0.300	0.584	0.704	0.201-2.471
Smoking	-1.085	0.579	3.513	0.061	0.338	0.109-1.051
Systolic blood pressure	0.037	0.048	0.598	0.439	1.037	0.945-1.139
Diastolic blood pressure	-0.003	0.083	0.002	0.968	0.997	0.847-1.172
TC	-0.276	0.714	0.149	0.700	0.754	0.187-3.076
TG	0.736	1.053	0.488	0.485	2.087	0.265-16.426
HDL-chol	0.829	2.810	0.087	0.768	2.291	0.009-564.45
LDL-chol	1.531	1.709	0.802	0.371	4.621	0.162-131.75
ApoA	-8.536	4.010	4.532	0.053	0.000	0.000-0.508
ApoB	5.705	3.290	3.007	0.083	300.349	0.488-20.646
ET-1	0.190	0.028	45.223	<0.001	1.210	1.144-1.278

TC, total cholesterol; TG, triglycerides; HDL-chol, high-density lipoprotein cholesterol; LDL-chol, low-density lipoprotein cholesterol; ApoA, apolipoprotein A; ApoB, apolipoprotein B; ET-1, endothelin-1; CI, confidence interval.

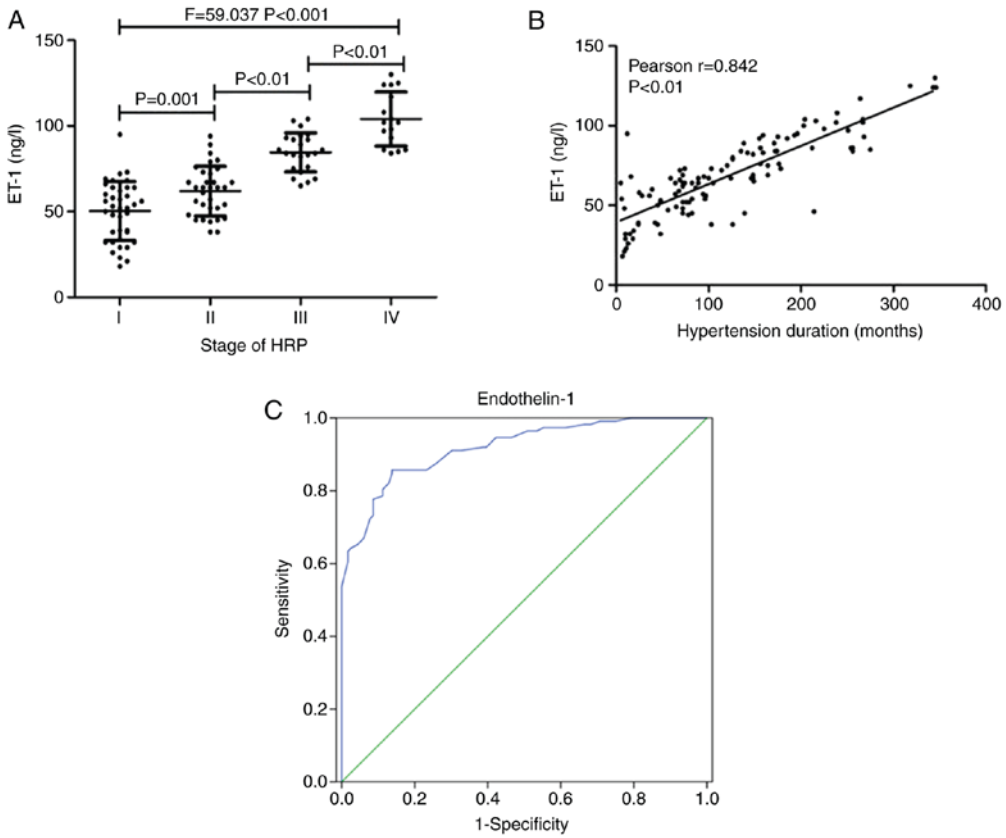

Figure 1. Plasma levels of ET-1 as a biomarker for HRP. (A) Plasma levels of ET-1 at different stages of HRP. (B) Correlation between plasma level of ET-1 and hypertension duration in patients with HRP. (C) Receiver operating characteristic curve for plasma level of ET-1 in HRP. ET-1, endothelin-1; HRP, hypertensive retinopathy.

risk of retinopathy is reduced if blood pressure is controlled effectively. This is why blood pressure was included in the regression analysis, since it may be affected by long-term use of anti-hypertensive drugs in patients with hypertension. However, the occurrence of HRP appears to be affected by multiple factors. Thus, logistic regression analysis was

performed to identify the risk factors for HRP in a sample of adults from Beijing. In the present study, it was identified that longer duration of hypertension and higher plasma level of ET-1 were risk factors for HRP.

ETs are the strongest known vasoconstrictors and form a peptide family that includes three subtypes. ET-1 is the most abundant and important of the three subtypes of ET and is primarily produced by vascular endothelial cells (31,32). Previous research has demonstrated that ET-1 serves a key function not only in the occurrence and development of hypertension, but also in target organ damage of hypertension, including carotid atherosclerosis (33), left ventricular hypertrophy fibrosis (34) and renal damage (35). Retinopathy reflects small blood vessel disease in patients with hypertension and the severity of HRP is significantly associated with target organ damage in hypertension (36). Therefore, the occurrence of HRP may also be associated with ET-1. In the present study, plasma ET-1 levels were measured in 112 patients with HRP and a positive correlation was identified between plasma level of ET-1 and the duration of hypertension. Higher levels of plasma ET-1 were also associated with more severe HRP.

In a normal physiological state, low concentrations of ET-1 serve key functions in the regulation and maintenance of retinal vasomotor and blood flow stability by binding specific receptors (37). However, in hypertension, the blood is in a highly solidified state, which causes the blood flow rate to slow down and results in tissue ischemia and hypoxia (38). ET-1 is released and accumulates when vascular endothelial cells are damaged due to ischemia and hypoxia (39,40). Furthermore, high concentrations of ET-1 may cause severe damage to the blood-retinal barrier, impaired endothelial cell function, increased vascular permeability and consequent retinal capillary leakage (41-43). Therefore, the vessel wall shear force changed with high blood pressure, which caused elevated plasma ET-1 levels. Furthermore, retinal arteriolar contraction, vascular endothelial dysfunction and other changes are caused by binding between ET-1 and the ET-1 receptor, resulting in thin blood vessels and other retinal lesions (44).

To evaluate the diagnostic value of ET-1 for hypertension retinopathy, the AUC of a diagnostic ROC curve was calculated. The AUC of ET-1 was demonstrated to be 0.918 and the sensitivity was 85.7% and specificity was 86.2% when the diagnostic threshold of ET-1 was 43.5 ng/l. Based on these results, is it proposed that ET-1 may be a useful diagnostic indicator for HRP.

In conclusion, in patients with hypertension from Beijing, hypertension duration, family history of hypertension, smoking, blood pressure and plasma level of ET-1 are associated with HRP. Hypertension duration and plasma level of ET-1 are risk factors for HRP. In addition, detecting the plasma level of ET-1 in patients with hypertension may be a useful diagnostic indicator for HRP.

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Availability of data and materials

The analyzed datasets generated during the present study are available from the corresponding author on reasonable request.

Authors' contributions

YW made substantial contributions to the conception and design. YZ contributed to the acquisition, analysis and interpretation of data. YZ was responsible for the acquisition, analysis and interpretation of data, and assisted in drafting the manuscript and revising it critically for important intellectual content. LZ and HL contributed to the analysis and interpretation of data, drafted the manuscript and revised it critically for important intellectual content. All authors have read and approved this manuscript.

Ethics approval and consent to participate

The present study was performed with the approval of the Ethics Committee of Beijing Friendship Hospital Affiliated to Capital Medical University (Beijing, China). All aspects of the study complied with the Declaration of Helsinki. In addition, all participants provided written informed consent for the use of their data in the present study.

Consent for publication

Not applicable.

Competing interests

All authors have no conflict of interest to declare.

References

1. Wang J, Chen H, Zhang H, Yang F, Chen RP, Li YB, Yang C, Lin SD, Chen LS, Liang GX and Cai DH: The performance of a diabetic retinopathy risk score for screening for diabetic retinopathy in Chinese overweight/obese patients with type 2 diabetes mellitus. Ann Med 46: 417-423, 2014.
2. Stryjewski TP, Papakostas TD and Vavvas D: Proliferative hypertensive retinopathy. JAMA Ophthalmol 134: 345-346, 2016.
3. Erden S and Bicakci E: Hypertensive retinopathy: Incidence, risk factors and comorbidities. Clin Exp Hypertens 34: 397-401, 2012.
4. Del Brutto OH, Mera RM, Viteri EM, Pólit J, Ledesma EA, Cano JA, Plaza KJ, Zambrano M and Costa AF: Hypertensive retinopathy and cerebral small vessel disease in amerindians living in rural ecuador: The atahualpa project. Int J Cardiol 218: 65-68, 2016.
5. Ong YT, Wong TY, Klein R, Klein BE, Mitchell P, Sharrett AR, Couper DJ and Ikram MK: Hypertensive retinopathy and risk of stroke. Hypertension 62: 706-711, 2013.
6. Sairenchi T, Iso H, Yamagishi K, Irie F, Okubo Y, Gunji J, Muto T and Ota H: Mild retinopathy is a risk factor for cardiovascular mortality in Japanese with and without hypertension: The Ibaraki prefectural health study. Circulation 124: 2502-2511, 2011.
7. Wong TY and Mcintosh R: Hypertensive retinopathy signs as risk indicators of cardiovascular morbidity and mortality. Br Med Bull 73-74: 57-70, 2005.
8. Kabedi NN, Kayembe DL, Mwanza JC, Lepira FB and Kayembe TK: Hypertensive retinopathy and its association with cardiovascular, renal and cerebrovascular morbidity in Congolese patients. Cardiovasc J Afr 25: 228-232, 2014.-
9. Schmieder RE: Hypertensive retinopathy: A window to vascular remodeling in arterial hypertension. Hypertension 51: 43-44, 2008.

10. Grosso A, Veglio F, Porta M, Grignolo FM and Wong TY: Hypertensive retinopathy revisited: Some answers, more questions. Br J Ophthalmol 89: 1646-1654, 2005.
11. Li D, Lv J, Liu F, Liu P, Yang X, Feng Y, Chen G and Hao M: Hypertension burden and control in mainland China: Analysis of nationwide data 2003-2012. Int J Cardiol 184: 637-644, 2015.
12. Li W, Gu H, Teo KK, Bo J, Wang Y, Yang J, Wang X, Zhang H, Sun Y, Jia X, *et al*: Hypertension prevalence, awareness, treatment and control in 115 rural and urban communities involving 47â€Š000 people from China. J Hypertens 34: 39-46, 2016.
13. Wang FH, Liang YB, Peng XY, Wang JJ, Zhang F, Wei WB, Sun LP, Friedman DS, Wang NL and Wong TY; Handan Eye Study Group: Risk factors for diabetic retinopathy in a rural Chinese population with type 2 diabetes: The handan eye study. Acta Ophthalmol 89: e336-e343, 2011.
14. World Medical Association. World Medical Association Declaration of Helsinki. Ethical principles for medical research involving human subjects. Bulletin of the World Health Organization 79: 373, 2001.
15. World Health Organization (WHO): Guidelines on Basic Training and Safety in Acupuncture. WHO, Geneva, 1999.
16. Kapil V, Khambata RS, Robertson A, Caulfield MJ and Ahluwalia A: Dietary nitrate provides sustained blood pressure lowering in hypertensive patients: A randomized, phase 2, double-blind, placebo-controlled study. Hypertension 65: 320-327, 2015.
17. Athikarisamy SE, Patole S, Lam GC, Dunstan C and Rao S: Screening for retinopathy of prematurity (ROP) using wide-angle digital retinal photography by non-ophthalmologists: A systematic review. Br J Ophthalmol 99: 281-288, 2015.
18. Downie LE, Hodgson LA, Dsylva C, McIntosh RL, Rogers SL, Connell P and Wong TY: Hypertensive retinopathy: Comparing the keith-wagener-barker to a simplified classification. J Hypertens 31: 960-965, 2013.
19. Gholamhossein Y, Behrouz H and Asghar Z: Diabetic retinopathy risk factors: Plasma erythropoietin as a risk factor for proliferative diabetic retinopathy. Korean J Ophthalmol 28: 373-378, 2014.
20. Finzi A, Cellini M, Strobbe E and Campos EC: ET-1 plasma levels, choroidal thickness and multifocal electroretinogram in retinitis pigmentosa. Life Sci 118: 386-390, 2014.
21. Bossard M, Pumpol K, van der Lely S, Aeschbacher S, Schoen T, Krisai P, Lam T, Todd J, Estis J, Risch M, *et al*: Plasma endothelin-1 and cardiovascular risk among young and healthy adults. Atherosclerosis 239: 186-191, 2015.
22. Höglund K, Lequarré AS, Ljungvall I, Mc Entee K, Merveille AC, Wiberg M, Gouni V, Lundgren Willesen J, Hanås S, Wess G, *et al*: Effect of breed on plasma endothelin-1 concentration, plasma renin activity and serum cortisol concentration in healthy dogs. J Vet Int Med 30: 566-573, 2016.
23. Poulter NR, Prabhakaran D and Caulfield M: Hypertension. Lancet 386: 801-812, 2015.
24. Mitchell GF: Arterial stiffness and hypertension: Chicken or egg? Hypertension 64: 210-214, 2014.
25. Zeeb H, Hegewald J, Schubert M, Wagner M, Dröge P, Swart E and Seidler A: Traffic noise and hypertension-results from a large case-control study. Environ Res 157: 110-117, 2017.
26. Rizzoni D and Muiesan ML: Retinal vascular caliber and the development of hypertension: A meta-analysis of individual participant data. J Hypertens 32: 225-227, 2014.
27. Muraoka Y, Tsujikawa A, Kumagai K, Akiba M, Ogino K, Murakami T, Akagi-Kurashige Y, Miyamoto K and Yoshimura N: Age- and hypertension-dependent changes in retinal vessel diameter and wall thickness: An optical coherence tomography study. Am J Ophthalmol 156: 706-714, 2013.
28. Li G, Shih YY, Kiel JW, De La Garza BH, Du F and Duong TQ: MRI study of cerebral, retinal and choroidal blood flow responses to acute hypertension. Exp Eye Res 112: 118-124, 2013.
29. Masaidi M, Cuspidi C, Giudici V, Negri F, Sala C, Zanchetti A, Grassi G and Mancia G: Is retinal arteriolar-venular ratio associated with cardiac and extracardiac organ damage in essential hypertension? J Hypertens 27: 1277-1283, 2009.
30. Schmieder RE: Hypertensive retinopathy. Ophthalmologica 18: 233-234, 2009.
31. Sarafidis PA and Bakris GL: Review: Insulin and endothelin: An interplay contributing to hypertension development? J Clin Endocrinol Metab 92: 379-385, 2007.
32. Lankhorst S, Kappers MH, van Esch JH, Danser AH and van den Meiracker AH: Mechanism of hypertension and proteinuria during angiogenesis inhibition: Evolving role of endothelin-1. J Hypertens 31: 444-454, 2013.
33. Jin Z, Luxiang C, Huadong Z, Zhiqiang X, Lihua H and Huiyun L: C-338A polymorphism of the endothelin-converting enzyme-1 gene and the susceptibility to carotid atherosclerosis. Microvasc Res 78: 128-131, 2009.
34. DeMing F: GW24-e1006 Effects of telmisartan on left ventricular hypertrophy and expression of endothelin-1 in spontaneously hypertensive rats. Heart 99: A30-A31, 2013.
35. Heimlich JB, Speed JS, O'Connor PM, Pollock JS, Townes TM, Meiler SE, Kutlar A and Pollock DM: Endothelin-1 contributes to the progression of renal injury in sickle cell disease via reactive oxygen species. Br J Pharmacol 173: 386-395, 2016.
36. Habib A, Alomari MA, Khaleghi M, Morgenthaler NG, Struck J, Bergmann A, Mosley TH, Turner ST and Kullo IJ: Plasma C-terminal pro-endothelin-1 is associated with target-organ damage in African Americans with hypertension. Am J Hypertens 23: 1204-1208, 2010.
37. Salvatore S and Vingolo EM: Endothelin-1 role in human eye: A review. J Ophthalmol 2010: 354645, 2010.
38. Chen Y, Hu S, Wu L, Fang X, Xu W and Shen G: Clinical practice guidelines for hypertension in China: A systematic review of the methodological quality. BMJ Open 5: e008099, 2015.
39. Li X, Liu KL, Zheng JQ, Chi MG, Dong JJ, Dong SJ and Gong ZH: Pharmacological characterization of 3-azabicyclo[3,2,1] octane-1-yl-l-leucyl-d-tryptophanyl-d-4-Cl-phenylalanine: A novel ET(A) receptor-selective ant. Pulm Pharmacol Ther 21: 780-787, 2008.
40. Prayitnaningsih S, Sujuti H, Hamid AA, Permatasari N and Widodo MA: The effect of hypertension on intraocular pressure and apoptosis of retinal ganglion cell through ET-1 signaling pathway activation in trabecular meshwork of hypertension rat model. Acta Ophthalmologica 93, 2015.
41. Tran HV, Emoto N, Vignon-Zellweger N, Nakayama K, Yagi K, Suzuki Y and Hirata KI: Analysis of ET-1 system in mild and severe pulmonary arterial hypertension in mice. Life Sciences 93: e47-e47, 2013.
42. Vizza CD, Letizia C, Badagliacca R, Poscia R, Pezzuto B, Gambardella C, Nona A, Papa S, Marcon S, Mancone M, *et al*: Relationship between baseline ET-1 plasma levels and outcome in patients with idiopathic pulmonary hypertension treated with bosentan. Int J Cardiol 167: 220-224, 2013.
43. Gu X, Li H, Zhu X, Gu H, Chen J, Wang L, Harding P and Xu W: Inverse correlation between plasma adropin and ET-1 levels in essential hypertension: A cross-sectional study. Medicine (Baltimore) 94: e1712, 2015.
44. Oku H, Fukuhara M, Komori A, Okuno T, Sugiyama T and Ikeda T: Endothelin-1 (ET-1) causes death of retinal neurons through activation of nitric oxide synthase (NOS) and production of superoxide anion. Exp Eye Res 86: 118-130, 2008.