Papers

Value of routine funduscopy in patients with hypertension: systematic review

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Abstract

Objective To evaluate the additional value of funduscopy in the routine management of patients with hypertension.
Design Systematic review.
Participants Adults aged 19 or more with hypertensive retinopathy.
Data sources Medline, Embase, and the Cochrane Library from 1990.
Review methods Studies were included that assessed hypertensive retinopathy with blinding for blood pressure and cardiovascular risk factors. Studies on observer agreement had to be assessed by two or more observers and expressed as a κ statistic. Studies on the association between hypertensive retinopathy and hypertensive organ damage were carried out in patients with hypertension. The association between hypertensive retinopathy and cardiovascular risk was carried out in unselected normotensive and hypertensive people without diabetes mellitus.
Results The assessment of microvascular changes in the retina is limited by large variation between observers. The positive and negative predictive values for the association between hypertensive retinopathy and blood pressure were low (47% to 72% and 32% to 67%, respectively). Associations between retinal microvascular changes and cardiovascular risk were inconsistent, except for retinopathy and stroke. The increased risk of stroke, however, was also present in normotensive people with retinopathy. These studies did not adjust for other indicators of hypertensive organ damage.
Conclusion Evidence is lacking that routine funduscopy is of additional value in the management of hypertensive patients.

Introduction

Since 1939 the Keith, Wagener, and Barker classification has been used to assess retinal changes associated with hypertension. From the 1980s onwards, screening for hypertension and antihypertensive treatment have improved considerably and the severity and frequency of retinal changes associated with hypertension seem to have diminished.[1 2] In the recent guidelines of the Joint National Committee and the European Society of Hypertension, funduscopy is still recommended as part of the routine examination of hypertensive patients, although its value is being questioned.[3 4]

We carried out a systematic search to determine the usefulness of routine funduscopy in hypertensive patients. Firstly, we reviewed the literature on the reliability of detecting the various retinal changes associated with hypertension. Then we reviewed articles published since 1990 on the prevalence of retinal changes and their association with blood pressure, other indicators of hypertensive organ damage, and cardiovascular morbidity and mortality. We excluded studies in patients with hypertensive urgencies and emergencies as this is a separate group in whom funduscopy provides essential information for diagnosis and treatment.

Keith, Wagener, and Barker classification of hypertensive retinopathy

Grade I—slight or modest narrowing of the retinal arterioles, with an arteriovenous ratio ≥ 1:2

Grade II—modest to severe narrowing of retinal arterioles (focal or generalised), with an arteriovenous ratio < 1:2 or arteriovenous nicking

Grade III—bilateral soft exudates or flame-shaped haemorrhages

Grade IV—bilateral optic nerve oedema

Methods

We systematically searched Medline, Embase, and the Cochrane Library for articles on hypertension and retinopathy published since 1990 in adults aged 19 or more. Two investigators (BJHvdB and CAAH) independently carried out the search using the terms retinopathy, retinal arteriolar narrowing, arteriovenous nicking, AV nicking, arteriovenous ratio, or AV ratio, combined either with observer agreement, observer variability, or kappa, or with hypertension, blood pressure, microalbuminuria, left ventricular hypertrophy, intima-media thickness, stroke, myocardial infarction, ischaemic heart disease, or cardiovascular mortality.

We use the term hypertensive retinopathy to describe all retinal changes included in the Keith, Wagener, and Barker classification (box). We use the term retinal microvascular changes to refer to narrowing of the retinal arterioles and arteriovenous nicking (see figs A and B on bmj.com). The term retinopathy was originally used to denote soft exudates and flame-shaped haemorrhages only (see fig C on bmj.com), but in the studies reviewed here retinopathy also encompasses microaneurysms, blot haemorrhages, and hard exudates.

We included studies on the reliability of detecting changes to the retina if retinal photographs were independently assessed by

Figures showing retinal changes are on bmj.com

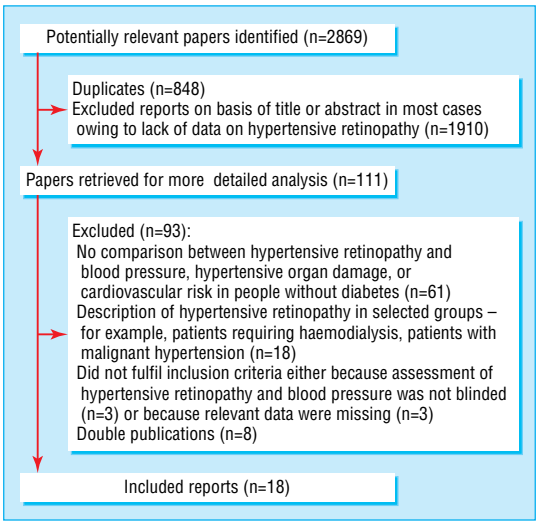

Fig 1 Selection of articles

two or more observers and if variability of detecting retinal changes associated with hypertension could be expressed as a κ statistic.

For the association between retinal changes and hypertensive organ damage we included studies of hypertensive patients only. For the association between hypertensive retinopathy, cardiovascular risk, and blood pressure, we included population based or cohort studies with unselected normotensive and hypertensive people. In all studies, retinal changes had to be assessed without knowledge of blood pressure and cardiovascular risk factors, and diabetes mellitus had to be excluded, analysed separately, or adjusted for in multivariate analysis. Searches were carried out in the second half of October 2004.

Statistical analysis

We used κ statistics to express the proportion of agreement for the various retinal changes associated with hypertension, correcting for agreement expected by chance.[5] We included both weighted and unweighted κ statistics, where weighted κ provides a scaled probability score so that the sum of the weight equals the number of observations.

For the association between blood pressure and retinal changes we considered the various retinal changes as a diagnostic test for hypertension. We calculated sensitivity, specificity, and positive and negative predictive values. Pooled odds ratios were calculated for the association between hypertensive retinopathy and hypertensive organ damage. We used a random effects model to generate summary measures and confidence intervals. Heterogeneity was examined using the I^2 statistic, which indicates the proportion of variability in the weighted mean differences attributable to heterogeneity.[6] To assess the association between hypertensive retinopathy and cardiovascular risk, we took the relative risk after multivariate analysis.

Results

We identified 111 reports with possible data on the association between hypertensive retinopathy and blood pressure, hypertensive organ damage, and cardiovascular risk (fig 1).

Variability in detecting retinal changes

Six studies had data on interobserver agreement for hypertensive retinopathy using retinal photographs. We found no such data for direct funduscopy. One study was excluded because we could not calculate κ statistics.[7] The most extensive study on observer agreement for hypertensive retinopathy was the atherosclerosis risk in communities study in which three readers graded a random sample of 206 retinal photographs.[8] Table 1 lists the κ statistics of this and other studies. In these studies, interobserver agreement was fair or moderate for focal arteriolar narrowing (κ 0.3 to 0.4) and arteriovenous nicking (κ 0.4 to 0.6). Agreement was excellent for haemorrhages and exudates. A computerised grading method was used to assess the arteriovenous ratio.[9] With this method, agreement was good (κ 0.7 to 0.8).

Retinal changes and blood pressure

Four large population based studies examined the association between hypertensive retinopathy and blood pressure.[1 12 14–16] Hypertension was defined as the use of antihypertensive drugs, or history of hypertension or blood pressure ≥ 140/90 mm Hg in the cardiovascular health study and atherosclerosis risk in communities study or ≥ 160/95 mm Hg in the Beaver Dam eye study and Blue Mountains eye study.

In one study, age and sex standardised prevalence of hypertensive retinopathy was 12% in white Europeans and 18% in people of Afro-Caribbean origin.[10] Table 2 lists the prevalence of retinal abnormalities for the other studies.

The sensitivity for hypertensive retinopathy ranged from 3% to 21%, indicating a low prevalence of retinal abnormalities in hypertensive patients. In contrast, specificity ranged from 88% to 98%, and therefore retinopathy was rarely observed in normotensive patients. The positive predictive value, or the chance of hypertension given the presence of hypertensive retinopathy, ranged from 47% to 70% for haemorrhages and exudates, 53% to 66% for arteriovenous nicking, and 49% to 72% for focal arteriolar narrowing (table 3). The negative predictive value, or the chance of normotension in the absence of hypertensive retinopathy, ranged from 43% to 67% for haemorrhages and exudates, 44% to 66% for arteriovenous nicking, and 32% to 59% for focal arteriolar narrowing. Diagnostic accuracy could not be assessed for the arteriovenous ratio as normal and abnormal values were not defined.

Table 1 Kappa statistics for hypertensive retinopathy in studies included in systematic review

Type of retinal change and study	Unweighted κ	Weighted κ
Any retinopathy:		
Sharp et al[10]	Afro-Caribbeans 0.72; white Europeans 0.75	Not reported
Haemorrhages and exudates:		
Atherosclerosis risk in communities study[8]	0.76	0.76
Cardiovascular health study[11]	0.88	Not reported
Blue Mountains eye study[12]	0.90	Not reported
Arteriovenous nicking:		
Atherosclerosis risk in communities study[8]	0.59	0.56
Cardiovascular health study[11]	0.43	Not reported
Focal arteriolar narrowing:		
Atherosclerosis risk in communities study[8]	0.39	0.29
Cardiovascular health study[11]	0.31	Not reported
Arteriovenous ratio*:		
Atherosclerosis risk in communities study[8]	0.73	0.79
Cardiovascular health study[11]	0.81	Not reported
Blue Mountains eye study[13]	Not reported	0.75

*Computer assisted grading method.

Table 2 Characteristics of studies of retinal changes in patients with hypertensive retinopathy. Values are numbers (percentages) unless stated otherwise

Study	No of participants	Age range (years)	Participants with hypertension*	Retinal changes		
				Focal arteriolar narrowing (%)	Arteriovenous nicking† (%)	Haemorrhages and exudates (%)
Cardiovascular health study[14]	2056	69-97	1424 (59)	9.6	7.6	8.3
Beaver Dam eye study[1]	4311	43-84	1479 (34)	13.5	2.2	7.8
Atherosclerosis risk in communities study‡[15]	10 358	48-73	4595 (44)	14.9	14.3	7.0
Blue Mountains eye study[16]	3614	43-86	1656 (46)	7.9	8.9	Not reported
Blue Mountains eye study[12]	3275	≥49	1447 (44)	Not reported	Not reported	9.9

*Use of antihypertensive drugs or a history of hypertension and blood pressure ≥140/90 mm Hg in cardiovascular health study and atherosclerosis risk in communities study and ≥160/95 mm Hg in the Beaver Dam eye study and Blue Mountains eye study.
†Different definitions used.
‡Included patients with diabetes.

Retinal changes and other indicators of organ damage

Four studies examined the association between hypertensive retinopathy and echocardiographically determined left ventricular hypertrophy.[17–20] One study failed to give the number of patients with events; however, the age and sex adjusted odds ratio (95% confidence interval) for left ventricular hypertrophy was 1.92 (1.03 to 3.60) when retinopathy was present.[21] Figure 2 gives details of the other studies. The pooled odds for left ventricular hypertrophy in the presence of hypertensive retinopathy was 2.22 (1.36 to 3.62), with little heterogeneity ($I^2 = 29.1\%$). Two studies examined the association between hypertensive retinopathy and microalbuminuria (odds ratios 1.51, 0.84 to 2.68 and 4.98, 1.97 to 12.60).[18 22] We were unable to pool the data because of significant heterogeneity ($I^2 = 78.3\%$). Three population based studies reported on the association between hypertensive retinopathy and intima-media thickness.[11 23 24] In the cardiovascular health study and atherosclerosis risk in communities study only the presence of haemorrhages and exudates was associated with increased intima-media thickness. In the Rotterdam eye study a lower arteriovenous ratio was associated with an increased intima-media thickness; other retinal abnormalities were not reported. We were unable to compare the studies because different techniques were used to assess the associations.

Retinal changes and cardiovascular risk

Hypertensive retinopathy as an independent predictor of cardiovascular risk was examined in six different populations, totalling 16 000 participants. We excluded two studies because blood pressure and patient history were known to the investigators before funduscopy.[25 26] Table 4 lists the association between hypertensive retinopathy and cardiovascular risk after adjustment in multivariate analysis. Risks of coronary heart disease,

Table 3 Diagnostic accuracy (%) of various retinal changes for hypertension in studies included in systematic review

Study	Generalised or focal arteriolar narrowing				Arteriovenous nicking				Haemorrhages and exudates			
	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Sensitivity	Specificity	Positive predictive value	Negative predictive value
Cardiovascular health study[14]	12	94	72	46	9	94	66	44	9	94	70	43
Beaver Dam eye study[1]	19	89	49	68	3	98	53	66	11	94	47	67
Atherosclerosis risk in communities study*[15]	21	89	61	59	18	88	55	57	10	95	62	57
Blue Mountains eye study[16]	11	95	66	52	12	93	59	56	Not reported	Not reported	Not reported	Not reported
Blue Mountains eye study*[12]	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	13	93	58	57

*People with diabetes included.

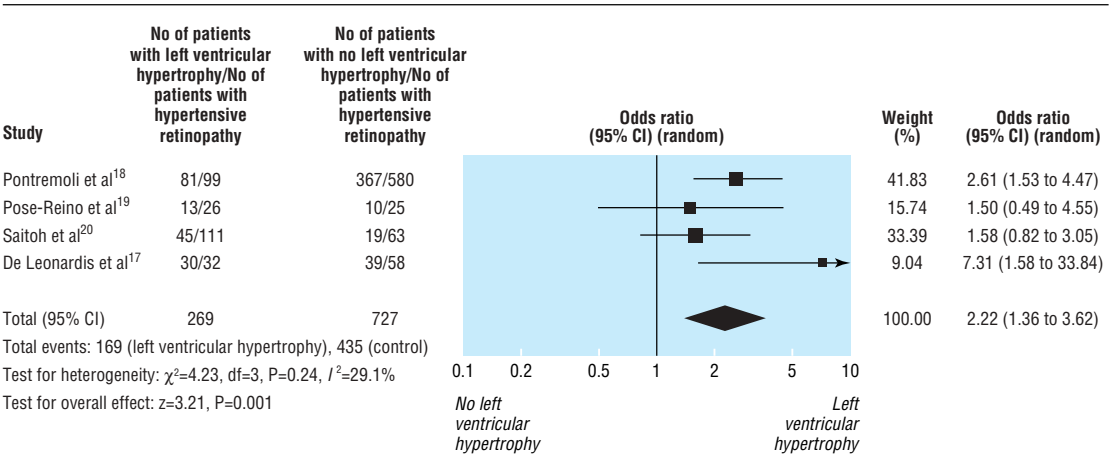

Fig 2 Odds ratios (95% confidence intervals) for association between hypertensive retinopathy and left ventricular hypertrophy

stroke, or death from cardiovascular disease differed with regard to retinal microvascular changes. Data on the association between retinopathy and stroke were more consistent: relative risk of stroke 3.4 (1.0 to 11.3) for men in the Shibata study and 2.6 (1.6 to 4.2) for men and women in the atherosclerosis risk in communities study. In the cardiovascular health study the odds ratio for stroke was 2.0 (1.1 to 3.6).

In the atherosclerosis risk in communities study and the Beaver Dam eye study, associations between retinal abnormalities and stroke were stratified by hypertension status. The relative risk of stroke in the atherosclerosis risk in communities study was 2.6 (1.2 to 5.6) with retinopathy and hypertension compared with 2.0 (0.5 to 8.4) in normotensive people. In the Beaver Dam eye study, the odds ratio for death from cardiovascular disease in people aged 43-74 with retinopathy and hypertension or diabetes, or both was 2.3 (1.2 to 4.2) compared with 1.5 (0.4 to 5.3) for those without hypertension and diabetes. The odds ratio for those aged 75-84 was 2.0 (1.0 to 4.0) if retinopathy and hypertension or diabetes, or both were present and 1.8 (0.4 to 8.4) if only retinopathy was present.

Discussion

In this systematic review we found limited additional value of funduscopy in the routine management of patients with hypertension, except in emergency cases.

The evaluation of hypertensive retinopathy is subject to large variability between observers, especially microvascular changes. Only haemorrhages and exudates can be reliably assessed in retinal photographs. We found no data on observer agreement using direct funduscopy. Recently, a computerised grading method has been developed to increase reproducibility of retinal microvascular changes, but this method is not widely available.

The low sensitivity of retinal abnormalities associated with hypertension indicates that hypertensive retinopathy is not common in hypertensive people. Less than half the retinal changes associated with hypertension cannot be explained by high blood pressure (low positive predictive value). In both the Beaver Dam eye study and the Blue Mountains eye study little difference was found in the presence of haemorrhages and exudates between normotensive and hypertensive people aged over 65.[1 30] Various other conditions have been associated with hypertensive retinopathy, such as ethnicity,[10 21] smoking,[23 31 32] intima-media thickness,[11 23 31] carotid plaque score,[31 33] carotid artery stiffness,[33] serum cholesterol concentration,[23 27 32] diabetes,[27 32] and body mass index.[27 32] The high specificity indicates that hypertensive retinopathy is rare in patients with normal blood pressure. Half the people without hypertensive retinopathy, however, still have hypertension (low negative predictive value). So funduscopy cannot reliably determine whether a patient is normotensive or hypertensive.

The presence of hypertensive retinopathy doubles the risk of left ventricular hypertrophy. Data on the association between hypertensive retinopathy and microalbuminuria are inconsistent. Patients with haemorrhages and exudates have a higher intima-media thickness; for other retinal abnormalities this association is conflicting or absent.

Evidence that hypertensive retinopathy is an independent predictor of cardiovascular risk is based on two large studies in which hypertensive patients with retinal haemorrhages or exudates had a twofold higher risk of stroke. Neither study, however, examined or adjusted for other indicators of hypertensive organ damage (left ventricular hypertrophy, microalbuminuria, and intima-media thickness). Furthermore, the association between retinopathy and stroke was also observed in normotensive people, suggesting that besides blood pressure, other factors are responsible for these retinal changes.

A recent paper reported on the associations between hypertensive retinopathy, blood pressure, and mortality from cardiovascular disease.[34] The authors found a strong association between hypertensive retinopathy and hypertension. Although this association was significant in most studies, the low predictive values we calculated indicate that funduscopy cannot reliably determine whether a patient has hypertension. Only for stroke is

Table 4 Associations between retinal changes and cardiovascular risk in studies included in systematic review. Values are relative risks (95% confidence intervals) unless stated otherwise

Study	Design	Follow up (years)	End points	No of participants	Arteriovenous crossings	Focal arteriolar narrowing	Generalised arteriolar narrowing*	Haemorrhages and exudates	Any retinopathy (grade II or higher)†
Beaver Dam eye study‡[27]	Case control	10	Death from coronary heart disease or stroke	1611	1.0 (0.5 to 1.9)§	1.4 (0.8 to 2.4)§	1.5 (1.1 to 2.1)§	1.8 (1.2 to 2.7)§	Not reported
Atherosclerosis risk in communities study‡[15]	Population based	3	Stroke	10 358	1.6 (1.0 to 2.5)	1.1 (0.7 to 1.8)	1.2 (0.7 to 2.3)	2.6 (1.6 to 4.2)	Not reported
Atherosclerosis risk in communities study‡[28]	Population based	3	Coronary heart disease	9648	Not reported	Not reported	Men 1.1 (0.7 to 1.8), women 2.2 (1.0 to 4.6)	Men 1.1 (0.6 to 2.3), women 1.8 (0.8 to 4.2)	Not reported
Cardiovascular health study¶**[11]	Cross sectional	—	Coronary heart disease	2050	1.1 (0.7 to 1.6)	0.9 (0.6 to 1.4)	0.8 (0.6 to 1.0)	1.7 (1.2 to 2.6)	Not reported
Cardiovascular health study¶**[11]	Cross sectional	—	Stroke	2050	1.4 (0.7 to 2.6)	1.2 (0.6 to 2.4)	1.1 (0.7 to 1.8)	2.0 (1.1 to 3.6)	Not reported
Shibata study‡[29]	Population based	15.5	Stroke	2302	Not reported	Not reported	Not reported	Not reported	Men 3.4 (1.0 to 11.3)

*Lowest versus highest quintile of the arteriovenous ratio, using computerised method.
†Keith, Wagener, and Barker classification.
‡Multivariate analysis adjusted for age, ethnicity, blood pressure or use of antihypertensive drugs, diabetes, cholesterol, and smoking.
§Odds ratios (95% CIs).
¶Multivariate analysis adjusted for age, ethnicity, and blood pressure or use of antihypertensive drugs.
**People with diabetes excluded.

What is already known on this topic

Funduscopy is recommended in the routine management of hypertensive patients

The usefulness of funduscopy is being questioned

What this study adds

Funduscopy is of limited additional value in hypertensive patients, unless a hypertensive emergency is suspected

the association with retinopathy significant and consistent. This association is also observed in people without hypertension and is not corrected for other indicators of hypertensive organ damage. Hence the additional value of funduscopy in the management of patients with hypertension still needs to be determined.

The included studies have several limitations. Firstly, in all the studies hypertensive retinopathy was established on a photograph of one eye. As hypertension is a systemic disease, retinal changes would be expected in both eyes. Some retinal abnormalities may thus have been a sign of unilateral eye disease instead of hypertension. Secondly, most of the studies used a broad definition for hypertensive retinopathy, including microaneurysms, hard exudates, and blot haemorrhages. These are not included in the original classification and may have a different association with hypertension. Thirdly, hypertension may have been misclassified, as blood pressure was measured only once or twice. Fourthly, people with diabetes were included in the atherosclerosis risk in communities study and Beaver Dam eye study. Diabetic retinopathy is a known risk factor for cardiovascular disease and may have confounded the association between hypertensive retinopathy and cardiovascular risk. Multivariate analysis may not have totally accounted for this effect. Finally, only middle aged and older people were included in the studies, although the association between hypertensive retinopathy, blood pressure, and risk of cardiovascular disease gets stronger in those under 60.[27] Future research should consider a younger population (<60 years) and other indicators of hypertensive organ damage.

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