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ORIGINAL ARTICLE

Prevalence and correlates of advanced retinopathy in a large selected hypertensive population. The Evaluation of Target Organ Damage in Hypertension (ETODH) study

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Abstract

Objective. To describe the prevalence of advanced retinal microvascular lesions and their associations with cardiac and extracardiac signs of target organ damage (TOD) in a large selected hypertensive population. *Methods.* A total of 2172 non-diabetic untreated and treated uncomplicated essential hypertensives consecutively attending for the first time our hospital outpatient hypertension clinic and included in the Evaluation of Target Organ Damage in Hypertension (ETODH), an observational ongoing registry of hypertension-related TOD, were considered for this analysis. Advanced hypertensive retinopathy was defined by the presence of any of the following lesions: flame-shaped haemorrhages, soft exudates or cotton wool spots and papilloedema. Left ventricular hypertrophy (LVH), carotid structural abnormalities, such as plaques and intima media (IM) thickening, and microalbuminuria were diagnosed according to the 2003 ESH/ESC guidelines criteria. *Results.* Among the whole study population, 33 patients (1.5%) were found to have advanced hypertensive retinopathy. Patients with these retinal lesions were similar to those without for age, body mass index, known duration of hypertension, smoking habit, total serum cholesterol, fasting blood glucose and prevalence of antihypertensive treatment; whereas mean systolic and diastolic blood pressures were higher in the former group. The prevalence rates of LVH, carotid plaques, carotid IM thickening and microalbuminuria in patients with and without retinopathy were 57%, 67%, 69%, 19% and 25%, 47%, 44%, 12%, respectively. In a multivariate logistic regression analysis, advanced retinopathy was significantly associated with LVH (OR=4.0), carotid IM thickening (OR=2.9), carotid plaques (OR=2.8), but not with microalbuminuria. *Conclusions.* Our study indicates that: (i) advanced retinopathy is a rare finding in non-diabetic hypertensive patients seen in a specialist setting; (ii) a strong relation exists between retinal microvascular lesions and cardiac and macrovascular markers of TOD.

Key Words: *Advanced retinopathy, hypertension, target organ damage*

Introduction

It is well known that long-standing hypertension causes damage to eye microcirculation (1–3), and detection of hypertensive retinal microvascular abnormalities, which include a wide spectrum of lesions such as generalized and focal retinal narrowing, arteriovenous (AV) crossings, exudates and haemorrhages, may be relevant in classifying the total cardiovascular risk and in decision making of therapeutic strategies (4). Advanced hypertensive retinopathy, characterized by haemorrhages and exudates with or without papilloedema, is a marker of severe retinal circulation changes, secondary to abnormal vascular permeability, necrosis of the capillary and precapillary arteriole walls and retinal ischaemia (5,6).

The prognostic impact of these critical retinal lesions in untreated hypertensives was reported for the first time by Keith et al. (1) more than 60 years ago in a prospective study including patients with a wide spectrum of retinal microvascular alterations (grades I–IV). The presence of optic disk oedema (grade IV

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retinopathy), haemorrhages and/or exudates (grade III) was associated with a 5-year survival rate of 1% and 20% respectively, against 70% of mild (grade I) and 54% of moderate (grade II) arteriolar changes. The modern antihypertensive therapy has markedly reduced such severe microvascular complications and the prognosis of these patients has also improved (7).

Nowadays, in developed countries, most patients with hypertension present early and advanced signs of retinopathy are rarely observed, whereas early arteriolar changes, i.e. arteriolar narrowing and/or AV crossings, are the dominant features (8). These early signs, detected in clinical practice by traditional ophthalmoscopy, provide limited information on cardiovascular prognosis or the subclinical cardiac and extracardiac target organ damage (TOD). Several studies, mostly based on largely qualitative grading methods, have shown a high prevalence of arteriolar narrowing and AV crossings in uncomplicated essential hypertensives (9–11) and a lack of correlation of these microvascular abnormalities with well prognostically validated markers of TOD (12,13). Therefore, it is doubtful whether the assessment of early signs of hypertensive retinopathy by clinic ophthalmoscopy, a method with a poor reproducibility, can be used to define TOD and total cardiovascular risk.

For these reasons, the ESH/ESC 2003 guidelines (14) have not listed arteriolar narrowing and AV crossings among manifestations of TOD and have classified the advanced retinopathy (grades III or IV) as an associated clinical condition, because the presence of haemorrhages, exudates and/or papilloedema has been considered a marker of severe hypertensive complications. Unlike the ESH/ESC 2003 guidelines, the WHO/ISH 2003 guidelines (15) have classified grade III or IV retinopathy among signs of TOD. Despite the clinical relevance of advanced retinopathy, few studies regarding the prevalence of these retinal lesions have been recently published. Thus, the purpose of the present study was to describe the prevalence of grade III and IV retinopathy and its relationship to cardiac and extracardiac TOD in a large sample of selected hypertensive subjects, referred to our outpatient clinic and enrolled in the Evaluation of Target Organ Damage in Hypertension (ETODH) study.

Methods

Patients

The ETODH study is an ongoing registry of widespread hypertension-related TOD and concomitant cardiovascular risk factors in white adult subjects with essential hypertension referred to our hospital outpatient clinic, aimed at estimating their total cardiovascular risk, according to the recommendations of the WHO/ISH 1999 (16) and ESH/ESC 2003 European (14) hypertension guidelines. From January 1999 to February 2004, a total of 2500 untreated [high blood pressure (BP) defined as a systolic BP (SBP)$\geqslant$140 mmHg and/or diastolic BP (DBP)$\geqslant$90 mmHg] and treated hypertensive patients were included in this registry. The main exclusion criteria were the presence of: clinical or laboratory evidence of heart failure, coronary artery disease, atrial fibrillation, previous stroke, valvular defects, secondary causes of hypertension and other important concomitant diseases. All patients underwent the following procedures: clinic BP measurement, routine blood chemistry, urinalysis, electrocardiogram, 24-h urine collection for microalbuminuria, non-mydriatic retinography, cardiac, carotid and renal ultrasonography. The study was approved by the Ethic Committee of the Ospedale Maggiore Policlinico. Patients gave their written consent after explanation of the nature and purpose of the study.

BP measurement

Sitting BP was measured in the outpatient clinic by a physician, using a mercury sphygmomanometer, as detailed in reference (8). The averages of three SBP and DBP consecutive values were used as reference office values.

Retinography

The retinal photography procedure and its assessment have been previously reported (8). Briefly, all patients underwent a bilateral non-mydriatic retinography. Images were captured using an analogic camera, set in order to obtain two photographs centred on the macula. The images, printed on professional film were immediately examined for quality. Trained observers who were unaware of the participant's characteristics evaluated the retinal photographs. The following abnormalities were systematically graded: (I) diffuse arteriolar narrowing (when an arteriovenous ratio equal to or lower than least at 1:2 was observed); (II) AV crossings (when any degree of depression of the vein in a vascular crossing situated at more than one papillar diameter from the papilla was detected; (III) flame-shaped haemorrhages (Fig. 1), blot haemorrhages, soft exudates (cotton wool spots); (IV) papilloedema and retinal haemorrhages (Fig. 2) and or/exudates (17).

In each of the quadrants of both eyes, the presence of each grade of retinopathy (I–IV) was judged as definite, probable or absent. The patient was classified according to the most advanced lesion that was judged as definite or probable in any of the quadrants. Reproducibility of retinal photographic grading was performed in 200 of 2172 patients. Intra- and inter-grade kappa statistics of retinal artery features were 0.91 and 0.89, respectively.

Echocardiography and carotid ultrasonography

Technical details were given elsewhere (13). In brief, M-mode, two-dimensional and Doppler echocardiographic examinations were performed using commercially available instruments. Left ventricular mass (LVM) was estimated from end-diastolic LV internal diameter (LVIDd), interventricular septum (IVS) and posterior wall thickness (PWT) by Devereux's formula (18) and indexed to body surface area (BSA). LVH was diagnosed when LVMI was $\geqslant 125$ g/m^2 in men and 110 g/m^2 in women (14).

Carotid plaques were sought in the near (anterior) and far (posterior) walls of the entire extracranial carotid tree based on the presence of a focal wall thickening > 1.3 mm (14). Intima media thickness (IMT) was measured in the posterior wall of both common carotids (5, 10, 15, 20 and 25 mm caudally to the bifurcation). Carotid IM thickening was diagnosed when average IMT exceeded 0.8 mm (14). As previously reported in our laboratory, the intra-observer and the inter-observer coefficients of variation for LVMI are 7.4% and 8.6%, respectively, and for common carotid IMT 9.2% and 10.1% (19).

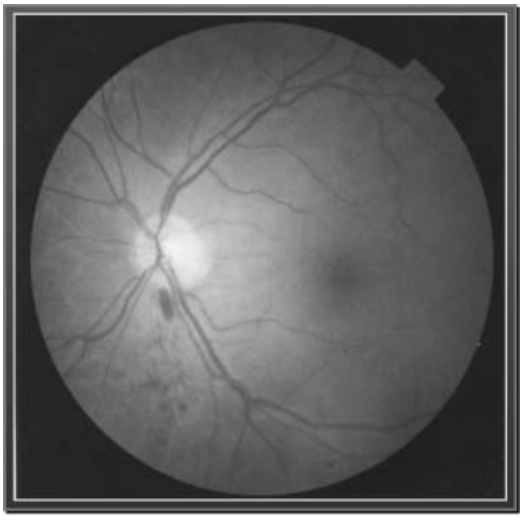

Figure 1. Advanced hypertensive retinopathy: flame-shaped haemorrhages and generalized retinal arteriolar narrowing.

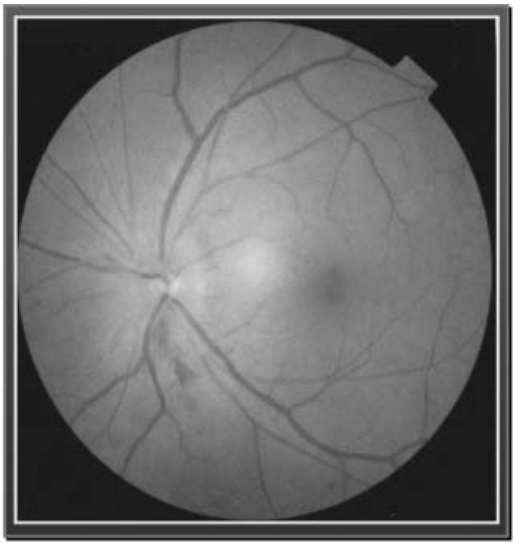

Figure 2. Advanced hypertensive retinopathy: papilloedema and flame-shaped haemorrhages.

Microalbuminuria

Twenty-four-hour urinary albumin concentration was measured by a commercially available radioimmunoassay kit (Sclavo SPA, Cinisello Balsamo, Italy). The detection limit of the method was 0.5 m/l. Microalbuminuria was defined as a urinary albumin excretion rate $\geqslant 30$ mg per 24 h and < 300 mg per 24 h.

Statistical analysis

Statistical analysis was performed by the SAS System (SAS Institute Inc. Cary, NC, USA). Data are reported as means $\pm$ SD or percentages. The probability of advanced retinopathy (III and IV degree) was assessed by calculating the odds ratios (OR) and their confidence limits, separately for demographic and clinical variables. A logistic multivariate analysis (backward procedure) was performed to identify such variables that were significantly and independently associated with advanced retinopathy. The limit of statistical significance was set at $p < 0.05$.

Results

Three hundred and twenty-eight of the 2500 patients included in ETODH study between January 1999 and July 2003 were ineligible for the present analysis because 150 (6%) had known diabetes mellitus and 178 (7.2%) suboptimal retinal photographs.

Of the 2172 patients, 1129 were men and 1043 women (Table I); mean age was 52.0 ± 12.3 years, older persons (age > 65 years) prevalence 15.2%.

Mean clinic SBP and DBP values were 146.8 ± 17.8 and 93.1 ± 8.7 mmHg, respectively; 69.8% of patients were regularly treated with antihypertensive drugs. With regard to other cardiovascular risk factors, 660 patients (30.4%) were definitely overweight (BMI > 27.8 kg/m^2 in men and > 27.3 kg/m^2 in women) 608 (28.0%) had hypercholesterolaemia (serum total cholesterol > 6.5 mmol/l), and 491 (22.6%) were smokers.

Among the whole study population, 33 patients (1.5%) were found to have grade III or IV hypertensive retinopathy as shown by non-mydriatic retinography. Patients with advanced retinopathy were similar to those without it (22% with normal fundal examination, 45% with narrowing and 33% with AV crossings) for age, BMI, known duration of hypertension, smoking habit, total serum cholesterol, fasting blood glucose and prevalence of antihypertensive treatment. Mean SBP and DBP values were higher in patients with advanced retinopathy, despite the fact that they had more complex therapeutic regimens.

The prevalence rates of LVH, according to the sex-specific criterion of 125/110 g/m^2, carotid plaques, carotid IM thickening and microalbuminuria in patients with and without advanced retinopathy were 57%, 67%, 69%, 19% and 25%, 47%, 44%, 12%, respectively.

In a multivariate logistic regression analysis, grade III and IV fundal changes were significantly correlated with LVH (OR 4.01, 95% CI 1.99–8.06, $p < 0.0001$) carotid IM thickening (OR 2.90, 95% CI 1.37–6.12, $p < 0.005$), carotid plaques (OR 2.81, 95% CI 1.21–5.83, $p < 0.005$) but not with microalbuminuria (OR 1.71, 95% CI 0.63–4.58, $p = 0.2$) and male sex (OR 2.41, 95% CI 1.01–4.53, $p < 0.05$) (Fig. 3).

Discussion

The ETODH study provides an opportunity to examine the prevalence of advanced retinal microvascular abnormalities, and their associations with clinical variables and various markers of cardiac and extracardiac TOD in a large population of non-diabetic essential hypertensives referred to a hospital outpatient hypertension clinic during the last 5 years. The presence of retinal microvascular lesions was determined by a qualitative grading of retinal photographs of both eyes according to a standardized protocol by two readers blinded to clinical characteristics of subjects examined. In the current study, we have been able to demonstrate that: (i) advanced hypertensive retinopathy, as clinically assessed from eye ground photography, is rare in a cohort of prevalently middle-aged subjects seen in a specialist setting; (ii) LVH, carotid structural changes and male sex were the most important independent predictors of advanced retinal lesions.

Table I. Demographic, clinical and laboratory characteristics of the whole study population (I), of patients with (II) an without (III) advanced retinopathy.

	I	II	III
Age (years)	52.0 ± 12.3	51.4 ± 13.3	52.1 ± 12.3
Gender (men/women)	1129/1043	23/10	1106/1033
Body mass index (kg/m^2)	26.1 ± 4.3	26.3 ± 3.1	26.1 ± 4.3
Clinic systolic blood pressure (mmHg)	146.8 ± 17.8	155.9 ± 22.1	146.6 ± 17.7
Clinic diastolic blood pressure (mmHg)	93.1 ± 9.7	98.5 ± 13.0	93.0 ± 9.6
Heart rate (beats/min)	72.8 ± 12.3	74.0 ± 10.2	72.8 ± 12.3
Duration of hypertension (> 5 years, %)	34.2	43.2	33.4
Overweight (%)	30.4	27.2	30.5
Hypercholesterolaemia (%)	28.1	30.3	28.0
Current smoking (%)	22.1	34.2	22.4
Elderly (%)	15.2	15.1	15.3
Antihypertensive treatment (%)	68.9	75.5	68.8
LVM/BSA (g/m^2)	106.1 ± 24.7	132.6 ± 32.7	105.7 ± 24.4
Carotid IMT (mm)	0.76 ± 0.15	0.75 ± 0.14	0.71 ± 0.15
Urinary AE (mg/24 h)	23.2 ± 127.3	19.1 ± 21.7	23.3 ± 128.2
LVH (%)	25	57	25
CT (%)	47	69	44
CP (%)	44	67	47
MA (%)	12	19	12

Data is reported as means ± SD, percentages or absolute numbers. LVM, left ventricular mass; BSA, body surface area; IMT, intima media thickening; AE, albumin excretion; LVH, left ventricular hypertrophy; CT, common carotid intima media thickening; CP, CP, carotid plaques; MA, microalbuminuria.

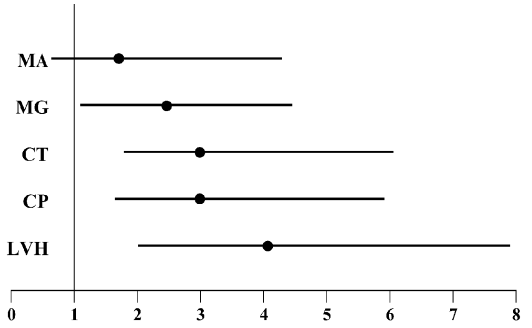

Figure 3. Predictors of advanced hypertensive retinopathy: odds ratio (solid circle) and 95% confidence interval (horizontal lines). MA, microalbuminuria; MG, male gender; CT, common carotid intima media thickening; CP, carotid plaques; LVH, left ventricular hypertrophy.

The following aspects of our findings deserve to be discussed. First, the prevalence of advanced retinopathy (haemorrhages, exudates with or without papilloedema) is much lower than that of other prognostically validated markers of TOD, such as LVH, carotid wall alterations and microalbuminuria. Among our study population, retinal grade III and IV patterns were found in less than 2% of patients, whereas subclinical signs of cardiac, carotid and renal involvement occurred in 57%, 67% and 19% of the patients, respectively. To define TOD, in the present study, we chose the cut-off values suggested in the recent ESH/ESC guidelines for hypertension (14), i.e. LVH $\geqslant$125 g/m^2 in men and $\geqslant$110 g/m^2 in women; vascular damage: common carotid IMT $>$0.8 mm or plaques, microalbuminuria $>$30 mg/24 h. Even by using the most restrictive criteria for definition of LVH (LVMI $>$134 g/m^2 in men and $>$110 g/m^2 in women) or carotid alterations (IMT $>$0.9 mm and/or plaques $>$1.5 mm), the prevalence of ultrasonographic markers of TOD remained significantly higher (45% and 40%, respectively) than the 1.5% prevalence of advanced retinopathy.

Second, our findings add a new piece of evidence on the relationship between advanced retinopathy and hypertension-dependent TOD, as we could show that patients with severe retinal complications have more severe cardiac and carotid wall alterations compared to those without these retinal features. In an attempt to define clinical variables associated with advanced microvascular lesions in the retina, we used a multiple logistic regression analysis. In this model LVH, carotid IM thickening, plaques and male gender (but not clinic BP) were independently and significantly related to advanced retinopathy. These results suggest that among cardiovascular TOD, LVH is the most important predictor of advanced retinopathy, and may be considered ''the haemoglobin A1C of blood pressure'', since it is an objective measure of both severity and duration of high BP.

Third, the more pronounced cardiac and vascular TOD in patients with advanced retinal lesions was not associated with a significantly greater renal involvement, as assessed by the urinary albumin excretion. This result may be due to the relatively small sample study. Furthermore, microalbuminuria is known to be highly variable and was measured only once in our population.

Some limitations of our study deserve to be mentioned. These results have been obtained in a selected population of non-diabetic hypertensive patients referred to a specialist centre and should not be extended to the hypertensive patients cared by general practitioners, as in the hypertensive population as a whole the rate of advanced retinopathy is probably lower. In addition, since the study sample included only Caucasian subjects, living in a developed country, extrapolation to a non-white population or to patients living in developing countries may be unreliable. Finally, a further important limitation is related to the small absolute number of patients with advanced retinopathy found in our survey.

Previous studies

In a retrospective, case control study including patients with and without coronary heart disease carried-out in the mid-1960s, O'Sullivan et al. (20) found that haemorrhages and exudates with or without papilloedema were present in about 12% of subjects and the retinal artery changes were correlated to BP status, electrocardiographic signs of LVH and a previous history of hypertension. More recently, Palatini et al. (21) examining 340 hypertensive subjects mostly with borderline or mild hypertension found that less than 2% of subjects had grade III or IV retinopathy, according to Keith classification. In a cross-sectional survey by Fuchs et al. (11) the prevalence of haemorrhages and/or soft exudates, assessed with direct ophthalmoscopy by internists and cardiologists, was 2.5%.

Further insights on this issue come from large-scale population-based surveys: the prevalence of retinal abnormalities other than arteriolar narrowing or AV crossings in these studies varied from 7% (22,23) to 8% in non-diabetic subjects (24). The higher prevalence of advanced retinal changes compared to our data can be explained as follows: (i) definition of retinopathy in these studies included features unrelated to hypertension (vitreous haemorrhages, laser photocoagulation scars, venous beading, new

vessels at the disc); (ii) mean age was significantly greater than our study: 60 years in the Beaver Dam Eye study (22), 58 years in the ARIC study (23) and 78 years in the Cardiovascular Health Study, respectively (24); (iii) in two studies, retinal photography procedures were performed between 1993 and 1995 (22,23) and in the CHS study (24) between 1997–1998; therefore these data do not closely reflect the current epidemiological situation.

In conclusion, data from this study, including a selected hypertensive population of mostly middle-aged subjects without diabetes referred during the last 5 years to a specialist setting, indicate that advanced retinopathy is rarely observed and is related to ultrasonographic markers of cardiac and extracardiac TOD. The marginal prevalence of retinal lesions in a hypertensive cohort with high rates of LV and carotid wall alterations suggests that haemorrhages and/or exudates should be considered, according to the ESH/ESH 2003 (14) guidelines, a clinical associated condition rather than markers of TOD. Finally, hypertensive patients with severe or widespread TOD, being at high risk of advanced retinopathy, should systematically undergo fundoscopic examination.

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