Prevalence and determinants of glaucoma

An epidemiologic approach

The Rotterdam Study

I. Dielemans

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Prevalentie en determinanten van glaucoom

Een epidemiologische benadering

Het ERGO onderzoek

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Contents

Publications and manuscripts based on the studies described in this thesis

Chapter 3

Dielemans I, Vingerling JR, Wolfs R, Hofman A, Grobbee DE, Jong de PTVM. The prevalence of glaucoma in a population-based study in the Neterlands: The Rotterdam Study. In press, Ophthalmology.

Chapter 4

Dielemans I, Vingerling JR, Hofman A, Grobbee DE, Jong de PTVM. Primary open-angle glaucoma, intraocular pressure and diabetes mellitus in the general elderly population: The Rotterdam Study. Submitted.

Chapter 5

Dielemans I, Vingerling JR, Algra D, Hofman A, Grobbee DE, Jong de PTVM. Primary open-angle glaucoma, intraocular pressure and systemic blood pressure in the general elderly population: The Rotterdam Study. In press, Ophthalmology.

Chapter 6

Dielemans I, Vingerling JR, Hofman A, Schotman S, Grobbee DE, Jong de PTVM. Correlates of optic disc parameters in the general population. Submitted.

Chapter 7

Dielemans I, Vingerling JR, Algra D, Hofman A, Grobbee DE, Jong de PTVM. Reliability of intraocular pressure measurement with the Goldmann applanation tonometer in epidemiological studies. Graefe's Arch Clin Exp Ophthalmol 1994; 232:141-4.

Chapter 1

Introduction

Glaucoma is an eye disease characterized by damage to the optic nerve head and related visual field defects, often accompanied by elevated intraocular pressure.[1] Glaucoma is an important cause of blindness, particularly in the elderly[2]. One may divide glaucoma in primary glaucoma without known preceding cause, and secundary glaucoma. Primary glaucoma may be genetically determined. The term secundary glaucoma refers to glaucoma caused by some known antecedent or concomitant ocular disease. Furthermore, primary glaucoma can be classified on anatomic basis into four major divisions: open-angle glaucoma, angle closure glaucoma, mixed glaucoma and congenital glaucoma.[3] Primary open-angle is the most frequent type of glaucoma, but its pathogenesis is not well understood.[4]

In former times, the presence of an elevated intraocular pressure was considered necessary and sufficient to make a diagnosis of glaucoma. Nowadays solitary elevated intraocular pressure is called ocular hypertension and for the diagnosis primary open-angle glaucoma the emphasis lies on glaucomatous visual field defects even without elevated intraocular pressures.[5,6,7] It is unknown whether the sensitivity of the eye for a certain level of intraocular pressure is decisive for the development of glaucomatous visual field defects, and whether glaucoma with normal intraocular pressures is a different disease entity from glaucoma with elevated intraocular pressures. Studies on risk factors for primary open-angle glaucoma, with and without elevated intraocular pressures, have been inconclusive.[4,8]

This thesis focuses on epidemiologic studies on primary open-angle glaucoma. The main part is devoted to the relation of putative risk factors with primary open-angle glaucoma and intraocular pressure whereby a distinction was made between glaucoma with elevated and normal intraocular pressures, respectively.

In chapter 2 the current epidemiologic knowledge on primary open-angle glaucoma has been reviewed. The following four chapters are based on the Rotterdam Study, a population-based study of subjects aged 55 years and over. Chapter 3 deals with the distribution of primary open-angle glaucoma and relating characteristics in the Rotterdam Study. In chapter 4,5 and 6 putative risk factors, including diabetes mellitus and systemic blood pressure, are discussed in relation to primary open-angle glaucoma, intraocular pressure and optic disc parameters. Chapter 7 deals with a reproducibility study of intraocular pressure measurement. In chapter 8, some methodological considerations are given in relation to the previous studies, with a review of the results of these studies and some suggestions for further research.

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Chapter 2

Epidemiology of primary open-angle glaucoma

Primary open-angle glaucoma (POAG) is an important cause of blindness, particularly in the elderly. It has been estimated that glaucoma was the second cause of irreversible blindness among whites, after age-related macular degeneration1. Of all blindness, 11.1 percent might be due to glaucoma.[1] POAG is by far the most frequent type of glaucoma but nevertheless little is known about its pathogenesis.[2]

The present study updates an earlier review of epidemiologic data on POAG[2]. We will successively discuss diagnosis, prevalence, incidence and risk factors of POAG.

Diagnosis

The diagnosis of POAG is classically based on a triad of glaucomatous defects of the visual field, cupping of the optic disc and elevated intraocular pressure (IOP). The diagnosis of POAG is made after exclusion of other types of glaucoma, like congenital, developmental and secondary glaucoma. If the diagnostic triad is incomplete, there is no general agreement regarding diagnosis. There is, however, a lack of standardized criteria for elevated IOP, optic disc cupping and glaucomatous visual field defect. These points make comparability among different studies difficult. For the purpose of this review, POAG is defined by the presence of a glaucomatous visual field defect and optic disc cupping, independent of the level of IOP. Because it was suggested by several authors[3,4] that POAG with IOP within normal limits could be a disease different from POAG with elevated IOP, the following definitions were added: In case POAG is present without random IOP > 21 mmHg, it is defined as normal-tension glaucoma. In contrast, when POAG occurs with random IOP > 21 mmHg, this is defined as high-tension glaucoma. Nerve fiber layer defects are thought to be an important sign of glaucoma, but until now this has not been used as a diagnostic criterium in population-based studies.

Prevalence

The relevance of prevalence studies of POAG lies primarily in providing data for health services planning. Furthermore, comparison of prevalence figures from different populations or at different times may yield etiologic clues to the disease. It is evident that variation in prevalence estimates across studies could possibly be due to differences in methodology.[2] The most valid prevalence studies are those that examine every participant by perimetry, tonometry and ophthalmoscopy. Those community-based studies that not have based their prevalence figures on examinations of the populations involved[5-9] are excluded, since studies have shown that a considerable proportion of POAG cases in

population studies had previously not been diagnosed.[10-13] Population studies with screening by Schiotz tonometry, using only history taking[14], or with an unclear sample selection[15,16], which might influence their prevalence figures[2] were also excluded from this review.

Studies that presented age-specific prevalence figures for POAG are shown in Tables 2.1, 2.2 and 2.3. There were the following marked differences between these studies. In Ferndale[10], Friedman perimetry was performed on every third person and, in addition, on persons with an IOP greater than 20 mmHg and 'enlarged' optic cups. In Framingham[17], Goldmann perimetry was performed on persons with a positive history of glaucoma, an IOP greater than 21 mmHg and/or a cup/disc ratio greater than 0.4 on funduscopy. In Dalby[11], Baltimore[12], Beaver Dam[13], Rotterdam[18] and Barbados[19], every participant was screened with perimetry, tonometry and ophthalmoscopy. In Dalby[11], Baltimore[12] and Rotterdam[18] visual field defects detected with automatic perimetry had to be confirmed with Goldmann perimetry.

There were differences in definition of POAG (Table 2.2). In Ferndale[10], Framingham[17], Dalby[11], Rotterdam[18] and Barbados[19], all persons with the diagnosis POAG had to have glaucomatous visual field defects. In Baltimore[12], 88 percent of those with the diagnosis POAG had a glaucomatous visual field defect. Other criteria used in this study[12] were asymmetry of optic nerve head cupping of 0.4 or more, or significant and compatible disc- and nerve fibre layer abnormalities.[20] In Beaver Dam[13], 80 percent of those with the diagnosis POAG had glaucomatous visual field defects. Additional criteria used in this study were cup/disc ratio of 0.8 or more or asymmetry of cup/disc ratio of 0.2 or more in combination with an IOP of 22 mmHg or more in the involved eye.

Despite differences in methodology and definition, age-specific prevalence figures of POAG of the studies in Ferndale, Framingham, Dalby and Baltimore (white persons) are very similar. In Rotterdam, the prevalence of POAG in the age-group of 55-65 years was slightly lower than the other studies. In Beaver Dam, higher prevalence figures are given than all other studies, especially in the age-group of 75 years and older. Even when their definition of POAG is restricted to persons with a glaucomatous visual field defect, they still have higher prevalences of POAG in all age-groups. This could have been due to differences in perimetry procedures and disc grading. Prevalence figures of POAG in studies on black persons in Baltimore and Barbados are much higher.

In addition, various studies[10,11,12,17] have shown that 40 to 50 percent of the previously undetected cases with POAG[13,18] present with a normal IOP at screening.

Incidence

Comparison of incidence rates is of etiologic interest since these are theoretically not affected by differences in survival rates. The incidence of POAG in a defined population has not been adequately measured. Several studies have involved selected groups of persons.[21,22,23] Other studies did not find sufficient numbers of new cases[20,23], or had substantial loss to follow-up.[22,24,25]

The best available follow-up study was performed by Bengtsson[25], who re-examined 58 percent (N=591 persons, ages > 60 yrs) of the cohort study in Dalby, after about 10 years of follow-up. Of these persons, 2 percent (12 cases) had developed glaucomatous visual field defects.

Incidence estimates were theoretically derived from age-specific prevalence figures from the studies in Ferndale[10] and Framingham.[27] This resulted in a five-year incidence of 0.2 percent at age 55 years that increased to about 1 percent at age 75 years. These incidence estimates should be interpreted as approximations of the true incidence rates.

Risk factors

The most important putative risk factors of POAG that will be discussed below are classified as demographic, genetic, systemic and ocular factors (Table 2.4).

Demographic factors

Age

The population-based studies with age-specific prevalence figures of POAG have all shown a varying but strong relation between the prevalence of POAG and advancing age (Table 2.3). It has been sugested that the risk of having POAG increased with 1.74 (1.45-2.09, 95% confidence interval) for each 10-year increment in age.[13]

Sex

In most studies no significant sex differences in glaucoma prevalence have been found.[2,10,13,27] By contrast, the studies in Framingham[17] and Rotterdam[18] have shown a three times higher POAG prevalence in males.

Race

It has been suggested that POAG may be more common in populations of African descent.[2] Age-adjusted prevalence rates for POAG were four to seven times higher in blacks as compared with whites.[12,19]

Genetic Factors

A positive family history of glaucoma is known to increase the risk of disease.[2] The exact mode of transmission has not been determined. POAG is estimated to be hereditary in approximately one-fourth to one-fifth of the cases, with percentages ranging from 5 to 50 percent. The risk for siblings ranges from 4 to 40 percent.[2]

Systemic Factors

Diabetes mellitus

Few studies have suggested that diabetes mellitus is associated with POAG.[30-36] It is possible that diabetes mellitus increases the susceptibility of the optic nerve to field defects, either because of common genetic factors or because of the effect of diabetes mellitus on the small vessels of the eye.[2] Another possible mechanism is that elevated blood glucose may induce an osmotic gradient and attract fluid into the intraocular space, which may result in an elevated IOP.[33] A decrease in trabecular outflow has also been suggested.[32]

Blood pressure

Various studies have suggested that a decrease in blood pressure relative to IOP, after blood loss, hypotensive crises or antihypertensive therapy, increases the risk of having POAG[2] or normal-tension glaucoma.[37,38] It is also possible that hypertension may predispose to glaucomatous visual field loss, either directly, through small vessel disease, or indirectly, by increasing the IOP.[38] Small vessel disease can decrease blood flow to the optic nerve[39] and this could increase the risk of field loss. Associations between high-tension glaucoma and high blood pressure have been suggested by few studies.[40-42] However, no associations between POAG and systemic blood pressure have been found by others.[36,43-45] Evidence for an indirect mechanism comes from many other studies, reporting an association between blood pressure and IOP.[31,46-52] This association could be due to the effect of blood pressure on the filtration of aqueous fluid in the ciliary body; an increase in the passive production of aqueous humour would occur with increasing blood pressure.[32]

Ocular Factors

Intraocular pressure

Because of the variability of IOP, it is difficult to define what is meant by 'abnormal' values. Using a cut-off level of 21, which is over two standard deviations above the mean, based on occasional measurements per person, may be inappropriate. However, high IOP's are usually defined in these terms

and this is the approach followed here.

It has been suggested that the risk of having field defects in persons with IOP over 21 mmHg is approximately five to six times higher than in persons with a lower IOP.[2] On the other hand, about 3-8 percent of the population older than 40 years has IOP's above 21 mmHg[2,12,23] and most of these persons never develop POAG.[2] Besides, about half of all glaucomatous eyes have screening IOP's below 21 mmHg.[2,10,11,12,17] Although the relative risk of high IOP for visual field defects is high, IOP explains only 50 percent of the field defects developing in a population.

High myopia

High myopia has also been considered to increase the risk of having POAG.[2] However, the diagnosis of POAG presents some difficulties in persons with high myopia, because the appearance of the optic disc can be misleading. In addition, myopic fundus changes can give rise to field defects that resemble those found in glaucoma.[2]

Conclusions

In recent epidemiologic studies, the diagnosis of POAG has been principally based on the presence of glaucomatous defects of the visual field and optic disc cupping, independent of the level of IOP. The most valid prevalence studies are those that examine every participant by perimetry, tonometry and ophthalmoscopy on both eyes. The prevalence estimates for POAG rise with age. Typical estimates are about 0.9 percent in subjects aged 65 years, 2.0 percent in subjects aged 75 years, and 3.0 percent in subjects aged 85 years. About 40 percent of the POAG cases have normal tension glaucoma. Despite differences in methodology and definition, relatively similar prevalence figures of POAG are present across populations. Higher prevalence figures are given in the Beaver Dam Eye Study[13] which could have been due to differences in diagnostic procedures.[25]

Incidence estimates of POAG, based on a limited amount of evidence, suggest a five-year incidence of 0.2 percent at age 55 years, that increases to 1 percent at age 75 years.

Risk factors for POAG have been investigated in a number of epidemiologic studies. Except for age, a positive family history of POAG, and elevated IOP, no definite risk factors for POAG have yet been established. There is, however, evidence to suggest that diabetes mellitus and blood pressure may be associated with POAG.

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Table 2.1
Summary of population-based studies of glaucoma

Study location	Age (years)	No. of participants (% of population)	Screening methods[a]	Perimetry
Ferndale[10]	40-74	4,321 (92)	H,T,O,VF(1/3)	Friedman
Framingham[17]	52-85	2,433 (84)	H,T,O	Goldmann
Dalby[11]	55-70	1,511 (78)	H,T,O,VF	Competer/ Goldmann
Baltimore, white persons[12,26]	>40	2,913 (76)	H,T,P,VF	Humphrey/ Goldmann
Baltimore, black persons[12,26]	>40	2,395 (84)	H,T,P,VF	Humphrey/ Goldmann
Beaver Dam[13]	>42	4,926 (83)	H,T,P,VF	Henson
Rotterdam[18]	>54	3,062 (80)[e]	T,O,VF	Humphrey/ Goldmann
Barbados[19]	40-85	4,709 (84)	H,T,P,VF	Humphrey

[a] H,history;T,applanation tonometry; O,ophthalmoscopy; P,optic disc photography; VF,visual field testing
[b] VFD,visual field defect; GI.disc, glaucomatous disc; IOP,intraocular pressure; NFLA,nerve fiber layer abnormality. See Table 2.2 and text for specific definitions.
[c] median IOP
[d] only untreated cases were considered

Diagnostic criteria[b]	Mean IOP (mmHg)	No. of POAG cases (% prevalence)	No. of POAG cases presenting with normal IOP (proportion of all cases)
VFD,GL.disc	16	20 (0.47)	7 (0.35)
VFD in glaucoma suspects	17	28 (1.43)	15 (0.53)
VFD,GI.disc	?	13 (0.86)	8 (0.62)
VFD,GI.disc,NFLA	17	32 (1.10)	9 (0.55)[d]
VFD,GI.disc,NFLA	17	100 (4.20)	55 (0.55)[d]
VFD,GI.disc,IOP	15[c]	104 (2.1)	33 (0.32)
VFD,GI.disc	15	34 (1.1)	7 (0.39)[d]
VFD,GI.disc	18	309 (6.7)	?

Table 2.2
Specific definitions of glaucomatous visual field defect and glaucomatous disc in epidemiological studies

Study location	glaucomatous visual field defect	glaucomatous disc
Ferndale[10]	seidel or Bjerrum scotoma, Roenne's nasal step, tubular visual field	excessive excavation
Framingham[17]	arcuate or paracentral scotoma, nasal step, advanced field loss	CDR≥0.5 or difference between eyes ≥0.2
Dalby[11]	a repeatable visual field defect consistent with glaucoma	glaucomatous cupping of the optic disc
Baltimore[12,26]	paracentral or arcuate scotoma of at least 0.4 log-unit depth, nasal step, central and temporal island	CDR≥0.7 or width narrowest rim of <0.15
Beaver Dam[13]	visual field defect compatible with the diagnosis of glaucoma	CDR≥0.8 or difference between eyes ≥0.2
Rotterdam[18]	paracentral or arcuate scotoma of at least 0.4 log-unit depth, nasal step, central and temporal island.	CDR≥0.5 or difference between eyes ≥0.2
Barbados[19]	one or more absolute defects in the central 30° or positive results of hemimeridional analyses using the ICEPACK program.	at least two signs were present: CDR≥0.7, width narrowest rim ≤0.1, notching, difference between eyes ≥0.2, disc hemorrhages.

CDR = cup/disc ratio

Table 2.3
Age-specific prevalences of Primary Open Angle Glaucoma in epidemiological studies.

age-groups (years)	Ferndale (1966) n=4,231	Framingham (1977) n=2,433	Dalby (1981) n=1,511	Baltimore (1991) whites n=2,913	Baltimore (1991) blacks n=2,395	Beaver Dam (1992) n=4,926	Rotterdam (1993) n=3,062	Barbados (1994) n=4709
40-45				0.92	1.23			1.4
45-49						1.0		
50-54	0.3			0.41	4.05			4.1
55-59	0.9	0.5	0.4			1.3	0.2	
60-64	0.5	0.7	0.8	0.88	5.51		0.2	0.4
65-69	1.1	0.9	1.5			2.7	0.9	6.7
70-74	1.3	1.7		2.89	9.15		1.8	14.8
75-79		2.0					1.6	
80-84		4.4		2.16	11.26	6.3	3.1	2.1
85-89							3.3	23.2

Table 2.4
Risk factors for Primary open-angle glaucoma

Risk factor	Studies references	Risk	95% Confidence interval
Age	10-13,17,18	OR 1.74 per 10 years[13]	1.45,2.09
Gender	17,18	OR 3.6 for men[18]	1.7,7.1
Family history of glaucoma	2	RR 4-16 for first degree relatives	
Diabetes mellitus	29-36	OR 2.80 for HTG[35]	1.01,7.77
		OR 3.11 for HTG[36]	1.12,8.66
Hypotension	37,38	? for NTG	
Hypertension	39,41,42	OR 2.33 for HTG[42]	0.99,5.47
Intraocular pressure > 21 mmHg	2,12	RR > 5-6[2]	
		RR > 12[12]	

OR, odds ratio
RR, relative risk

Chapter 3

The prevalence of glaucoma in a population-based study in the Netherlands: The Rotterdam Study

Abstract

Purpose

The objective of this study is to assess the prevalence of primary open-angle glaucoma (POAG) in a defined population in Rotterdam, The Netherlands.

Methods

The Rotterdam Study is a single-center prospective cohort study of a total population of over 10,000 people, aged 55 years or more. For the present analysis the first 3,062 consecutive, unselected, non-institutionalized participants were examined according to standard protocols, including perimetry. The diagnosis of POAG was based on the presence of a glaucomatous visual field defect in combination with either a vertical cup/disc ratio of 0.5 or over or a cup/disc ratio asymmetry of 0.2 or over, or an intraocular pressure (IOP) over 21 mmHg, with open and normal anterior chamber angles.

Results

The overall prevalence of POAG in the present study was 1.10% (95% CI 1.09,1.11). Age-specific prevalence figures increased from 0.2% (95% CI 0.16,0.24) in the age-group of 55-59 years, to 3.3% (95% CI 2.57,4.04) in the age-group of 85-89 years. Men had a more than three times higher risk of having POAG than women (odds ratio 3.6). POAG had not been previously diagnosed in 52.9% of the cases, and of them 38.9% had IOP's ≤ 21 mmHg. A visual acuity of 0.1 or less due to glaucoma was present in 8.8% the POAG cases.

Conclusion

The overall prevalence of POAG in the present study was 1.1%. The prevalence of POAG was higher in men than in women. Of the untreated cases 38.9% had IOP's ≤ 21 mmHg.

Introduction

Glaucoma is a disease of the optic nerve, which is often, but not always, accompanied by an elevated intraocular pressure (IOP). Characteristic of the disease are the generation of typical, progressive visual field defects. The most commonly occurring type of glaucoma is primary open-angle glaucoma (POAG). Overall prevalence figures of POAG in white populations range from 0.4% to 4.1%, depending on the screening procedure and definitions used.[1] According to the Model Reporting Area for Blindness Statistics of the U.S., glaucoma was responsible for 11.1% of all cases of blindness in the registration.[1]

The aim of the present study is to describe the prevalence of glaucoma in a defined population in Rotterdam, The Netherlands.

Subjects and Methods

Population

The present study was performed as part of the Rotterdam Study. The Rotterdam Study is a single-center prospective cohort study of over 10,000 residents, aged 55 years or more, of the suburb of Ommoord of Rotterdam, The Netherlands. The objective of the Rotterdam Study is to investigate the determinants of chronic, disabling cardiovascular, neurogeriatric, locomotor, and ophthalmologic diseases. The study has been approved by the Medical Ethics Committee of the Erasmus University, and written informed consent was obtained from all participants. All participants were at random selected from the Registry office but the invitations to participate were sent according to their postal code.

After informed consent was obtained, home interviews were taken by specially trained interviewers, in which information was collected about former and present medical status and family medical history. A medical investigation was carried out in a specially equiped examination center in the center of the suburb.

The overall participation rate was 80 percent of the eligible persons in the total Rotterdam Study, which is highest in the age-group of 55-65 years (84 percent) and declined with age (70 percent in the age-group of 85 years and older). In the present analysis, of the 4,318 eligible persons who were invited randomly to participate in the study from May 1991 until January 1993, 3,338 persons (77 percent) were interviewed at home. Of these, 3,062 (71 percent) consecutive, unselected, non-institutionalized persons had an ophthalmological investigation at the research center.

Measurements

The glaucoma screening was performed in three phases by two ophthalmological residents and three perimetrists. In the first phase of the glaucoma study, after autorefraction (Topcon RMA 2000), the best-corrected visual acuity was determined with the Lighthouse Distance Visual Acuity Chart (2nd edition). If this acuity improved with a pin-hole, the pin-hole acuity was noted down. Slitlamp examination was focused on abnormalities of the anterior chamber angle, cornea, iris and lens. The method of von Herick[2] was used to determine the width of the chamber angle. The intraocular pressure was measured with the Goldmann applanation tonometer (Haag-Streit, Bern, Switzerland) and the median of three consecutive measurements was taken.[3] Within the frame of the tight examination schedule subjects were given twenty minutes prior to the IOP measurement 200ml of a 75 gram glucose solution in order to perform a glucose tolerance test. The 76-point suprathreshold screening test of the Humphrey perimeter (Humphrey Visual Field Analyzer, Zeiss) was used to detect visual field defects in the central 30 degrees. A near refractive correction, appropriate for age, was used. The perimetry screening was performed on both eyes. Three or more contiguously missed points on the screening test were taken as evidence for a visual field defect. The blind spot and outer test points were not counted as missed points. The reliability of a test result was given by the perimeter, but the judgement of the technician about patient's responses and fixation was decisive. After perimetry, one drop of Tropicamide 0.5% and one drop of Phenylephrinehydrochloride 5% were administered in both eyes. After 40 minutes, photographs were taken from the macular area and the optic disc. Direct and indirect ophthalmoscopy was performed to assess the vertical cup/disc ratio (VCDR), in relation to the contour of the cup. These subjective assessments were used in the analyses. Any other abnormality of the optic discs and macular area was noted. Finally, one drop of Thymoxamine 5% was administered in both eyes. IOP was measured again in mydriasis in subjects with narrow angles, a history of possible acute glaucoma and in subjects with eye complaints developing during mydriasis. Subjects who showed a rise in IOP of over 7 mmHg were referred to the ophthalmologic department of the Erasmus University Rotterdam.

In the second phase of the glaucoma study, which was planned two weeks after the first phase, visual fields were retested with the same 76-point screening test in subjects with a visual field defect or unreliable visual field test in the first phase.

In the third phase of the glaucoma study, a few weeks later, subjects with a visual field defect or unreliable visual field test in the second phase of the

study, were recalled for perimetry on both eyes with the Goldmann perimeter, made by a skilled perimetrist, following standard criteria[4] and without knowledge of former visual field defects. Intraocular pressure was remeasured with the previously described

technique. Gonioscopy was performed when a glaucomatous visual field defect was present; a Goldmann 3-mirror contactlens was used to judge if the anterior chamber angle was open following the Shaffer grading system, to determine the degree of pigmentation and the presence of other abnormalities.

A random sample of 44 subjects with a normal 76-point supra-threshold Humphrey test also had a visual field examination in the second and third phase.

The subjective determination of the vertical cup/disc ratio of 25 randomly selected optic discs were compared, in a masked way, with the results of the analyses of photographs of the same optic discs with an automatic system.

Classification of glaucomatous visual fields

Glaucomatous visual field defects on the Goldmann perimeter included the following types of field defects that could not be explained by other ocular or neurological abnormalities: a paracentral or full arcuate scotoma of at least 0.4 log units in depth; nasal step of at least 10 degrees in width present to at least two isopters; central and/or temporal islands.[4]

Criteria for POAG

The diagnosis of POAG was based on the presence of a glaucomatous visual field defect on Goldmann perimetry in combination with either a VCDR of 0.5 or more or a difference in VCDR of 0.2 or more or an IOP greater than 21 mmHg, with open and normal anterior chamber angles.

Data analysis

Mean IOP of both eyes was calculated by 5 years age-categories for men and women separately. The association between IOP, age and gender was evaluated with linear regression analysis. The prevalence of POAG was calculated by 10 years age-categories for men and women separately, and by 5 years age categories for men and women together. The association between POAG, age and gender was further evaluated with logistic regression analysis. The association of narrow anterior chamber angles with age and gender was also evaluated with logistic regression analysis. The odds ratio, obtained from logistic regression analysis, served for the indication of the relative risk.

Results

Average IOP was 14.6 mmHg and median IOP was 14.0 mmHg for both eyes. The relation between average IOP and sex is shown in Figure 3.1. Average IOP did not significantly change with age (coefficient of linear regression -0.004 mmHg/yr, 95% CI 0.016, 0.024) and was 0.3 mmHg lower in women than in men (95% CI -0.5, 0.3). The percentage of eyes with an IOP over 21 mmHg was 2.2% (95% CI 2.2, 2.2). A difference of over 2 mmHg between both eyes was observed in 7% (95% CI 6.8, 7.2) of the subjects.

The median VCDR was 0.3 for both eyes and both sexes. The vertical cup/disc ratio increased not significantly with age (coefficient 0.001 disc diameter/yr, 95% CI 0.000, 0.002) and no significant differences between both genders existed (coefficient -0.015 VCDR for women, 95% CI -0.028, 0.002). A VCDR $\geq$ 0.5 was found in at least one eye in 19.2% of the study population; thus a VCDR $\geq$ 0.8 was present in 2.2%. A difference of 0.2 disc diameter or more between both eyes occurred in 5.0% of the subjects. Optic disc hemorrhages were noted in 0.2% of the subjects. No significant difference existed between the subjective and automatic determination of the 25 randomly selected optic discs (Paired t-test, $P < 0.05$).

Narrow angles, determined with the method of von Herick, were present in 2.4% of the subjects; 2.7% in women and 1.8% in men. The prevalence of narrow angles was not significantly associated with age (logistic regression, Odds Ratio 1.03, 95% CI 1.00, 1.05). Women had a two times higher chance of having narrow angles than men (logistic regression, Odds Ratio 2.17, 95% CI 1.27-3.70). No person with a narrow angle had glaucomatous visual field defects.

A visual field defect or unreliable test was present in 563 (18.4%) of the 3,062 subjects and 530 (94.2%) out of this 563 subjects underwent a repetition of the screening test in the second phase. In 239 subjects (7.8%) an abnormal visual field test was present in the second phase and of them 205 subjects (85.8%) underwent Goldmann perimetry in the third phase. This resulted in a glaucomatous visual field defect in 45 eyes of 34 (1.1%) subjects. Other kinds of visual field defects were left out of consideration. None of the 44 subjects with a normal visual field in phase 1 had glaucomatous visual field loss in phase 2 or 3.

In the present study 1.1% (95% CI 1.09,1.11) (34 cases) had POAG on at least one eye (Table 3.1). In 53% the diagnosis of POAG was new. Of the new POAG cases 39% had IOP's $\leq$ 21 mmHg. No other types of glaucoma were present, nor were there subjects with a glaucomatous field defect who did not met the other diagnostic criteria for POAG. The prevalence of POAG in men was three times higher than in women (OR = 3.6). The prevalence of POAG increased from 0.2% (95% CI 0.16,0.24) in the age-group of 55-59 years to 3.3% (95% CI

2.57,4.04) in the age-group of 85-89 years (Table 3.2).

Visual acuity of 0.1 or lower due to POAG existed in three persons (all men) in four eyes.

In three pilot studies in different populations age 28 to 74, the median IOP was lowered by 1.5 mmHg after intake of 200 ml of 75 gram glucose solution.

In three cases an acute glaucoma occured after application of the mydriatics that was cured without sequelae by Nd-Yag laser iridotomy.

Discussion

In this study we observed an overall prevalence of POAG of 1.1%. The prevalence of POAG was related with age and was higher in men than in women. The diagnosis glaucoma was made for the first time in 53% of the POAG cases and of them 39% had IOP's ≤ 21 mmHg.

The distribution of the IOP corresponds well with other studies.[5-9] In the study from David[6] the median IOP was 14 mmHg, as in the present study. In other studies[5,7,8,9] the mean or median IOP was 1-2 mmHg higher compared with our study, which could have resulted from the influence of the glucose solution that was given prior to the IOP measurement. As a consequence, the percentage of eyes with an IOP over 21 mmHg in the present study was approximately half the percentage of eyes with elevated IOP in the other studies. The prevalence of IOP differences of over 2 mmHg between both eyes corresponded well with the estimate of 7.7% obtained in the Framingham Eye Study.[7] In contrast to our study, several studies[5-9] have found a relation between age and IOP. A possible explanation for this difference in relation between age and IOP is that this relation has been found in study populations that included younger age-groups. No sex differences in IOP were found in a few studies.[5,6,7] Other studies[8,9] have found a slightly higher IOP in women than in men. In our study, women had slightly lower IOP than men, but differences were small.

The median VCDR observed in our study corresponds well with other studies.[5,7] In a study of Klein et al[5], a grading system for fundus photographs of the optic disc was used, which may result in more accurate outcomes. In the Framingham Eye Study[7] a subjective interpretation of the cup/disc ratio was made by several investigators, which has probably resulted in a higher variability. The percentage of eyes with VCDR over 0.4 was 27.8% in the study from Klein, 10.9% in the Framingham Eye Study, and 19.4% in the present study. A difference of VCDR of 0.2 or more between both eyes occurred in 6.8% of the subjects in the Framingham Eye Study, and in 5% of the subjects in our study. An association between cup/disc ratio and age was reported in the Framingham Eye Study. Klein et al[6] reported a prevalence of optic disc hemorrhage of 0.9%,

which was only slightly higher than the 0.2% in the present study and within the confidence limits of our estimate.

The visual field screening procedure resulted in the selection of 1.1% of subjects with glaucomatous visual field defects on one or both eyes. This result is in agreement with the outcome of a study of Bengtsson.[10]

Studies from which age-specific prevalence data for POAG are known are tabulated in table 2.[1,5,7,9,11] From this table we can conclude that below age 65 years, the present study shows half the prevalence of POAG compared to other studies. The studies in Ferndale, Framingham and Dalby showed a prevalence of 0.8%, 0.8% and 0.9%, respectively, in the age-group of 55-69 years, whereas in Rotterdam the prevalence of POAG in the same age-group was 0.4%. Of course, due to the limited sample size, there is some overlap in this age-group between the confidence intervals of the point estimates. In the age-group of 80 years and over, the prevalences of POAG in Rotterdam were lower than the prevalences of Framingham, but higher than the prevalences of the Baltimore Eye Survey for white Americans. The prevalence of POAG in the age-group 80-84 years was 4.4% in Framingham and 3.1% in Rotterdam, whereas the prevalence of POAG in the age-group 80-89 years was 2.16% in Baltimore and 3.1% in Rotterdam. The study in Beaver Dam showed the highest prevalences of POAG in all age-categories. A partial explanation for this difference in prevalence is that in Beaver Dam a visual field defect was not necessary for the diagnosis of POAG in contrast to the present study. But even when we use their definition of POAG in the Rotterdam study, it would only increase the overall prevalence from 1.1% to 1.5%, which is still beneath the 2.1% overall prevalence of POAG in Beaver Dam. In addition, differences in visual field testing procedure may have resulted in differences in prevalence; in Dalby[10], Baltimore[11] and Rotterdam visual field defects detected with automatic perimetry had to be confirmed with Goldmann perimetry. In Beaver Dam only automatic perimetry was performed. In the present study, 53% of the cases with POAG were newly discovered. This figure is similar as in a study of Hollows.[9] In a study of Bengtsson[10] however, none of the glaucoma cases were previously treated.

Of the 53% newly found POAG cases, 39% had IOP's $\leq$ 21 mmHg. This percentage would remain the same when corrected for the possible influence of the glucose drink as the IOP's were $\leq$ 18 mmHg. The percentage of subjects with normal IOP's in untreated POAG cases is only slightly lower than the 50%[9] and the 61%[10] observed in other studies.

There is conflicting evidence regarding the association of POAG with gender. In the Framingham Eye Study[7] a higher prevalence of glaucoma among males was observed, like in our study. Bengtsson[10] has found a higher prevalence

of POAG among females. In other studies[5,9,11] no sex difference in glaucoma prevalence was observed. The small number of POAG cases could have resulted in the relation between POAG and gender as found in the present study. An argument in favor of a real difference is that differences in gender were consistently present in all age-categories. Furthermore, it may be that this sex-difference in prevalence of POAG is more pronounced in older age-groups. Combining prevalence results with younger age-groups may equalize the sex-difference. If there exists a real difference in prevalence of POAG in men and women, some unknown factors related with gender predispose or protect for POAG at the age of 55 years and over.

In conclusion, the overall prevalence of POAG was 1.1% in this study, which is similar to prevalence figures of glaucoma in other studies on white persons. Men had a three times higher risk of having POAG than women. Age-adjusted rates showed a lower frequency of POAG till the age of 65 years in comparison with other studies, which suggests that POAG starts at an older age in Rotterdam.

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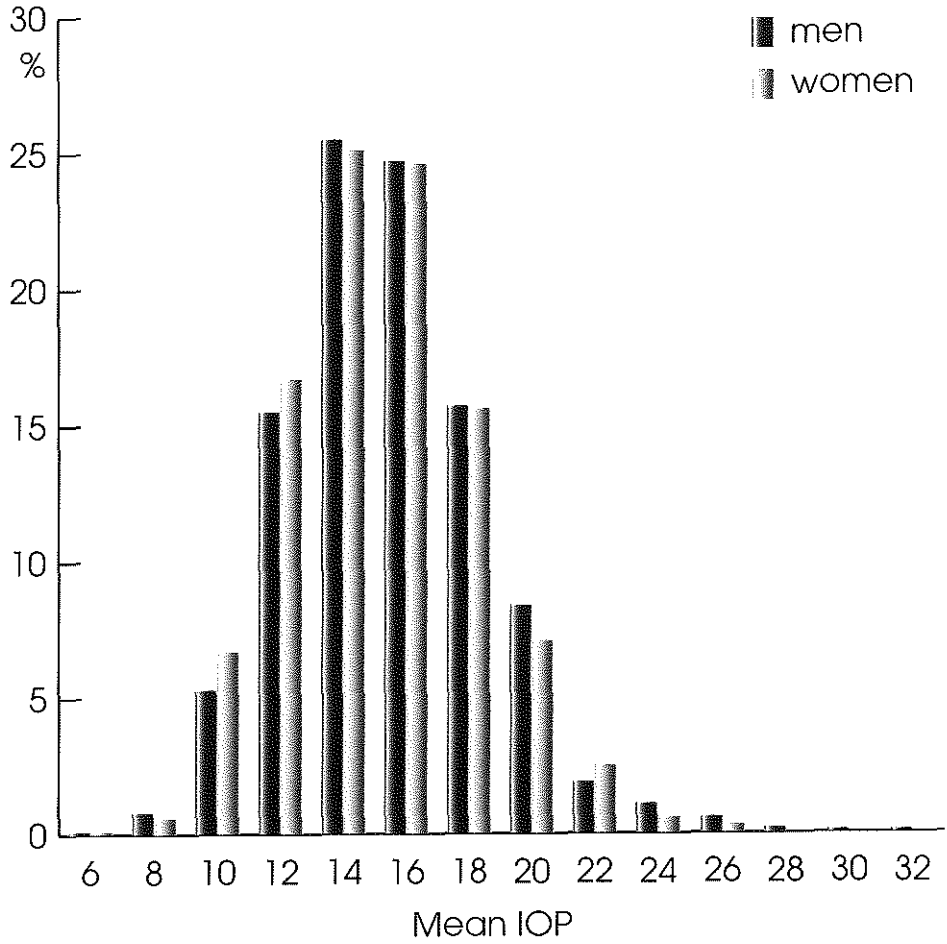
Table 3.1
Prevalence of Primary Open Angle Glaucoma (n=3,062) according to the Rotterdam criteria

	Men		Women		Total	
age-groups (years)	total number	cases	total number	cases	total number	cases
55-64	461	1 (0.2%)	657	1 (0.2%)	1118	2 (0.2%)
65-74	515	12 (2.3%)	730	5 (0.7%)	1245	17 (1.4%)
75+	250	10 (4.0%)	449	5 (1.1%)	699	15 (2.2%)
Total	1226	23 (1.9%)	1836	11 (0.6%)	3062	34 (1.1%)

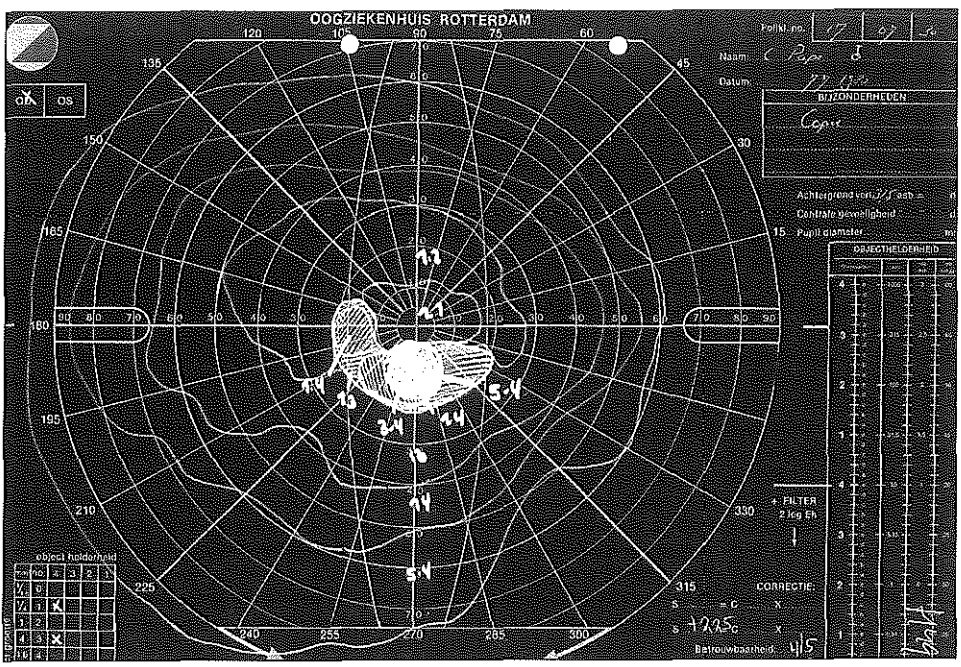
Table 3.2
Age-specific prevalences of Primary Open Angle Glaucoma in epidemiological studies

age-groups (years)	Ferndale (1966)[9]	Framingham (1977)[7]	Dalby (1981)[10]	Baltimore (1991)[11]	Beaver Dam (1992)[5]	Rotterdam (1993)
40-45				0.92		
45-49					1.0	
50-54	0.3			0.41		
55-59	0.9	0.5	0.4			0.2
60-64	0.5	0.7	0.8		1.3	0.2
60-64	0.8	0.8	0.9	0.88		0.4
65-69	1.1	0.9	1.5		2.7	0.9
65-69						1.3
70-74	1.3	1.7		2.89		1.8
75-79		2.0				1.6
80-84		4.4		2.16	6.3	3.1
80-84						2.1
85-89						3.3
						3.1

Figure 3.1
Mean IOP of the right and the left eye in men and women.



Glaucomatous visual field defect with Goldman perimetry



Chapter 4

Primary open-angle glaucoma, intraocular pressure and diabetes melllitus in the general elderly population: The Rotterdam Study

Abstract

Purpose

The purpose of this study is to investigate the presence of primary open-angle glaucoma and intraocular pressure associated with newly diagnosed diabetes mellitus.

Methods

Subjects participating in The Rotterdam Study (n=4,178, ages 55 years and over) were examined according to standard protocols, including a medical history interview, perimetry, applanation tonometry, funduscopy and a non-fasting glucose tolerance test. Glaucoma was defined by the presence of a glaucomatous visual field defect. A distinction was made between high-tension glaucoma and normal-tension glaucoma. The relation of glaucoma and intraocular pressure with newly diagnosed diabetes mellitus and blood glucose was analyzed using regression analysis.

Results

The presence of diabetes mellitus was associated with an overall rise of mean intraocular pressure of both eyes of 0.31 mmHg (95% confidence interval 0.12, 0.50), and with a three-fold increased presence of high-tension glaucoma (odds ratio 3.11, 95% confidence interval 1.12, 8.66). Normal-tension glaucoma was not associated with diabetes mellitus. A 10 mmol/l higher random serum glucose level was associated with a mean intraocular pressure that was on average 0.41 mmHg (95% confidence interval -0.02, 0.84) higher and with an odds ratio of 2.82 (95% confidence interval 0.92, 8.58) for high-tension glaucoma. A rise of 10 mmol/l of serum glucose on a glucose tolerance test was associated with an overall rise of mean intraocular pressure of 0.59 mmHg (95% confidence interval 0.26, 0.92) and with an odds ratio of 1.88 (95% confidence interval 0.81, 4.32) for high-tension glaucoma.

Conclusion

Newly diagnosed diabetes mellitus and high levels of blood glucose are associated with elevated intraocular pressure and high-tension glaucoma.

Introduction

One of the putative risk factors of primary open-angle glaucoma is diabetes mellitus. Various epidemiological studies have suggested that diabetes mellitus is associated with primary open-angle glaucoma[1-6] and with intraocular pressure.[1,2,3,7-11] No relation[12] or a negative relation[13] between diabetes and intraocular pressure have been observed. In the Framingham Eye Study and the Beaver Dam Eye Study these relations have been investigated in the community.[6,10,11] The present study focuses on the relation between primary open-angle glaucoma and intraocular pressure, and diabetes mellitus and serum glucose levels in a population-based study in Rotterdam, The Netherlands.[14]

Material and methods

Population

The present study was performed as part of The Rotterdam Study. The Rotterdam Study is a single-center prospective follow-up study of a cohort of 11,854 people, aged 55 years or more, living in a suburb of Rotterdam, The Netherlands. The design of the study has been described previously.[14] The study has been approved by the Medical Ethics Committee of the Erasmus University. Written informed consent was obtained from all participants. The objective of the study is to clarify the determinants of occurrence of chronic, disabling cardiovascular, neurogeriatric, locomotor, and ophthalmologic diseases. The study comprises an extensive home interview, followed by two visits at the examination center for a clinical examination.

From June 1990 until January 1993 7,120 residents had been invited and 5,673 subjects had actually participated. The overall participation rate was 80%. Because visual field examination often was impossible in the institutionalized persons, we confined the analyses presented here to the non-institutionalized individuals aged 55 to 95 years (4,266 subjects). In 4,178 persons (98%) data on intraocular pressure, diabetes mellitus and blood glucose were available. All persons but those who used antidiabetic medication had a glucose tolerance test. Because the intraocular pressure was measured after the oral glucose load, which could have influenced the intraocular pressure measurements, people using antidiabetic medication were excluded from the study. So 4,012 persons (94%) were included in the present analyses.

Measurements

The glaucoma screening was performed in three phases.[15] In the first phase, the intraocular pressure was measured three times on each eye with the Goldmann applanation tonometer (Haag-Streit, Bern, Switzerland)[16] and the median value was used in the analysis.

In the same phase the 76-point suprathreshold screening test of the Humphrey perimeter (Humphrey Visual Field Analyzer, Zeiss, Oberkochen, Germany) was used to detect visual field defects in the central 30 degrees. Three or more contiguously missed points on the screening test were taken as indication for a visual field defect. The reliability of a test result was stated by the perimeter and ultimately determined by the technician. In mydriasis direct ophthalmoscopy was performed to assess the vertical cup/disc ratio, in relation to the contour of the cup. In the second phase of the study, which was performed two weeks after the first phase, visual fields were retested with the same 76-point screening test in subjects with an abnormal or unreliable visual field test in the first phase. In the third phase, carried out within a few weeks after the second phase, subjects with an abnormal or unreliable visual field test in the second phase of the study, were recalled for perimetry with the Goldmann perimeter. Perimetry was performed according to a standard protocol[17] and without knowledge of former visual field defects. Remeasurement of the intraocular pressure and gonioscopy was performed when a glaucomatous visual field defect was present, which could not be explained by other ocular abnormalities.

The definition of primary open-angle glaucoma was based on the presence of a glaucomatous visual field defect on Goldmann perimetry[17] in combination with either a vertical cup/disc ratio of 0.5 or greater or a difference in cup/disc ratio of 0.2 or more between the right and left eye, or an intraocular pressure greater than 21 mmHg, with a normal and open anterior chamber angle, without any other abnormality that could have caused the visual field defect. High-tension glaucoma was defined as primary open-angle glaucoma with an intraocular pressure of more than 21 mmHg in at least one of the two measurement sessions in phase one and phase three, in the same eye as the visual field defect, or any treatment for glaucoma. Normal-tension glaucoma was defined as primary open-angle glaucoma with intraocular pressure of 21 mmHg or less and no treatment for glaucoma.

Newly diagnosed diabetes mellitus was considered present if the random serum glucose level or the serum glucose level two hours after a non-fasting glucose load (75 grams) was higher than 11.0 mmol/l. Subjects using antidiabetic medication (tablets or insulin) were excluded from the analyses.

Height and weight were measured in indoor clothing and without shoes. Body mass index was calculated as weight divided by the square of height (kg/m^2).

Analysis

The relation between mean intraocular pressure of both eyes and diabetes mellitus was studied by comparison of average intraocular pressure and linear regression. IOP was taken as a continuous variable and diabetes as a dichotomous variable (present, absent) in the linear model. The association with diabetes was expressed in terms of linear regression coefficients with 95% confidence limits.

The relation between mean intraocular pressure of both eyes and random serum glucose level was also studied with linear regression analysis. Intraocular pressure and serum glucose level were entered as continuous variables in the linear model. Regression coefficients were expressed per 10 mmol/l glucose.

The relation between high-tension glaucoma and random serum glucose was studied using logistic regression analysis. Serum glucose values were entered as continuous variables, and primary open-angle glaucoma was entered as a dichotomous variable (present, absent) in the regression model. The associations with primary open-angle glaucoma were expressed as odds ratio's per 10 mmol/l glucose, which is an approximation of the relative risk. The association of diabetes mellitus with high-tension glaucoma was studied in the same way.

All analyses were adjusted for age, sex and body mass index, and when appropriate for systolic blood pressure.

Results

Mean values of intraocular pressure are shown for subjects without diabetes and with untreated diabetes, for men and women separately, in age-groups below 70 years and 70 years or older (Table 4.1). Newly diagnosed diabetes was associated with a slightly, but consistently higher mean intraocular pressure than absence of diabetes. No significant effect for age or sex was observed. With linear regression the presence of newly diagnosed diabetes was associated with a significant overall rise in mean intraocular pressure of 0.31 mmHg (95% confidence interval 0.12, 0.50).

A rise of 10 mmol/l of random serum glucose level was associated with a borderline significant overall rise in mean intraocular pressure of 0.41 mmHg (95% confidence interval -0.02, 0.84). For the post-load glucose levels this association was 0.59 mmHg (95% confidence interval 0.26, 0.92). No significant difference existed between women and men. Additional adjustment for systolic blood pressure did not significantly change the association between mean intraocular pressure and blood glucose.

A 10 mmol/l higher random serum glucose level was associated with a 2.82 (95% confidence interval 0.92, 8.58) higher risk of having high-tension glaucoma.

For the post-load glucose levels this association was 1.88 (95% confidence interval 0.81, 4.32). Additional adjustment for systolic blood pressure did not significantly change the association between serum glucose and high-tension glaucoma.

Newly diagnosed diabetes mellitus was related with an odds ratio of 3.11 (95% confidence interval 1.12, 8.66) for high-tension glaucoma, after adjustment for age, sex and body mass index. In persons with normal-tension glaucoma no case of newly diagnosed diabetes mellitus was present, as a consequence odds ratio's could not be calculated.

Discussion

Our findings in this cross-sectional study in a population aged 55 years and over suggest that newly diagnosed diabetes mellitus and elevated serum glucose levels are associated with a higher mean intraocular pressure and high-tension glaucoma.

The relation between diabetes and intraocular pressure found in this study was similar to what was found in case-control studies[1,2,3,7,8,9] and in population-based studies[9,10]. The same was the case with the relation between serum glucose and intraocular pressure, which was also found in case-control studies[7,8,18] and in a smaller population-based study.[11]

In the present study, the associations between diabetes, blood glucose and intraocular pressure were the same in women and men. This was also found in other studies.[8,12] In two studies[3,13] on diabetic persons slightly higher intraocular pressure was found in women. Some studies[11,18] did not analyse the difference in associations between women and men.

Few epidemiological studies have suggested that diabetes mellitus is associated with primary open-angle glaucoma[2,3,6] or, like in our study, with high-tension glaucoma.[4,5] Most of these studies[2,3,4,5] have considered diabetic persons as those receiving medication for their disease. In the Beaver Dam Eye Study the presence of diabetes mellitus was defined as either a history of treatment of diabetes or a glycosylated hemoglobin level greater than two standard deviations above the mean and a casual blood sugar level of greater than 11.1. They have found that diabetes mellitus was related with an odds ratio of 1.84 (95% confidence interval 1.09, 3.11) for primary open-angle glaucoma, which was lower than that was found in the present study for high-tension glaucoma. A possible explanation is that persons with normal-tension glaucoma were included in the analyses of the Beaver Dam Eye Study, which could have led to a lower odds ratio. In the Framingham Eye Study[10,11], where the presence of diabetes mellitus was based on the presence of diabetic retinopathy, whether or not they

were known to be diabetic, no association could be observed between diabetes and primary open-angle glaucoma. Because the glucose test could have influenced the level of intraocular pressure and people who were treated for their diabetes mellitus were excluded from having a glucose load, in the present study, only untreated persons at baseline unknown with diabetes mellitus were considered. This exclusion could have led to an underestimation of the association that was found between diabetes mellitus and primary open-angle glaucoma, because the diabetes mellitus could have had longer and more serious pathologic influence on persons that were already treated for their diabetes mellitus.

In the present study, associations between diabetes and normal-tension glaucoma could not be assessed, because of the small number of persons with normal-tension glaucoma.

An association between blood glucose and both intraocular pressure as well as high-tension glaucoma was observed in this study. In additional analyses it appeared that these associations were not significantly influenced by systolic blood pressure, therefore the relations between blood glucose, intraocular pressure, and high-tension glaucoma are not confounded by systolic blood pressure.

The mechanism of the association between blood glucose and intraocular pressure is not clear. Possibly the elevated blood glucose may induce an osmotic gradient and attract fluid into the intraocular space, which may result in an elevated intraocular pressure.[7] In another study[5] a slight decrease in the coefficient of outflow with increasing severity of diabetic retinopathy has been found, apart from the advanced proliferative form. Armaly et al[12] suggested that more than one effect may exist and effects may act in opposite directions. Furthermore, it is possible that diabetes mellitus increases the susceptibility of the optic nerve fibers, leading to visual field defects, either because of common genetic factors, because of the effect of diabetes mellitus on the small vessels of the eye,[1] or due to diabetic neuropathy.

In conclusion, the present population-based cross-sectional study confirms earlier mainly case-control studies that diabetes mellitus and blood glucose are associated with a higher intraocular pressure and with high-tension glaucoma.

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Table 4.1
Intraocular pressure (IOP) of subjects without diabetes mellitus and with newly diagnosed diabetes mellitus*

	Women			Men			Total
	55-69 yrs	70-94 yrs	total	55-69 yrs	70-94 yrs	total	55-94 yrs
Without diabetes mellitus†:							
number	n=1303	n=965	n=2268	n=912	n=576	n=1488	n=3756
mean IOP	14.46	14.37	14.42	14.72	14.65	14.69	14.52
SD	2.95	3.08	3.01	3.06	3.30	3.16	3.08
Newly diagnosed diabetes‡:							
number	n=65	n=85	n=150	n=52	n=54	n=106	n=256
mean IOP	14.95	14.65	14.78	15.29	14.69	14.98	14.86
SD	2.47	2.85	2.69	3.38	3.04	3.21	2.91

* Values are means with standard deviations in parentheses.

† Glucose levels ≤ 11.0 mmol/l.

‡ Glucose levels ≥ 11.0 mmol/l.

Chapter 5

Primary open-angle glaucoma, intraocular pressure and systemic blood pressure in the general elderly population: The Rotterdam Study

Abstract

Purpose

The purpose of this study was to investigate the association between primary open-angle glaucoma, intraocular pressure and systemic blood pressure.

Methods

Subjects participating in the Rotterdam Study (n=4,187, age 55 yrs and over) were examined according to standard protocols, including a medical history interview, intraocular pressure (IOP) measurement, perimetry, funduscopy and blood pressure measurement. Primary open-angle glaucoma (POAG) was defined by the presence of a glaucomatous visual field defect. Additionally, the distinction was made between high-tension glaucoma, defined as POAG with an IOP of over 21 mmHg, and normal-tension glaucoma, defined as POAG with an IOP of 21 mmHg or less. The relation between blood pressure and hypertension with IOP, POAG, high-tension glaucoma and normal-tension glaucoma was studied by means of regression analysis.

Results

A systolic blood pressure or diastolic blood pressure that was 10 mmHg higher was associated with an IOP that was on average 0.23 mmHg (95% confidence interval (CI) 0.19 - 0.27) or 0.24 mmHg (0.16 - 0.32) higher, respectively. The presence of hypertension was associated with a 0.66 mmHg higher mean IOP (0.39 - 0.93). A 10 mmHg higher systolic blood pressure was associated with an odds ratio (OR) of 1.22 (1.03-1.46 95% confidence interval) for high-tension glaucoma and 0.90 (0.72-1.12) for normal-tension glaucoma. Hypertension was associated with an OR of 2.33 (0.99-5.47) for high-tension glaucoma, and 0.77 (0.22-2.72) for normal-tension glaucoma.

Conclusion

Systemic blood pressure and hypertension are associated with IOP and high-tension glaucoma. No association was found between blood pressure or hypertension and normal-tension glaucoma.

Introduction

Vascular conditions have received considerable attention in studies of primary open-angle glaucoma (POAG), but results concerning their association with POAG are ambiguous or contradictory.[1-8] No significant relation between systemic blood pressure and glaucoma has been observed in several studies.[1-4] Two studies[5,6] have found an association between systolic blood pressure and normal-tension glaucoma. In other studies an association between systemic blood pressure and high-tension glaucoma was observed.[7,8] Elevated intraocular pressure (IOP) is the most important known risk factor of glaucoma.[9] Few studies have investigated the relation between IOP and cardiovascular characteristics in the community.[10,11,12] In these studies, the cardiovascular variable that had the strongest correlation with IOP was systolic blood pressure. The objective of the present study was to assess the relation between POAG, IOP and systemic blood pressure in a population-based study.

Material and methods

Population

The present study was performed as part of the Rotterdam Study. The Rotterdam Study is a single-centre prospective follow-up study of a cohort of over 10,000 residents, aged 55 years or more, of Ommoord, a suburb of the city of Rotterdam, The Netherlands. The design of the study has been described in detail previously.[13] The study has been approved by the Medical Ethics Committee of the Erasmus University, and written informed consent was obtained from all participants. The objective of the Rotterdam Study is to clarify the determinants of occurrence of chronic, disabling cardiovascular, neurogeriatric, locomotor, and ophthalmologic diseases. The study comprises an extensive home interview, followed by two or three visits at the examination centre for a clinical examination.

From June 1990 until January 1993 7,120 residents of Ommoord had been invited and 5,673 subjects had actually participated. The overall participation rate was 80%. We confined our sample for this analysis to the non-institutionalized individuals aged 55 to 95 years, because visual field data from persons in nursing homes were found in a pilot study to be often unreliable or impossible to make, which left 4,266 subjects. Of these, for 4,187 persons (98%) data on glaucoma and blood pressure were available and these persons were included in the present analyses.

Procedures

The protocol for glaucoma screening has been described previously.[14] The glaucoma screening was performed in three phases.

In the first phase, the intraocular pressure was measured three times on each eye with the Goldmann applanation tonometer (Haag-Streit, Bern, Switzerland). The median value of the three measurements was taken.[15] The 76-point suprathreshold screening test of the Humphrey perimeter (Humphrey Visual Field Analyzer, Zeiss, Oberkochen, Germany) was used to detect visual field defects in the central 30 degrees. In the second phase of the study, which was performed two weeks after the first phase, visual fields were retested with the same 76-point screening test in subjects with an abnormal or unreliable visual field test in the first phase. In the third phase, carried out within a few weeks after the second phase, subjects with an abnormal or unreliable visual field test in the second phase of the study, were recalled for perimetry with the Goldmann perimeter. Perimetry was performed according to a standard protocol[16] and without knowledge of former visual field defects. Remeasurement of the IOP and gonioscopy were performed when a glaucomatous visual field defect was present, which could not be explained by other ocular abnormalities.

Blood pressure was measured in the sitting position at the right upper arm with a random-zero sphygmomanometer. The average of two measurements, separated by a count of the pulse rate, was used in the analysis.[17] Hypertension was defined as a systolic blood pressure of 160 mmHg or over and/or a diastolic blood pressure of 95 mmHg or over. Isolated systolic hypertension was defined as a systolic blood pressure of 160 mmHg or over in combination with a diastolic blood pressure of 90 mmHg or less. The use of medication was asked during the home interview and was checked at the examination center by the examining physician. Codes of the Anatomical Therapeutic Chemical (ATC) classification index were used to classify the antihypertensive medication. The categories used in this study were beta-blocking agents, diuretics, vasodilators, angiotensin converting enzyme inhibitors and calcium channel blockers.

Height and weight were measured in standing position without shoes. Body mass index was calculated as weight in kilograms divided by height in squared meters.

Definitions of POAG (Table 5.4)

The diagnosis of POAG in the Rotterdam study has been described earlier[14], and was made according to two definitions. In the first definition, according to the Rotterdam criteria POAG was based on the presence of a consistent glaucomatous visual field defect in combination with either a vertical

cup/disc ratio of 0.5 or greater or a difference in cup/disc ratio of 0.2 or more between the right and left eye, or an IOP greater than 21 mmhg, with a normal and open anterior chamber angle, without any other abnormality that could have caused the visual field defect. High-tension glaucoma was defined as POAG with an IOP of more than 21 mmHg in at least one of the two measurement sessions in phase one and phase three, in the same eye as the visual field defect, or treatment for glaucoma. Normal-tension glaucoma was defined as POAG with an IOP of 21 mmHg or less and no treatment for glaucoma. A second definition of POAG used in this study had similar criteria as those used in the Beaver Dam Eye Study (BDES).[18] This includes the presence of at least two of the three following features: visual field defect compatible with the diagnosis of glaucoma, cup/disc ratio of 0.8 or greater or difference in cup/disc ratio of 0.2 or more in involved eye, and IOP of 22 mmHg or more in the involved eye.

Analysis

The relation between systolic blood pressure, diastolic blood pressure and mean IOP of both eyes was studied using linear regression analysis. IOP and blood pressure values were entered as continuous variables in the regression model. The associations with blood pressure were expressed in coefficients of linear regression per 10 mmHg.

The association of hypertension with the mean IOP of both eyes was also studied with linear regression. Hypertension was entered as a dichotomous variable (present, absent) and the mean IOP as a continuous variable in the linear model.

The relation between the use of antihypertensive medication and mean IOP of both eyes was studied with linear regression. The use of one or more antihypertensive drugs was entered as a dichotomous variable and mean IOP of both eyes as a continuous variable in the linear model.

The relation between the use of a certain kind of antihypertensive medication and mean IOP of both eyes was studied by means of linear regression. The use of an antihypertensive drug was entered as a dichotomous variable and mean eye IOP of both eyes as a continuous variable in the linear model.

The relation between systolic blood pressure, diastolic blood pressure and POAG was studied using logistic regression analysis. Blood pressure values were entered as continuous variables, and glaucoma was entered as a dichotomous variable (present, absent) in the regression model. The associations with blood pressure were expressed in prevalence odds ratio's per 10 mmHg. The association of hypertension with POAG was also studied with logistic regression analysis. Hypertension and glaucoma were entered as dichotomous variables in the logistic

model. All analyses were adjusted for age and sex, and when appropriate for body mass index, antiglaucoma and antihypertensive medication.

Results

Mean values of IOP, blood pressure and body mass index are shown for men and women separately, in age-groups below 70 years and 70 years or older (Table 5.1). IOP did not vary by age and gender. Systolic blood pressure and pulse pressure increased with age, especially in women. Diastolic blood pressure decreased slightly with age, and was the same in men and women. Body mass index was the same in both age-groups but women had a slightly higher mean body mass index than men.

Relations of systolic blood pressure and diastolic blood pressure with mean IOP of both eyes are shown in table 2. A systolic blood pressure or diastolic blood pressure that was 10 mmHg higher was associated with an IOP that was on average 0.23 mmHg (0.19-0.27 95% CI) or 0.24 mmHg (0.16-0.32) higher, respectively.

In general, relations between blood pressure and mean IOP were stronger in the age-group of 55-69 years compared with the age-group of 70 years or older. Women in the youngest age-group had a stronger association between systolic blood pressure and IOP than men in the same age-group. In the oldest age-group men showed stronger associations than women.

Associations between the presence of hypertension and mean IOP of both eyes are shown in Table 3. Hypertension was related to a 0.66 mmHg higher mean IOP. However, hypertension, including the use of antihypertensive drugs was not associated with IOP. Isolated systemic hypertension was associated with a 0.65 mmHg higher IOP. Analysis according to different classes of antihypertensive medication revealed that only the use of beta-blocking agents was associated with a significantly lower mean IOP (-0.67 mmHg, SE 0.14).

The prevalence of POAG, defined in different ways, is shown in Table 4. The prevalence of POAG according to the Rotterdam criteria was 1.00% (N=42), following the BDES criteria 1.31% (N=55).

The prevalence of POAG by quartiles of systolic blood pressure is shown in Figure 1. Subjects treated with antihypertensive medication were included in the highest blood pressure category. The prevalence of POAG was higher in a higher blood pressure category.

The associations of systolic blood pressure and diastolic blood pressure with POAG are shown in Table 5. A rise of 10 mmHg of systolic blood pressure or diastolic blood pressure was associated with a 1.08 or 1.00 (means no) higher probability of having POAG, respectively, when POAG was defined according to

the Rotterdam criteria. POAG defined according to the BDES[18] showed higher odds ratio's, namely 1.15 or 1.10, respectively, with significant results for systolic blood pressure. The strongest relation was found for high-tension glaucoma, with an odds ratio of 1.22 for systolic pressure. Odds ratio's for normal-tension glaucoma were not significantly different from 1. Adding IOP or cardiovascular risk factors such as diabetes mellitus, serum cholesterol, cigarette smoking and angina pectoris, for adjustment for possible confounding of the association between POAG, high-tension glaucoma or normal-tension glaucoma and systolic blood pressure, did not change the odds ratio's.

Relations between systemic hypertension and POAG are shown in Table 6. Hypertension, hypertension including anti-hypertensive treatment, and isolated systolic hypertension were related with odds ratio's of 1.55, 1.94 or 1.49, respectively, for POAG according to the Rotterdam criteria. The results for POAG defined according to the BDES[18] were very similar. Again the strongest relation was found for high-tension glaucoma, with an odds ratio of 2.33. Normal-tension glaucoma did not show any association with hypertension.

Discussion

Associations with IOP

In this study, we found that an increase of systolic blood pressure and diastolic blood pressure was related to a higher mean IOP of both eyes, and that the use of beta-blocking agents was related with a significantly lower mean IOP. Furthermore, high-tension glaucoma was related with high systolic blood pressure and presence of hypertension. Some methodological comments have to be made. The design of this study was cross-sectional. The inference of the observed associations in causal terms has therefore to be made with caution and restraint. In addition, although this was a large population sample, the number of POAG cases was limited. This is also a reason for caution in the interpretation of our findings.

The relation of systolic blood pressure and IOP found in this study is similar to what was found in other studies.[10,11,12,19,20,21] A few studies did also find a relation between IOP and diastolic blood pressure[11,19,20], but we did not.

In a study of David et al[22] hypertension was defined as the use of antihypertensive medication. No association was found in that study between the use of antihypertensive medication and IOP. In our study, hypertension defined as systolic blood pressure of 160 mmHg or over and/or diastolic blood pressure of 95 mmHg or over, was related to higher IOP, but inclusion of the use of antihypertensive medication resulted in a disappearance of the association between IOP and hypertension. The relation between blood pressure and IOP

may result from a common physiologic factor such as the effect of generalized sympathetic tone or serum corticosteroids.[23]

Associations with POAG

A positive relation between high-tension glaucoma and systolic or diastolic blood pressure has been observed before.[7,8] One study[8] has shown a relation between normal-tension glaucoma and treatment for hypertension, which is not confirmed by the present study. Some studies[2,3] have not found a significant relation between high-tension glaucoma and systolic blood pressure, diastolic blood pressure or treatment for hypertension. In other studies[1,4] no significant differences were found between high-tension and normal-tension glaucoma in relation to cardiovascular factors, including blood pressure[4], or arterial pressure expressed as ankle-to-brachial ratio's[1], as an indicator for peripheral atherosclerosis.

The present study showed a relation between systolic blood pressure and hypertension with high-tension glaucoma. No relation was observed between blood pressure and normal-tension glaucoma. In additional analyses it appeared that these relations were not confounded by IOP. Since there is a clear relation between blood pressure and IOP[10,11,12], and IOP is the strongest risk factor presently known for POAG[9], it may be concluded that systemic blood pressure, in particular systolic blood pressure is a risk factor for high-tension glaucoma.

In conclusion, the present study suggests that systolic blood pressure and diastolic blood pressure are positively associated with intraocular pressure. Of the antihypertensive medications, beta-blocking agents are associated with a lower intraocular pressure. High-tension glaucoma is associated with systolic blood pressure and hypertension, whereas normal-tension glaucoma is not associated with blood pressure or hypertension.

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Table 5.1
Baseline characteristics of the participants in the study*

	Women			Men			Total
	55-69 yrs	70-94 yrs	Total	55-69 yrs	70-94 yrs	Total	
Number of subjects	1401	1124	2525	997	665	1662	4187
Body mass index (kg/m2)	26.7	27.1	26.9	25.8	25.7	25.8	26.4
	(4.1)	(4.2)	(4.2)	(2.9)	(3.2)	(3.0)	(3.8)
IOP right eye (mmHg)	14.6	14.6	14.6	14.9	14.8	14.8	14.7
	(3.1)	(3.2)	(3.1)	(3.3)	(3.4)	(3.3)	(3.2)
IOP left eye (mmHg)	14.5	14.5	14.5	14.7	14.7	14.7	14.5
	(3.0)	(3.3)	(3.2)	(3.2)	(3.6)	(3.3)	(3.2)
IOP both eyes (mmHg)	14.5	14.5	14.5	14.8	14.7	14.8	14.6
	(3.0)	(3.1)	(3.0)	(3.1)	(3.3)	(3.2)	(3.1)
Systolic blood pressure (mmHg)	133.4	146.7	139.3	134.9	142.5	137.9	138.7
	(20.8)	(21.6)	(22.1)	(20.0)	(22.5)	(21.3)	(21.8)
Diastolic blood pressure (mmHg)	73.3	72.6	73.0	74.8	72.2	73.7	73.3
	(10.6)	(11.3)	(11.4)	(11.1)	(11.8)	(11.4)	(11.2)

*Values are means with standard deviations in parentheses.

Table 5.2
Associations between systemic blood pressure and intraocular pressure*

	Women		Men		Total
	55-69 yrs	70-94 yrs	55-69 yrs	70-94 yrs	55-94 yrs
Systolic blood pressure					
	0.32	0.15	0.25	0.19	0.23
	(0.04)	(0.04)	(0.05)	(0.06)	(0.02)
Diastolic blood pressure					
	0.32	0.14	0.21	0.32	0.24
	(0.08)	(0.08)	(0.09)	(0.11)	(0.04)

*Results are coefficients of linear regression with standard errors in parentheses. The unit of increase of blood pressure was taken as 10 mmHg. Overall coefficients were adjusted for age, sex, body mass index, treatment for glaucoma and treatment for systemic hypertension. Coefficients for women and men separately had the same adjustments except for sex.

Table 5.3
Associations between hypertension and intraocular pressure (mmHg)

	IOP	Adjusted IOP[3]	Difference in adjusted IOP (SE)
Normotension (n=2381)	14.57	13.70	
Hypertension[1] (n=678)	15.23	14.36	+0.66 (0.14)
Hypertension or normotension with antihypertensive medication (n=1747)	14.69	13.74	+0.04 (0.10)
Isolated systolic hypertension[2] (n=499)	15.21	14.35	+0.65 (0.16)

[1]Hypertension = Systolic blood pressure ≥ 160 mmHg and/or diastolic blood pressure ≥ 95 mmHg.
[2]Isolated systolic hypertension = Systolic blood pressure ≥ 160 mmHg and diastolic blood pressure < 90 mmHg.
[3]Adjusted for age, sex and body mass index.

Table 5.4
Prevalence of POAG in the Rotterdam Study according to different definitions (n = 4,187)

Definition	Criteria	Prevalence (93% CI)	Number
1. POAG as defined in the Rotterdam Study:	Glaucomatous visual field defect and cup/disc ratio ≥ 0.5 disc diameter or difference in cup/disc ratio ≥ 0.2 disc diameter or IOP > 21 mmHg.	1.00% (0.70-1.30)	42
2. POAG as defined in the Beaver Dam Eye Study:	At least two of the following three criteria must be present: • glaucomatous visual field defect, • cup/disc ratio ≥ 0.8 disc diameter, • difference in cup/disc diameter ≥ 0.2 disc diameter, IOP > 21 mmHg.	1.31% (0.96-1.65)	55
3. High-tension glaucoma:	As 1, including IOP > 21 mmHg or treatment for POAG.	0.57% (0.34-0.80)	24
4. Normal-tension glaucoma:	As 1, including IOP ≤ 21 mmHg without treatment for POAG.	0.43% (0.23-0.63)	18

Table 5.5
Odds ratio's (95% confidence intervals) of systolic blood pressure and diastolic blood pressure in relation to POAG according to different criteria*

	POAG (RS)[1] OR (95% CI)	POAG (BDES)[2] OR (95% CI)	HTG (RS) OR (95% CI)	NTG (RS) OR (95%CI)
Systolic blood pressure	1.08	1.15	1.22	0.90
(per 10 mmHg)	(0.94-1.24)	(1.02-1.30)	(1.03-1.46)	(0.72-1.13)
Diastolic blood pressure	1.00	1.10	1.03	0.95
(per 10 mmHg)	(0.76-1.31)	(0.88-1.39)	(0.73-1.47)	(0.62-1.44)

*The unit of increase of blood pressure was taken as 10 mmHg.
Adjustments were made for age, sex and body mass index.
[1]RS = Rotterdam Study
[2]BDES = Beaver Dam Eye Study

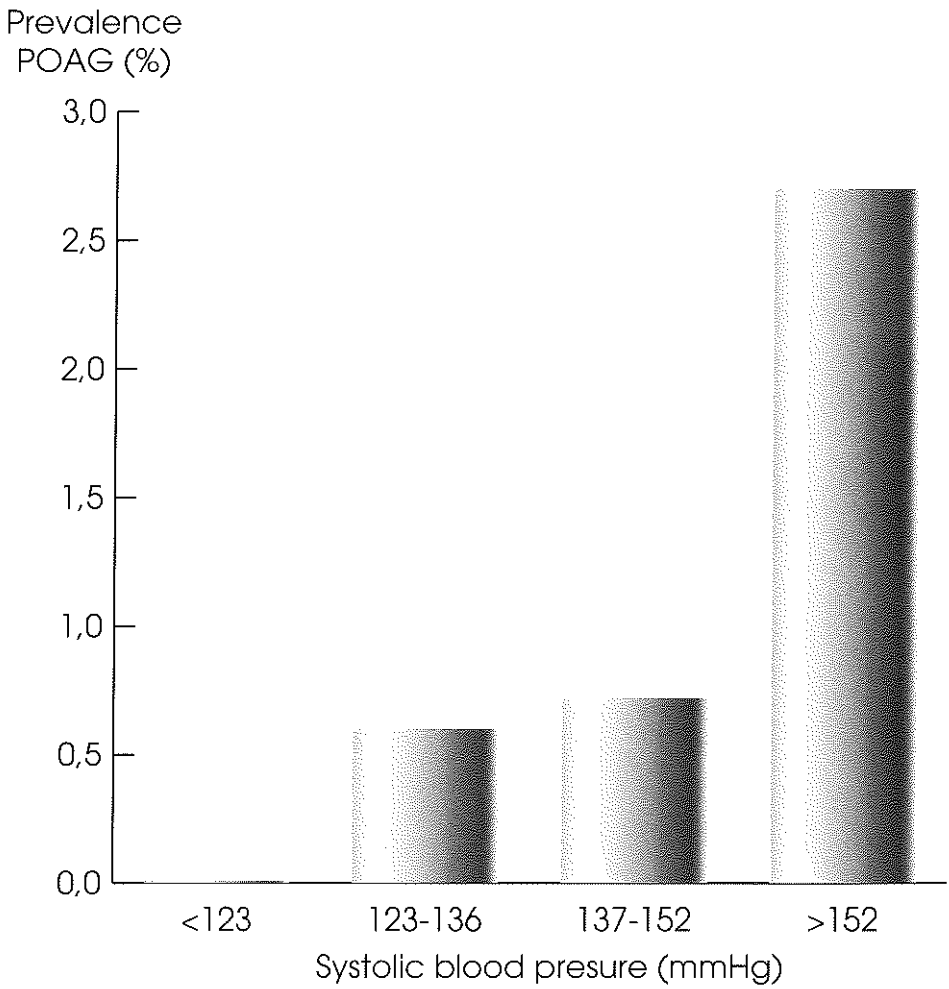
Table 5.6
Odds ratio's and 95% confidence intervals of hypertension in relation to different definitions of POAG*

	POAG (RS)[1]	POAG (BDES)[2]	HTG (RS)	NTG (RS)
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95%CI)
Hypertension: Systolic blood pressure ≥ 160 mmHg and/or diastolic blood pressure ≥ 95 mmHg	1.55 (0.78-3.10)	1.73 (0.95-3.17)	2.33 (0.99-5.47)	0.77 (0.22-2.72)
Hypertension or antihypertensive medication	1.94 (1.03-3.66)	1.84 (1.06-3.20)	2.11 (0.91-4.86)	1.73 (0.66-4.51)
Isolated systolic hypertension: systolic blood pressure ≥ 160 mmHg and diastolic blood pressure < 90 mmHg	1.49 (0.69-3.21)	1.32 (0.65-2.69)	1.78 (0.68-4.64)	1.11 (0.31-3.98)

*Adjustments were made for age, sex and body mass index.
[1]RS = Rotterdam Study
[2]BDES = Beaver Dam Eye Study

Figure 5.1
Prevalence of POAG* by quartiles of systolic blood pressure.

*POAG as defined in the Rotterdam Study.



Chapter 6

Optic disc parameters and the relation with age, gender, intraocular pressure, blood pressure and blood glucose in normal subjects

Abstract

To investigate the association between optic disc parameters such as disc, cup and rim area, cup volume, and horizontal and vertical cup disc ratio, and age, gender, intraocular pressure, systemic blood pressure and serum glucose in married couples.

Methods

A random sample of 250 non-institutionalized couples, aged 52 years and over, was selected out of subjects participating in a cross-sectional, population-based study. Optic disc and rim area, cup volume and cup/disc ratio's were analyzed with Imagenet on stereo slides of the optic nerve, intraocular pressure was measured with the Goldmann applanation tonometer, blood pressure with a random-zero sphygmomanometer, and random serum glucose was assessed by the glucose hexokinase method.

Results

In men, a 10 year higher age was associated with a larger disc area of 0.13 mm^2 (0.05, 0.21). In women, but not in men, a 10 mmHg higher intraocular pressure was associated with a rim area and disc area that was 0.27 mm^2 (0.09, 0.45) and 0.23 mm^2 (0.00, 0.46) smaller, respectively. Systolic blood pressure, diastolic blood pressure and serum glucose were not significantly associated with disc parameters.

Conclusion

In men, older age is associated with larger disc area's. In women a higher intraocular pressure is accompanied by smaller disc and rim area's. Systemic blood pressure and serum glucose are not associated with disc parameters. No correlation exists between disc parameters within married couples.

Introduction

It is generally accepted that characteristics of the optic disc like cup/disc ratio or neural rim area are associated with glaucoma. In only few studies the relation has been investigated between disc parameters, such as disc-, cup- and rim area, vertical and horizontal cup/disc ratio and cup volume, and other ocular or general variables[1-6], resulting in conflicting data concerning the relation with age and gender. A relation between disc parameters, like cup/disc ratio[4,5], rim area/disc area[5] and area of the rim of the optic disc[5], and age has been observed in some studies[4,5], but not in others.[1-3,6] A difference in disc parameters between women and men has been shown in population based studies.[4,7] In several studies computerized determinations of disc parameters have been employed.[5-8] In The Rotterdam Study, the impression had arisen that ophthalmoscopically determined cup/disc ratio's within marital couples showed more similarity than could be explained by chance. Such a correlation could theoretically have been explained by environmental factors. To our knowledge no data from other studies on this possibility are presently available.

The aim of the present study was to assess the relation between the disc parameters determined with an image analyzer and age, gender, intraocular pressure, systemic blood pressure and serum glucose. In addition, the correlation of disc parameters within marital couples was investigated.

Material and methods

Population

The present study was performed as part of The Rotterdam Study, a single-center prospective follow-up study of a cohort of over 10,000 people, aged 55 years or more, living in a suburb of the city of Rotterdam, The Netherlands.[9,10] The study has been approved by the Medical Ethics Committee of the Erasmus University.

From June 1990 until January 1993 7,120 residents had been invited and 5,673 subjects had actually participated. The overall participation rate was 80%. For the present study a random sample of 250 couples of non-institutionalized individuals was selected. Of 460 persons readable stereo transparencies of the optic nerve head (Topcon simultaneous stereoscopic fundus camera, TRC-SS, Topcon Instrument Corporation, Tokyo, Japan) were available of at least one eye. Measurements were corrected for the magnification produced by the optical system of the eye[11] and thus subjects with myopia of more than 8.0 dioptres, nuclear cataract, aphakia or pseudophakia were excluded (n=54), in order to obtain as much as possible absolute sizes of disc parameters.[8] Subjects who used antidiabetic medication (n=18) or who had a glaucomatous

visual field defect (n=4), were also excluded. This resulted in data from a total of 384 persons to be used in the present analysis.

Measurements

The measurements of disc parameters were performed using a digital image analyzer (Imagenet, PAR IS 2000, Topcon Instrument Corporation, Tokyo, Japan). The analysis of the simultaneous stereo photographs of the optic disc with this system was described in detail previously.[6,8] In summary, the two images from one stereo slide image were digitally stored. The investigator indicated four coincident points on the top, left, bottom and right margins of the optic disc on both images. The program then fitted the best ellipse around the optic disc using these four points to define the disc margin.
A transformation algorithm was used to allign the right and left images to generate a stereo pair. To determine the margin of the optic cup, an imaginary plane, the cup brim plane, was projected parallel to the points located at the disc margin and arbitrarily 150um below it. The intersection of this plane with the cup of the optic disc indicated the margin of the cup. Thereafter, the program calculated the disc-, rim- and cup area, vertical and horizontal cup/disc ratio and cup volume. For the magnification correction following Littmann[11] refraction and keratometry values were used. The intraocular pressure was measured with the Goldmann applanation tonometer following a standard protocol.[12] Blood pressure was measured in the sitting position at the right upper arm with a random-zero sphygmomanometer. The average of two measurements was used in the analysis.[13] Random serum glucose was assessed by the glucose hexokinase method.

Analysis

To measure the intra- and interobserver reproducibility, slides of 50 randomly selected eyes of 50 different subjects were analyzed twice by one observer and once by another observer in a masked way. Correlation coefficients of the optic disc parameters were calculated within and between observers.

The relation between these disc parameters of the right eye, age and gender was studied using linear regression analysis. Disc parameters and age were entered as continuous variables and gender as a dichotomous variable in a linear model. Coefficients were expressed per 10 years of age.

The relation between the disc parameters of the right eye and intraocular pressure, systolic blood pressure, diastolic blood pressure and random serum glucose was also studied using linear regression analysis. All variables were

entered as continuous variables in the linear model. Coefficients were expressed per 10 mmHg or 10 mmol/l for pressure and glucose variables respectively. The correlation of these disc parameters within marital couples was studied in a pairwise correlation matrix.

All analyses were adjusted for differences in age and sex, and, concerning the relation between age and rim area, also for disc area. Adding body mass index for adjustment did not change the coefficients significantly.

Results

Correlation coefficients of optic disc parameters within and between observers varied between 0.61 and 0.93 (Table 6.1). The optic disc parameter which correlated worst was the horizontal cup/disc ratio, with correlation coefficients of 0.61.

No significant differences existed between disc parameters of the right and left eye. Mean values of disc parameters of the right eye for women and men separately, in age-groups below 70 years and 70 years and older, are shown in Table 6.2. In the age-group of 70 years and older, men had significantly ($P<0.05$) larger disc and rim area's (2.47 mm^2 and 1.81 mm^2, respectively) than women (2.28 mm^2 and 1.67 mm^2, respectively).

The relations between disc parameters of the right eye and age, intraocular pressure, systolic blood pressure, diastolic blood pressure and serum glucose are shown in Table 6.3 for women and men separately. In women no significant relation between these disc parameters and age was found. In men, a 10 years increase in age was associated with a significant larger disc area of 0.13 mm^2 (0.05, 0.21). A 10 mmHg higher intraocular pressure in women was associated with a significant decrease in rim and disc area of 0.27 mm^2 (0.09, -0.45) and 0.23 mm^2 (0.00, 0.46), respectively. In men no significant relation was found between disc parameters and intraocular pressure. A higher systolic blood pressure, diastolic blood pressure or serum glucose was not associated with a significant change in disc parameters.

A pairwise correlation matrix was made (not shown) of each disc parameter of both discs for each couple. The correlation coefficients of the disc parameters between both persons of a couple were all smaller than 0.08. Correlation coefficients of disc parameters between the right and the left eye within one person were relatively high, variating from 0.82 for disc area to 0.50 for horizontal cup/disc ratio, with a mean of 0.66.

Discussion

The mean values of disc area, rim area, cup/disc ratio and cup volume in the present study were similar to values that have been reported by Varma et al[7] who have used Imagenet. Also in studies, in which planimetry was used, disc area, rim area, cup area and cup/disc ratio had similar values. Two other studies with the Rodenstock Optic Disc Analyzer[5,6] showed on average 40% smaller values. It has been shown that the rim area is correlated with the disc area[1,5,7,16] but there is also one report concluding that the average rim width was independent of the disc diameter.[17]

It was known that men had larger optic discs than women,[16,6] and one study[4] showed also larger cup/disc ratio's in men; this finding is not supported by the present study. Larger eyeball axial lengths have been reported in men[5] but with the use of a computerized system the disc parameters were found to be similar in men and women.[5] A possible explanation for larger discs in men could be that men have larger globe sizes and that globe size might affect the scleral canal size[5], which in turn determines the boundary of the disc size.

With increasing age a decrease in rim area and globe size was found in men and women.[5] In other studies, however, no association between disc parameters and age could be found.[1,2,6] The present study has shown a relation between age and disc area only in men. Why a relation between age and disc area should be present in men only, as has been found in the present study, is difficult to explain. In general the axial length of the eye becomes smaller with age in men and women[5], whereas in the present study larger disc area's in men compared to women were mainly found at older age. So the smaller globe size with increasing age does not seem to provide a satisfactory explanation. Another explanation for the larger disc area's in older men compared to women could be the higher mortality rate in men with smaller discs. A hint in this direction is the association between systolic blood pressure and disc size, but this relation reached only nearly significance in women (coefficient -0.03, SE 0.02). In a study among diabetic subjects by Klein et al[3], an increase in rim and disc area and a concomitant decrease in cup area was described with increasing age. In the non-diabetic control group no relation existed between age and rim area. Again this might point to a higher mortality rate in persons with diabetes mellitus and smaller discs.

Intraocular pressure, as the most important known risk factor for primary open-angle glaucoma, was associated with rim and disc area in women only. In a study on diabetic subjects[3] without the use of a computerized system, a higher intraocular pressure was associated with a smaller rim area in men and women. It is interesting to note that in the present study the decrease of rim area was caused mainly by a decrease in disc area and less by an increase in cup area. The disc area is not a stable characteristic.[3,5] Non-selected, population based longitudinal data are necessary to confirm these findings.

We found no association between random serum glucose or blood pressure and disc parameters. In contrast, in one case-control study[3] a larger rim area was found with longer duration of diabetes mellitus, progressive diabetic retinopathy and a higher glycosylated haemoglobin. Nor did we or others[3] find a significant association between high blood pressure and disc parameters.

Our impression, that disc parameters within married couples were more often similar than could be explaind by chance, could not be demonstrated. This makes environmental influences on disc parameters like eating habits, smoking or drinking less likely.

In conclusion, the present study suggests that in men, older age is associated with larger disc area's. In women, a higher intraocular pressure is accompanied by smaller disc and rim area's. Environmental factors do not seem to play a major role on the magnitude of disc variables.

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Table 6.1
Intra observer and inter observer variation for various optic disc parameters with the Image net system

	disc area	cup area	cup/disc ratio vertical	cup/disc ratio horizontal	cup volume
Within observers	0.93	0.87	0.86	0.61	0.90
Between observers	0.91	0.89	0.79	0.64	0.92

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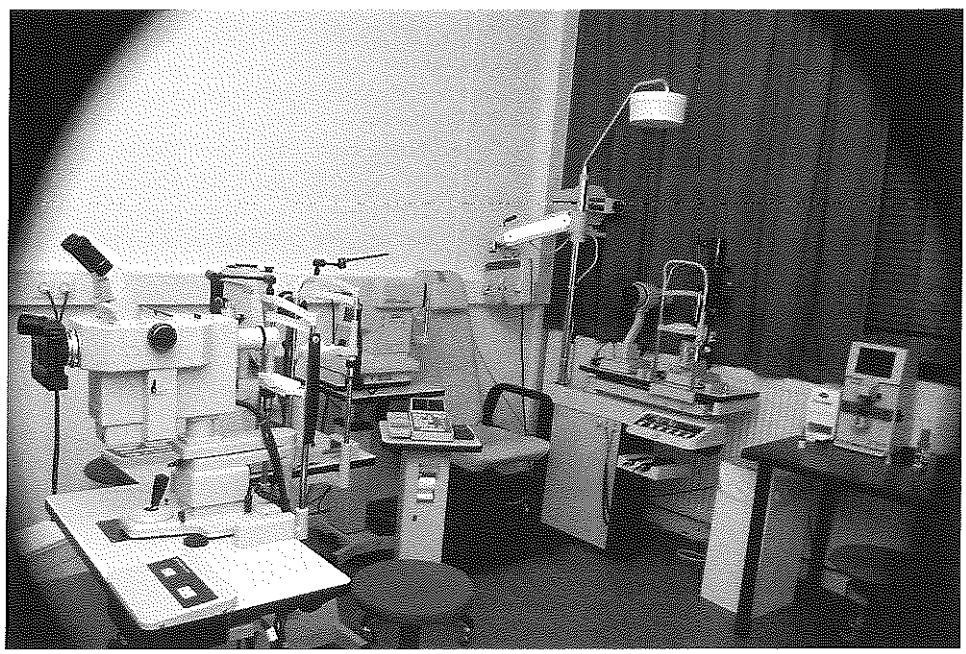

Table 6.2
Means and standard deviations (SD) of disc parameters of the right eye for men and women separately.

	Women			Men			Total
	52-69 yrs	70-84 yrs	total	52-69 yrs	70-84 yrs	total	52-84 yrs
	mean (SD)	mean (SD)	mean (SD)	mean (SD)	mean (SD)	mean (SD)	mean (SD)
number of eyes	162	42	204	137	43	180	384
disc area (mm^2)	2.35 (0.48)	2.28 (0.63)	2.34 (0.51)	2.40 (0.55)	2.47 (0.41)	2.41 (0.52)	2.37 (0.52)
cup area (mm^2)	0.62 (0.32)	0.61 (0.39)	0.62 (0.33)	0.68 (0.39)	0.66 (0.33)	0.68 (0.37)	0.65 (0.35)
rim area (mm^2)	1.73 (0.40)	1.67 (0.38)	1.71 (0.40)	1.17 (0.36)	1.81 (0.32)	1.73 (0.35)	1.72 (0.37)
vertical cup/disc ratio	0.53 (0.14)	0.54 (0.15)	0.53 (0.14)	0.54 (0.14)	0.54 (0.15)	0.54 (0.14)	0.53 (0.14)
horizontal cup/disc ratio	0.39 (0.14)	0.35 (0.14)	0.38 (0.14)	0.41 (0.16)	0.38 (0.16)	0.40 (0.16)	0.39 (0.15)
cup volume (mm^3)	0.20 (0.17)	0.17 (0.15)	0.20 (0.17)	0.24 (0.22)	0.22 (0.18)	0.23 (0.21)	0.22 (0.19)

Table 6.3
Regression coefficients and standard errors (SE) of age, intraocular pressure, systemic blood pressure, random blood glucose on disc parameters of right eyes.*

	disc area (mm^2)	rim area (mm^2)	cup area (mm^2)	cup/disc ratio vertical	cup/disc ratio horizontal	cup (mm^3)
volume	coefficient (SE)	coefficient (SE)	coefficient (SE)	coefficient (SE)	coefficient (SE)	coefficient (SE)
Women						
age	-0.05 (0.06)	-0.04 (0.04)	0.00 (0.04)	0.01 (0.02)	-0.01 (0.02)	-0.02 (0.02)
intraocular pressure	-0.23 (0.12)	-0.27 (0.09)	0.04 (0.07)	0.03 (0.03)	0.06 (0.03)	0.03 (0.04)
systolic blood pressure	-0.03 (0.02)	-0.02 (0.02)	-0.01 (0.01)	0.00 (0.01)	0.00 (0.01)	-0.01 (0.01)
diastolic blood pressure	0.01 (0.04)	-0.01 (0.03)	0.00 (0.02)	0.00 (0.00)	0.00 (0.00)	-0.01 (0.01)
serum glucose	0.02 (0.05)	0.00 (0.04)	0.01 (0.03)	0.00 (0.01)	0.02 (0.01)	0.00 (0.00)
Men						
age	0.13 (0.07)	0.10 (0.04)	0.04 (0.05)	0.02 (0.02)	0.01 (0.02)	0.01 (0.03)
intraocular pressure	-0.01 (0.13)	-0.04 (0.09)	0.02 (0.09)	0.01 (0.04)	-0.01 (0.04)	0.03 (0.05)
systolic blood pressure	0.00 (0.02)	0.00 (0.01)	0.00 (0.01)	0.00 (0.01)	0.00 (0.00)	0.00 (0.01)
diastolic blood pressure	0.04 (0.03)	0.00 (0.02)	0.04 (0.02)	0.01 (0.01)	0.01 (0.01)	0.02 (0.01)
serum glucose	-0.20 (0.21)	-0.11 (0.14)	-0.09 (0.15)	-0.01 (0.06)	0.04 (0.06)	-0.04 (0.09)

*Coefficients were adjusted for age when appropriate. The unit of increase of age, intraocular pressure, blood pressure and blood glucose was taken as 10 years, 10 mmHg and 10 mmol/l respectively.

Chapter 7

Reliability of intraocular pressure measurement with the Goldmann applanation tonometer in epidemiological studies

Abstract

The reproducibility of intraocular pressure (IOP) measurement with the Goldmann applanation tonometer was investigated as part of a population-based epidemiological study. A random sample of 62 subjects was examined in a first measurement session. The IOP was measured three times consecutively on both eyes according to a fixed protocol. The mean standard deviation (SD) of these measurements was 0.8 mmHg. After 10 minutes IOP was measured again. The mean intra-observer variation for the first measurement was 1.64 (SD 2.07) mmHg. For the median of the three measurements the intra-observer variation was 1.50 (SD 1.96) mmHg. The mean inter-observer values were 1.79 (SD 2.41) mmHg for the first measurement, and 1.60 (SD 2.15) mmHg for the median measurement. The correlation coefficient between the median values of the three measurements of both observers was 0.81. No systematic differences were found between both observers. Using the median value of three consecutive measurements improved the inter-observer variation by 11% (P=0.58) and the intra-observer variation by 9% (P=0.74) compared with a single measurement.

Introduction

The Goldmann tonometer for measurement of intraocular pressure (IOP) has been in use from 1957 onwards[5]. It is the accepted standard in ophthalmology[5,14,21]. In comparison with other measurement techniques, the Goldmann results are thought to be more accurate in a wider range of IOP values[4,10,19,21]. In practice, however, there is intra- and inter-observer variation[3,12,15,16,18,24]. IOP in epidemiological studies has been defined in many different ways as seen in Table 7.1. In most studies no validation for these techniques has been given. In order to check the reliability of IOP measurements in an epidemiological study we compared the reproducibility of the median of three consecutive measurements with a single measurement of IOP with the Goldmann applanation tonometer.

Subjects and methods

Subjects

Sixty-two persons were randomly selected out of the first 1,000 participants of the Rotterdam Study[7]. This is a population-based follow-up study of 11,854 people aged 55 years or over, concentrating on chronic disabling diseases in the elderly, including glaucoma and age-related macular degeneration. The study protocol had been approved by the medical ethical committee of the Erasmus University. The validation study of IOP measurement consisted of two parts.

In the **inter**-observer variation study, 17 men and 23 women, consecutive

participants of the Rotterdam Study, were included. Their mean age was 69.6 years (SD 7.7 years) and they had no corneal abnormalities. The IOP of first the right and then the left eye of each subject was taken three times by one observer. After 10 minutes a second series of three measurements were taken of both eyes in the same way by a second observer. Ten minutes was chosen as an arbitrary period between the two measurements series in order to keep the respondents not waiting too long. Both observers were well-trained and had taken applanation IOP's in over four thousand subjects. The sequence between the observers was chosen at random.

In the **intra**-observer study, an additional 22 consecutive participants of the Rotterdam Study, in the same age group as in the first part of the study (mean age 69.6 years, SD 6.6 years) and also without corneal abnormalities, were examined, using the same protocol. The only difference was that IOP measurements of each case were taken after 10 minutes by the same observer.

Study protocol

All readings were obtained with the same Goldmann tonometer (Haag-Streit, Bern, Switzerland), mounted on a Haag Streit 900 BM slit lamp with a standard blue filter. The calibration of the tonometer had been checked just before the study.

The protocol for IOP measurement was as follows. One drop of oxybuprocaïne 0.4% was instilled into each eye of the subject. Both inferior conjunctival sacs were touched with a dry fluorescein strip (Haag-Streit, Switzerland). Before each measurement the scale of the tonometer was set at 10 mmHg. If necessary, the upper eyelid was lifted by rotating a cotton-tip stick against the orbital rim, with great care to avoid

compression of the globe. The tip of the tonometer was illuminated with a wide-open slit at an angle of 45 degrees. The applanating prism, with its axis on 0 degrees, was slightly pressed against the center of the cornea. In case of a marked corneal astigmatism, the cotact area is elliptical rather than circular. The prism must be rotated so that the dividing line lies at about 45 degrees to the major axis of the ellipse[5]. The tonometer was raised or lowered in such a position that both semicircles were of equal size. Care was taken that the menisci were of equal circumference and of appropriate width, namely, approximately 0.05th part of the outer diameter of the semicircle. Strictly without looking at the dial, the rotating knob of the tonometer was set at a level in such a way that the inner aspect of both mires just touched. If the IOP fluctuated during the cardiac pulse cycle, the measurement was taken at mid-cycle. If the bar on the rotating dial touched a fixed bar of the tonometer that pressure was noted. If the

movable bar was free of the fixed bars, the intermediate pressure was taken. Subsequently, the dial of the tonometer was set again at 10. In this way, three consecutive measurements were performed on each eye and each value was recorded immediately after the measurement. The right eye was always measured first.

Data-analysis

The data were analysed by means of determination of standard deviations and coefficients of variation of three consecutive IOP measurements and of differences between median values of both observers. The coefficient of variation was defined as the standard deviation divided by the mean value of the three consecutive IOP measurements. Correlation coefficients were determined of median values of the two observers. The paired standard deviations of the three measurements of individual cases were compared between both observers using the Wilcoxon's test. Median values of the three consecutive measurements were compared between and within both observers using paired t-tests[6]. All P-values given are two-sided, with 0.05 taken as the level of significance.

Results

In the **inter**-observer study, 40 right and 39 left eyes (one subject wore a prosthesis) were examined. The differences between three consecutive IOP measurements taken by one observer varied between 0 and 5 mmHg. The standard deviations (SD) of these three measurements at the right eye were 0.7 mmHg for both observers (coefficient of variation (CV): 5%). At the left eye the SD was 0.8 mmHg (CV: 6%) for observer A and 0.9 mmHg (CV: 7%) for observer B. The mean of these four standard deviations was 0.8 mmHg. The level and variability of the IOP readings were independent of age and gender of the subjects.

The correlation coefficient of the median values for the two observers was 0.75 for the right eye and 0.87 for the left eye. Taking the mean of the values of both eyes the correlation coefficient was 0.81. The difference between the median values of the two observers had a mean of 1.60 mmHg, with a SD of 2.15 mmHg. The difference between the first measurements of the two observers had a mean of 1.79 mmHg, with a SD of 2.41 mmHg (table 2).

When comparing median values of the three consecutive IOP readings between the two observers, the second observer measured after 10 minutes lower values than the first. The average decrease was 0.7 mmHg (standard error=0.4 mmHg, P=0.07) for the right and 0.5 mmHg (standard error=0.2 mmHg,

P=0.04) for the left eye. Figure 1 shows the measured IOP at both occasions for both eyes.

In the **intra**-observer study both eyes of an additional 22 subjects were examined. The mean difference between the median values was 1.50 mmHg, with a SD of 1.96 mmHg. The mean difference between the first measurements of the series of three was 1.64 mmHg, with a SD of 2.07 mmHg (table 2).
The average decrease of the median values at the second measurement session was 0.9 mmHg for both eyes (P<0.01).

Discussion

The findings indicate that a protocol using the median of three readings of IOP measurement with the Goldmann tonometer gives a better reproducibility of the IOP than single IOP measurements. In comparison to the first single IOP measurement the inter-observer variation improved by 11% (P=0.58) and the intra-observer variation by 9% (P=0.74). For IOP measurements in a glaucoma clinic this may seem to be a small improvement given the fact that nowadays more emphasis is put on visual field and optic nerve head evaluation than on absolute values of IOP. However, in epidemiological studies where differences in IOP of 1 to 3 mmHg may point to a risk factor for glaucoma there is a need for reproducible and precise measurement techniques.

Because one IOP measurement is subject to variation[16], it was decided to perform each time three consecutive measurements to obtain a better estimate of the actual IOP. The standard deviation of the three consecutive IOP measurements at one occasion by one observer on one eye was 0.8 mmHg in this study. This figure is similar to the value for the SD from a study by Thorburn (0.9 mmHg) in which two consecutive measurements were made by the same observer[24]. However, in other studies this SD amounted to 3 mmHg[16] and 4.07 mmHg[20].

A fixed number of consecutive measurements was chosen, because each subsequent measurement lowers the IOP by 0.1 to 0.4 mmHg[16,17]. These values fit within the 0.5 to 0.7 mmHg difference that were found in this study after 10 minutes. Medians were used in stead of mean values in order to reduce the influence of inordinate values. The correlation coefficient of the median values between both observers was quite high (0.81) in this study. In a study with a variable number of measurements[18], the correlation coefficient was 0.71.

The standard deviation of the inter-observer differences in the present study was 2.15 mmHg. This figure was similar to the figure given in the study of Phelps and Phelps[18], who gave a value of 2.5 mmHg. The SD of the intra-observer differences was 1.96 mmHg in this study, which is similar to the value of 1.4 mmHg as found by Moses and Liu[16].

In this study a fixed protocol of IOP measurement was used to standardize effects of factors known to influence the result, such as the use of fluorescein. Applanation tonometry without the use of fluorescein resulted in a 5.62 mmHg lower mean IOP value in comparison to applanation tonometry with fluorescein use[20]. A dry fluorescein strip was used and not a mixture of fluorescein with a local anaesthetic drop, as the former was used in the original calibration technique of the Goldmann tonometer[5] and resulted in a 3.94 mmHg lower mean IOP value in comparison to the latter[20]. The menisci were of equal circumference and of appropriate width when the measurement was made and the measurement was taken in mid-cycle[5,14,18,20].

Conclusions

Goldmann applanation tonometry readings can vary with 6% when individual values are taken. The present study suggests that the reliability of IOP measurement with the Goldmann tonometer is improved by taking the median of three consecutive measurements compared with one IOP measurement.

Goldmann applanation tonometer

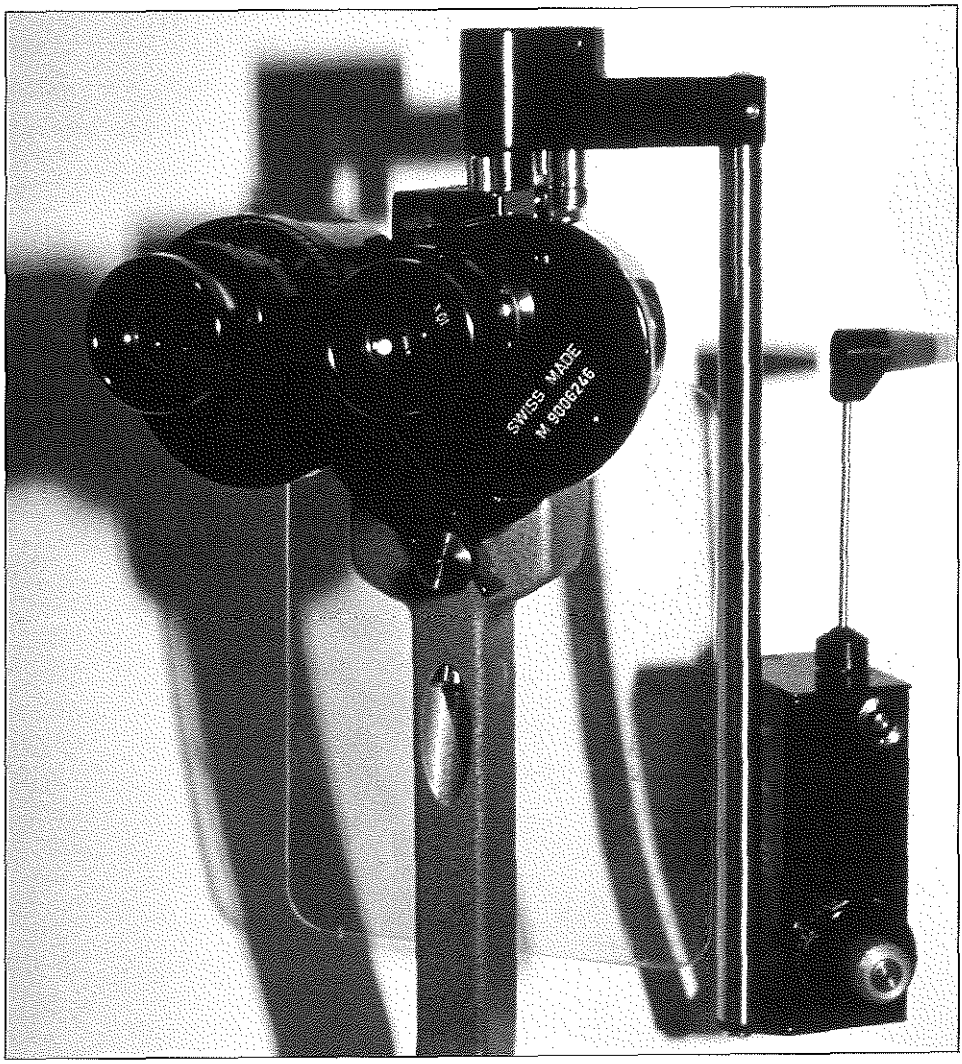

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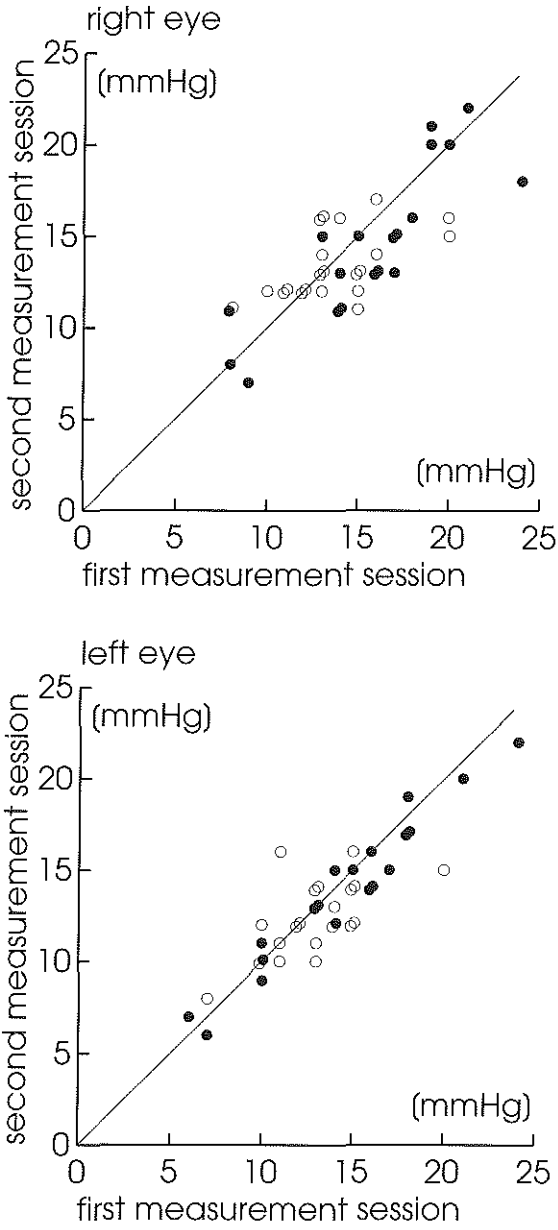
Table 7.1
Methods of defining intraocular pressure in validation studies and epidemiological studies by applanation tonometry with the Goldmann tonometer

Method	Reference
First single measurement value	1,3,11,12,15,19
Taking as many measurements until three successive readings were within 1 mmHg of each other	16,18
Mean of three consecutive readings	9
Mean of two consecutive readings	24
Median of three consecutive readings	23, this paper
No description	2,8,13,22

Table 7.2
Difference between first and median IOP measurements (mmHg) between and within observers

	First measurement (A)	Median of three measurements (B)	Difference (A-B)
Difference between observers			
mean	1.79	1.60	0.19 (11%)
SD	2.41	2.15	0.26 (11%)
n=79 eyes of 40 subjects			
Difference within observers			
mean	1.64	1.50	0.14 (9%)
SD	2.07	1.96	0.11 (5%)
n=44 eyes of 22 subjects			

Figure 7.1
IOP at first and second measurement session.



The drawn line denotes the line of identity. Each IOP represents the median value of three measurements (n=40). Closed and open circles indicate subjects in whom the first measurement was done by the first or second observer, respectively.

Chapter 8

General discussion

In this thesis several studies, based on subgroups of one population, are described. The overall aim was to enhance epidemiological knowledge on primary open-angle glaucoma. This chapter will concentrate first on some of the methodological issues that were raised by these studies and that also apply to further studies on the topic. Next, the evidence from the various studies will be reviewed. Finally, suggestions will be given as to along which lines epidemiological research in this field could be continued.

Methodological issues

Study design

The studies in this thesis were cross-sectional. Two issues should be considered: the supposed time-relationship between the determinant and the outcome, and the natural course among subjects with different levels of the outcome.

One may wonder to which extent the actual serum glucose and blood pressure levels taken during the survey reflect levels in the period in which they could have exerted their influence on the optic disc. Since the presence of diabetes mellitus or hypertension are relatively stable determinants, and have a cumulative effect over time, we feel confident to conclude that diabetes mellitus and hypertension are related to high-tension glaucoma.

If case fatality differs in persons with or without high-tension glaucoma, the relation between diabetes mellitus or hypertension with high-tension glaucoma may reflect determinants of survival.

Accuracy

Selection bias occurs if the relation between the determinant and the outcome is different for those who participate and those who are eligible but do not participate in a study. This might be the case when part of the non-response was selective and related to poor vision and poor physical health. We think, however, that the amount of possible bias was limited, because the overall response was high (80 percent).

Information bias of the determinant and outcome will lead to their misclassification, which can result in under- and/or overestimation of their true relation. In the Rotterdam Study, the examinations were standardized measurements and measured masked as to ophthalmological status. Therefore, the relations mentioned in these studies were only subject to random error, which may bear upon precision but does not effect validity.

Confounding can occur when an extraneous factor is associated with the determinant under study as well as with the outcome variable. The most

important putative confounders in these studies were age, sex and body mass index. The large numbers of subjects, and stratification or adjustment of the results for these confounders, enabled adequate control of their potential confounding influence in the analyses.

Precision corresponds to the amount of random error in a study, and is directly related to the statistical power of a study to detect existing relationships. Basically, there are two ways to increase precision: one is to reduce measurement error, and the other is to enlarge the size of the study. In the Rotterdam Study, the reproducibility of the assessment of several determinants was enhanced by taking dual measurements, e.g. blood pressure measurements, or could have been enhanced by further standardization of the measurement procedures, e.g. only fasting levels of glucose. The random variation in the assessment of the IOP was reduced by taking the median value of three consecutive measurements (chapter 7). Random variation in estimation of cup/disc ratio's of the optic nerve could have been reduced by using a more standardized and objective measurement technique, e.g. Imagenet (chapter 6). The random variation in the assessment of POAG was reduced by using highly standardized procedures of visual field testing (chapter 3). In the studies based on associations with IOP or POAG, the number of people that were included (over 4,000) had adequate power.

At one time, the presence of an IOP over 21 mmHg was considered necessary and sufficient to diagnose glaucoma. This concept is no longer valid, but in clinical practise elevated IOP is still an important sign for initiating glaucoma therapy. From an epidemiologic viewpoint, however, the diagnosis of POAG is principally based on the presence of a glaucomatous visual field defect and optic disc cupping, independent of the level of IOP.

Traditionally, studies in relation to POAG dichotomize the study population in presence or absence of POAG. If the outcome of interest is continuously distributed in the population, like IOP, categorization of the population would diminish the amount of information in the study.

Another question is whether and how to subtype POAG. One distinction among POAG is the one between high-tension glaucoma and normal-tension glaucoma. This classification is based on presumed different etiologies. Using a cut-off level of 21 mmHg may be inappropriate because of the variability of the IOP and the fact that its assessment is based on a occasional measurements. However, high IOP's are usually defined in these terms and this is the approach followed here.

Data-analysis

In the studies on associations, the principal outcome measures were IOP, optic disc characteristics and POAG. For analyzing the strength of these relations, we choose to use linear and logistic regression techniques, with corresponding standard errors and confidence intervals.

Observations in the Rotterdam Study

The basic research questions in the studies that are described in this thesis, referred to the distribution of IOP, characteristics of the optic disc, and the presence of POAG in an elderly population, according to demographic variables (age, gender) and to systemic factors (diabetes mellitus, hypertension). The evidence from the various studies in this thesis can be summarized as follows:

- Age is associated with POAG.
- Men have a three times higher risk of having POAG than women.
- Age and gender were not significantly associated with IOP.
- In the age-group of 70 years and older, men have larger disc and rim area's of the optic disc than women.
- Diabetes mellitus and serum glucose levels are associated with IOP and high-tension glaucoma.
- Diabetes mellitus and serum glucose levels are not associated with normal-tension-glaucoma.
- Systolic blood pressure, diastolic blood pressure and hypertension are associated with IOP.
- Systolic blood pressure and hypertension are associated with high-tension glaucoma.
- Systemic blood pressure is not associated with normal-tension glaucoma.
- Systemic blood pressure and serum glucose levels are not significantly associated with optic disc characteristics.
- IOP is inversely associated with rim- and disc area in women.

Age

That POAG is more prevalent with advancing age is well recognized. The major challenge for prospective studies on POAG is to identify factors that underlie the relation between age and POAG. Age is not significantly associated with IOP in an elderly population, but will be associated with IOP in a study population which includes also younger age-groups.[1-5] The association between age and disc- or rim area in men is not understood. Other studies on this subject are necessary to confirm this finding.

Gender

In prevalence studies of POAG in general, no sex-difference has been found.[1,5,6] Only in the Framingham Eye Study[3], as in our study, men have been found to have a higher prevalence of POAG than women. It may well be that this sex-difference in prevalence of POAG is more pronounced in older age-groups. Combining prevalence results with younger age-groups possibly would equalize the sex-difference. A follow-up study is necessary to determine if the age-specific incident rate is different for men and women.

Diabetes mellitus

Associations between diabetes mellitus or serum glucose and IOP, like in our study, have been found in several other studies.[7-13] A possible mechanism is that elevated blood glucose may induce an osmotic gradient and attract fluid into the intraocular space, which may result in an elevated IOP.[10] Another possible mechanism is the decrease in outflow coefficient of aqueous humour with increasing severity of diabetic retinopathy.[9] Few studies have suggested that diabetes mellitus is associated with POAG[11,12] or, like in our study, with high-tension glaucoma.[13,14] A follow-up study could find an answer on the question if an association exists between diabetes mellitus and normal-tension glaucoma.

Blood pressure

The relation between blood pressure and POAG is ambiguous. Hypertension may predispose to POAG or high-tension glaucoma[15,16], either directly through small vessel disease, compromizing the optic nerve circulation, or indirectly by increasing the IOP. On the other hand, it has been suggested that a decrease in blood pressure relative to IOP increases the risk of having POAG or normal-tension glaucoma.[17,18,19] We found evidence for the relation between hypertension and high-tension glaucoma, and no evidence was found for the relation of hypotension with POAG or normal-tension glaucoma. Our finding could be explained by two mechanisms. First, it could be that high-tension glaucoma is a different disease entity with different etiologic factors compared with normal-tension glaucoma. High-tension glaucoma was differentiated from normal-tension glaucoma by means of the IOP, but the association between hypertension and high-tension glaucoma was at least in part independent of IOP. Furthermore, hypertension may predispose to high-tension glaucoma through small vessel disease, which can decrease blood flow to the optic nerve, and that could increase the risk of field loss.[20] Secondly, hypertension may indirectly predispose to high-tension glaucoma by elevation of the IOP. The degree to which the optic disc is able to tolerate a certain level of IOP is a

possible decisive factor in the optic nerve damage. The association between blood pressure and IOP, as has been found in our study, has been reported in several other studies as well.[7,11,21-25] High blood pressure could increase the passive production of aqueous fluid in the ciliary body, with as a result an increase in IOP[10], and IOP is an important risk factor for POAG.

IOP

An inverse association between IOP with rim- and disc area has also been found in one other study, in persons with diabetes mellitus and needs to be confirmed by other studies.[26] Elevated IOP and decreasing rim area are well known factors associated with POAG. The relation between rim- and disc area is also not new.[27-29]

Clinical relevance of the findings of the Rotterdam Study

In these studies of the relations between blood pressure or diabetes mellitus with IOP, the mean difference in IOP was usually less than 1 and 2 mmHg for the relations with diabetes mellitus and blood pressure, respectively. This raises the question whether this is clinically relevant. The answer to this is not to be found on the individual level, but rather on the population level. IOP is known as an important risk factor for POAG. Even a slight decrease in IOP on population level would result in a decrease in prevalence of POAG in the population, and this would be a major health benefit. Although the average gain per individual would be small, the population gain might be substantial.[30]

Furthermore, subjects with hypertension had a 2.3 times higher risk of having high-tension glaucoma than subjects without hypertension. It is clear that this is of clinical relevance, especially in the oldest age-group where prevalence of POAG had increased to over 3 percent.

These considerations provide a strong argument to investigate whether intervention on risk factors for diabetes mellitus and hypertension can prevent POAG on a population level.

Suggestions for future research

The major part of this thesis was devoted to cross-sectional associations with IOP and POAG. An underlying assumption in the conduct of these studies was that IOP was an important risk factor for POAG.

Prospective follow-up studies would also provide a powerful way to investigate risk factors for IOP and POAG. Of particular interest in etiologic research in IOP or POAG are:

- The relation between blood pressure, normal-tension and high-tension glaucoma. Of particular interest is the role of small vessel disease in this regard, since this may be intermediate in the relation of blood pressure and POAG.
- The relation between diabetes mellitus with normal-tension glaucoma and high-tension glaucoma.
- Another possible contribution is the study on genetics of POAG.

Research on POAG is fundamentally motivated by the pursuit of ways to prevent blindness. Even though the precise pathophysiologic mechanisms through which the various risk factors, like age, gender, diabetes mellitus, serum glucose and systemic blood pressure, contribute to POAG remain to be elucidated, there is ample evidence that they contribute to POAG. The widespread prevalence of these conditions in the population justifies an attempt to prevent POAG on a population level by intervention on risk factors.

A quantitative outcome measure that can be objectively assessed is to be preferred. Optic disc parameters, measured in a highly standardized and objective way, with an image analyzer like Imagenet, reflect primarily optic disc damage due to POAG. Changes in their dimensions seem particularly apt as an important outcome measure in an intervention study on risk factors of POAG. Such research would in addition offer the opportunity to further investigate the relation between optic disc parameters IOP and POAG.

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Chapter 9

Summary

Glaucoma is an important cause of blindness, particularly in the elderly. Primary open-angle glaucoma (POAG) is the most prevalent and the least understood type of glaucoma. This thesis focuses on the epidemiology of POAG, in particular prevalence and determinants of this disease.

A review of the main epidemiologic findings of POAG concerning its frequency and risk factors is presented in chapter 2. This review describes community-based studies of POAG in populations in Western Europe and North America. The most valid prevalence studies are those that examine every participant by perimetry, tonometry and ophthalmoscopy. The prevalence of POAG rises with age. Typical estimates in white persons are about 0.9 percent in subjects aged 65 years, 2.0 percent in subjects aged 75 years and 3.0 percent in subjects aged 85 years. About 50 percent of the cases with POAG have normal intraocular pressures (IOP). Despite differences in methodology and definition, relatively similar prevalence figures of POAG are present across white populations. The prevalence of POAG in black populations is four to seven times higher. Incidence estimates of POAG in white populations suggest a five-year incidence of 0.2 percent at age 55 years, that increases to 1.0 percent at age 75 years. Except for age, a positive family history of POAG and elevated IOP, interesting evidence suggest that diabetes mellitus and blood pressure may be associated with POAG.

The prevalence of POAG in a defined population in Rotterdam, The Netherlands, is presented in chapter 3. For this study, a total of 3,062 unselected, non-institutionalized participants, ages 55 and over, were examined according to standard protocols, including perimetry, tonometry and ophthalmoscopy. The diagnosis of POAG was based on the presence of a glaucomatous visual field defect in combination with either a vertical cup/disc ratio of 0.5 or over or a cup/disc ratio asymmetry of 0.2 or over or an IOP of over 21 mmHg. The overall prevalence of POAG in this study was 1.1 percent (95% confidence interval 1.09, 1.11). Age-adjusted prevalence rates increased from 0.2 percent (0.16, 0.24) in the age-group of 55-59 years, to 3.3 percent (2.57, 4.04) in the age-group of 85-89 years. Overall, men had a more than three times higher risk of having POAG than women (odds ratio 3.6 (1.7, 7.1). POAG had not been previously diagnosed in 52.9 percent of the cases, and of them 38.9 percent had IOP's of less than 22 mmHg. A visual acuity of 0.1 or less due to POAG was present in 8.8 percent of the POAG cases, actually in three persons on four eyes.

The following three chapters are studies concerning determinants of primary open-angle glaucoma, that have been performed in the Rotterdam Study (n=4,187, participation rate 80 percent). A distinction was made between high-tension glaucoma and normal-tension glaucoma.

The relation of POAG and IOP with diabetes mellitus and serum glucose is discussed in chapter 4. The presence of diabetes mellitus was associated with an overall rise of mean intraocular pressure of both eyes of 0.31 mmHg (95% CI 0.12, 0.50), and with a three-fold increased presence of high-tension glaucoma (odds ratio 3.11, with a 95% confidence interval of 1.12, 8.66). Normal-tension glaucoma was not associated with diabetes mellitus. A rise of 10 mmol/l of serum glucose was associated with an overall rise of mean intraocular pressure of 0.41 mmHg (-0.02, 0.84), with an odds ratio of 2.82 (0.92, 8.58) for high-tension glaucoma. It was concluded that diabetes mellitus and high levels of serum glucose are associated with a high intraocular pressure and high-tension glaucoma.

Chapter 5 deals with the association between POAG, IOP and systemic blood pressure. A systolic blood pressure or diastolic blood pressure that was 10 mmHg higher was associated with an IOP that was on average 0.23 mmHg (95% confidence interval (CI) 0.19, 0.27), 0.24 mmHg (0.16, 0.32) higher, respectively. The presence of hypertension was associated with a 0.66 mmHg higher mean IOP (0.39, 0.93). A 10 mmHg higher systolic blood pressure was associated with an odds ratio of 1.22 (1.03, 1.46) for high-tension glaucoma. Hypertension was associated with an odds ratio of 2.33 (0.99, 5.47) for high-tension glaucoma. The conclusion of these results was that systemic blood pressure is associated with IOP and high-tension glaucoma. No association was found between systemic blood pressure and normal-tension glaucoma.

A study on the association between optic disc parameters and some general, ocular and systemic factors in men and women is described in chapter 6. For this study, a random sample of 250 couples was selected out of the subjects participating in the Rotterdam Study. All subjects were examined according to the normal standard protocols. In addition, the stereo slides of the optic nerve, of one random eye, were analyzed with Imagenet, a digital image analyzer of the optic disc. In men, a 10 year higher age was associated with a larger disc area of 0.13 mm^2 (0.05, 0.46). In women, a 10 mmHg higher intraocular pressure was associated with a rim and disc area of 0.37 mm^2 (0.09, 0.45) and 0.23 mm^2 (0.00, 0.46) smaller, respectively. A change in systolic blood pressure, diastolic blood pressure or blood glucose was not significantly associated with a change in disc parameters. It was concluded that in men, older age was associated with larger disc area's. In women, a higher intraocular pressure was associated with smaller disc and rim area's. Systemic blood pressure and blood glucose were not associated with disc parameters. No correlation existed between disc parameters within marital couples.

Another part of the Rotterdam Study was the determination of the reliability of IOP measurements (chapter 7), by comparing the reproducibility of the

median of three consecutive IOP measurements with a single measurement of the IOP with the Goldmann applanation tonometer. A random sample of 62 subjects was examined in a first measurement session. The IOP was measured three times consecutively on both eyes according to a fixed protocol. The mean standard deviation (SD) of these

measurements was 0.8 mmHg. After 10 minutes IOP was measured again. The mean intra-observer variation for the first measurement was 1.64 (SD 2.07) mmHg. For the median of the three measurements the intra-observer variation was 1.50 (SD 1.96) mmHg. The mean inter-observer values were 1.79 (SD 2.41) mmHg for the first measurement, and 1.60 (SD 2.15) mmHg for the median measurement. The correlation coefficient between the median values of the three measurements of both observers was 0.81. No systematic differences were found between both observers. Using the median value of three consecutive measurements improved the inter-observer variation by 11.% (P=0.58) and the intra-observer variation by 9% (P=0.74) compared with a single measurement.

In chapter 8, some of the methodological issues involved in the studies based on the Rotterdam Study are discussed, and the findings of these studies are reviewed. Important results are that diabetes mellitus and systemic blood pressure are associated with high-tension glaucoma and IOP.

Chapter 10

Samenvatting

Glaucoom is een belangrijke oorzaak van blindheid, met name bij mensen van hogere leeftijd. Primair open-kamerhoek glaucoom is de meest frequente en de minst begrepen vorm van glaucoom. Dit proefschrift richt zich voornamelijk op de prevalentie van primair open-kamerhoek glaucoom en op factoren die hiermee zijn gerelateerd.

Een overzicht van de belangrijkste bevolkingsonderzoeken met betrekking tot glaucoom is gegeven in hoofdstuk 2. Deze studies hebben betrekking op blanke populaties in West Europa en Noord Amerika. Ondanks verschillen in onderzoeksmethodes en definitie van glaucoom, worden ongeveer dezelfde ziekte frequenties gegeven in de verschillende blanke populaties.
Glaucoom komt vaker voor op hogere leeftijd; van de 65 jarigen heeft ongeveer 0,9 procent glaucoom, bij 75 jarigen is dit 2,0 procent en bij 85 jarigen 3,0 procent. In de negroide bevolking komt glaucoom vier tot zeven maal zo vaak voor. Ongeveer 50 procent van de mensen met glaucoom heeft normale oogdrukken. Verder wordt er geschat dat de incidentie van glaucoom in een periode van vijf jaar bij 55 jarigen 0,2 procent bedraagt, en bij 75 jarigen 1,0 procent. Leeftijd, het voorkomen van glaucoom in de familie en verhoogde oogdruk zijn bekende risiko factoren voor glaucoom. Daarnaast bestaat de indruk dat suikerziekte en verhoogde bloeddruk gerelateerd zijn aan glaucoom.

Hoe vaak glaucoom voorkomt in Ommoord is onderzocht binnen het Erasmus Rotterdam en Ouderen (ERGO) onderzoek (hoofdstuk 3). Voor deze studie zijn 3,062 ongeselecteerde, zelfstandig wonende mensen onderzocht van 55 jaar en ouder. Het onderzoek werd verricht volgens standaard protocollen, inclusief gezichtsveld onderzoek, oogdruk meting en oogspiegelen. De diagnose glaucoom werd gebaseerd op de aanwezigheid van een glaucomateus gezichtsveld onderzoek in combinatie met een glaucomateus afwijkende oogzenuw en/of een verhoogde oogdruk. Gemiddeld kwam glaucoom bij 1,1 procent van de mensen voor; onder 55 jarigen was dit 0,2 procent en dit nam toe tot 3,3 procent onder 85 jarigen. Over het geheel genomen kwam bij mannen meer dan drie keer zo vaak glaucoom voor dan bij vrouwen. In 52,9% van de glaucoom gevallen was het onbekend dat zij aan deze ziekte leden, en van deze mensen had 38,9 procent een normale oogdruk. Van alle mensen met glaucoom was 8,8 procent blind aan één of beide ogen ten gevolge van glaucoom.

De volgende drie hoofdstukken betreffen studies naar factoren die gerelateerd zijn aan het vóórkomen van glaucoom, en die verricht zijn binnen het ERGO onderzoek. Met uitzondering van hoofdstuk 6 zijn hiervoor 4.187 mensen onderzocht, gemiddeld 80 procent van het aantal mensen wat mee had kunnen doen met dit onderzoek. Er werd onderscheid gemaakt tussen hoge

druk glaucoom en normale druk glaucoom. De relatie van glaucoom en oogdruk met suikerziekte en bloed glucose is besproken in hoofdstuk 4. De aanwezigheid van suikerziekte was gerelateerd aan een 0,31 mmHg hogere oogdruk en met een drie maal zo frequent vóórkomen van hoge druk glaucoom. Normale druk glaucoom was niet gerelateerd aan suikerziekte. Een 10 mmol/l hoger bloed glucose was gerelateerd met een 0,41 mmHg hogere oogdruk en een 1,82 maal zo grote kans op hoge druk glaucoom. Er werd geen relatie gevonden tussen normale druk glaucoom en bloed glucose.

Hoofdstuk 5 gaat over de relatie tussen glaucoom, oogdruk en bloeddruk. Een 10 mmHg hogere bloeddruk kwam samen voor met een 0,24 mmHg hogere oogdruk. Wanneer iemand leed aan hoge bloeddruk, was de oogdruk 0,66 mmHg hoger. Een 10 mmHg hogere bloeddruk ging samen met een 1,22 grotere kans op het hebben van hoge druk glaucoom. De aanwezigheid van hoge bloeddruk was gerelateerd aan een 2,33 maal grotere kans op het hebben van hoge druk glaucoom. Geen relaties zijn gevonden tussen bloeddruk en normale druk glaucoom.

Een studie naar relaties tussen kwantitatieve kenmerken van de oogzenuw en enkele algemene, oogheelkundige en systeem factoren is beschreven in hoofdstuk 6. Voor deze studie is een willekeurige selectie gemaakt van 250 mannen en vrouwen van deelnemers uit het ERGO onderzoek. Al deze mensen zijn onderzocht volgens het standaard protocol. Daarnaast zijn de stereo dia's van het gedeelte van de oogzenuw wat te zien is in het oog, de papil genoemd, van een willekeurig oog per persoon geanalyseerd met Imagenet. Imagenet is een gecomputeriseerd beeldanalyse apparaat voor de oogzenuw. Bij mannen werd gevonden dat toenemende leeftijd samen ging met een grotere oppervlakte van de papil. Bij vrouwen was een hogere oogdruk gerelateerd met een kleinere oppervlakte van de rand en van de totale oppervlakte van de papil. Geen relaties werden gevonden tussen kenmerken van de papil en bloeddruk of bloed glucose.

In hoofdstuk 7 is de betrouwbaarheid van de oogdruk meting besproken zoals deze verricht wordt binnen het ERGO onderzoek. Vergeleken werd de reproduceerbaarheid van de mediaan van drie opeenvolgende oogdruk metingen met een enkele meting, bij 62 willekeurige ERGO deelnemers. Gebleken is dat het nemen van de mediaan van drie opeenvolgende oogdruk metingen ongeveer 10 procent minder variatie geeft vergeleken met een enkele oogdruk meting.

Hoofdstuk 8 is een discussie van een aantal onderzoeksmethodes met betrekking tot de glaucoom studies binnen ERGO. Daarnaast zijn de belangrijkste resultaten van deze studies weergegeven. Gebleken is dat suikerziekte en

verhoogde bloeddruk in belangrijke mate relateren aan hoge druk glaucoom en verhoogde oogdruk. Er is echter een grote noodzaak voor het verrichten van vervolgonderzoeken naar risiko factoren voor normale druk glaucoom.

Nawoord

Het resultaat van ruim drie jaar oogheelkundig onderzoek van ERGO deelnemers in Ommoord, en 9 maanden analyseren van de onderzoeksgegevens op de afdeling Epidemiologie en Biostatistiek, is weergegeven in dit proefschrift. Velen hebben tot de totstandkoming hiervan bijgedragen.

Paulus de Jong, initiator en promotor van het glaucoom onderzoek binnen ERGO, heeft voor mij de belangrijkste rol gespeeld. Hij heeft altijd gestreefd naar een zo groot mogelijke duidelijkheid binnen het onderzoek; wetenschappelijk verantwoord, maar met beide benen op de grond. Ik ben hem erg dankbaar voor de mogelijkheden en vrijheid die hij mij geboden heeft.

Bert Hofman, initiator van het ERGO onderzoek en tweede promotor van het glaucoom onderzoek, bezit het vermogen om, met een enorme wilskracht, mensen dingen te laten doen die ze nooit voor mogelijk hadden gehouden. Ik wil hem erg bedanken voor de tijd en energie die hij geïnvesteerd heeft in dit onderzoek.

Dit proefschrift is gebaseerd op studies binnen het ERGO onderzoek. De onderzoeksleiders Rick Grobbee, Bert Hofman, Paulus de Jong, Huib Pols en Frank van den Ouweland, wil ik bedanken voor het in goede banen leiden van het ERGO onderzoek en voor hun kritische commentaar op dit onderzoek.

Hans Vingerling is degene geweest met wie ik in Ommoord het oogonderzoek heb verricht. Als twee totaal verschillende mensen werkten we met elkaar samen. Ik wil hem heel erg bedanken voor alle steun die hij mij gegeven heeft.

Met Maxime Look, van de automatisering, biologe van achtergrond, zijn de allereerste data verwerkt en is een begin gemaakt met de analyses. Avonden zaten we achter de computer, toen ik nog niets van het computerprogramma BMDP begreep. Ik wil haar heel erg bedanken voor de goede en aangename samenwerking.

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oogheelkundig assistente een enorme betrokkenheid toonde bij het onderzoek.

De afdeling Oogheelkunde van het Dijkzigt ziekenhuis, onder supervisie van Paulus de Jong, wil ik heel erg bedanken voor de praktische ondersteuning van het oogonderzoek in Ommoord. Lous Ruempol, secretaresse van Paulus de Jong, wil ik bedanken voor het regelen van afspraken voor al die vergaderingen, en voor de persoonlijke ondersteuning.

Sylvia Schotman wil ik bedanken voor haar ijver waarmee ze dia's geanalyseerd heeft met Imagenet.

Allen die hebben meegewerkt aan ERGO, zoals interviewsters, medewerksters op het gezondheidscentrum, collega artsen, mensen op de hoogbouw voor de administratie en data verwerking, voor opslag en laboratorium bepalingen, secretariaat en beheer, wil ik bedanken voor de prettige samenwerking.

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The health centre where most of the investigations took place

Curriculum vitae

Ida Dielemans was born on March 5, 1961 in Rotterdam, The Netherlands. She passed secondary school in 1979 at the 'Caland College' in Rotterdam. After a short period of studying Fysical Geography in Utrecht, she started her medical training in 1980 at the Erasmus University in Rotterdam. After receiving her medical degree in 1987, she worked as an assistent in an ophthalmological practice in Amsterdam. In 1989 she started the work described in this thesis. Since September 1993 she is working as a trainee in ophthalmology at the university hospital Dijkzigt in Rotterdam.

Colofon

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