Graefe's Arch Clin Exp Ophthalmol (1990) 228:505–509

Graefe's Archive
for Clinical and Experimental
Ophthalmology

Protective effect of captopril on the blood-retina barrier in normotensive insulin-dependent diabetic patients with nephropathy and background retinopathy *

Michael Larsen[1], Eva Hommel[2], Hans-Henrik Parving[2], and Henrik Lund-Andersen[1]

[1] Department of Ophthalmology, Gentofte Hospital, University of Copenhagen, DK-2900 Hellerup, Denmark
[2] Hvidøre Hospital, Klampenborg, Denmark

Received February 9, 1990 / Accepted May 3, 1990

Abstract. The effect of 18 months' inhibition of angiotensin-converting enzyme by captopril on the leakage of fluorescein through the blood-retina barrier was examined in a prospective, randomized control study of 20 normotensive insulin-dependent diabetic patients with nephropathy and background retinopathy. After 18 months, 15 patients remained in the study. Fluorescein leakage remained nearly unchanged in the captopril-treated group, being 4.1 ± 4.1 (mean $\pm$ SD) $\times 10^{-7}$ cm/s at baseline and $4.2 \pm 4.1 \times 10^{-7}$ cm/s after 18 months' treatment. The permeability increased significantly ($P < 0.01$) from $3.3 \pm 2.2 \times 10^{-7}$ cm/s to $5.6 \pm 3.5 \times 10^{-7}$ cm/s at 18 months in the control group. Arterial blood pressure was nearly constant in both groups throughout the study. The results indicate that angiotensin-converting enzyme inhibition with captopril can arrest or delay a progressive breakdown of the blood-retina barrier in normotensive insulin-dependent diabetic patients with nephropathy and background retinopathy.

Introduction

Retinopathy, the most prevalent clinical manifestation of diabetic microangiopathy [10], is characterized by abnormal leakage of fluorescein through the blood-retina barrier. A gradual destruction of the barrier, giving rise to an increased leakage of intravenously injected fluorescein, is seen in parallel with the development of morphologic lesions and with increasing duration of diabetes [14]. The leakage can be demonstrated qualitatively by fluorescein angiography and quantitatively by posterior vitreous fluorometry [2, 10, 18].

Elevated arterial blood pressure seems to play a major role in the abnormal blood-retina barrier leakage of fluorescein in non-diabetic patients with essential hypertension [13] and in hypertensive insulin-dependent diabetic patients with diabetic nephropathy [29]. We have previously shown that antihypertensive treatment can decrease or even normalize the permeability in both types of patients and that the decrease is much more dramatic in diabetic than in non-diabetic patients [13, 29].

In diabetic nephropathy, a long-term protective effect of effective antihypertensive therapy on kidney function has been documented [21, 24–26], even in normotensive patients [28]. It is possible that this protective effect may also involve the blood-retina barrier. This hypothesis was examined in the present prospective, randomized control trial, in which angiotensin-converting enzyme was inhibited for 18 months in normotensive insulin-dependent diabetic patients with overt clinical nephropathy and background retinopathy. Captopril was used because it is well tolerated and is effective in hypertensive diabetic nephropathy [5, 27]. Blood-retina barrier permeability was assessed by vitreous fluorometry.

Patients and methods

Subjects

We examined the records of all insulin-dependent diabetic patients with albuminuria of >300 mg/24 h (200 μg/min) who attended the outpatient clinic at Hvidøre Hospital in 1985 [28]. Of the 180 patients found, 107 suffering from arterial hypertension (blood pressure, $>160/95$ mmHg, WHO criteria) were excluded from further investigation. Of the remaining 73 patients, 35 fulfilled the following criteria and were invited to participate in the present study: serum creatinine levels of <120 μ*M* or a glomerular filtration rate of >60 ml min^{-1} 1.73 m^{-2}, an average of three or more consecutive blood pressure measurements of $<150/90$ mmHg, the absence of edema, no medication apart from oral contraceptives, an age of <50 years, and onset of diabetes before the age of 41 years.

There were 2 patients who did not wish to participate and 2 with histories of adverse reactions to fluorescein injection; the remaining 31 patients gave fully informed consent to participate. Upon the initial examination, 11 patients were excluded who had

* The authors have no commercial or proprietory interest in the drugs or instruments used in this study

Offprint requests to: M. Larsen

proliferative retinopathy or macular edema or had previously undergone retinal photocoagulation treatment. The remaining 20 patients, who all had background retinopathy, were included in the study.

All patients were insulin-dependent from the time of diagnosis and all received at least two daily injections of highly purified porcine insulin. Diabetic nephropathy was diagnosed according to previously described criteria [25]. All patients remained on their normal diabetes diet (without sodium or protein restriction) throughout the study.

The patients were randomly assigned to either captopril treatment (10 patients) or no treatment. After baseline examination, treatment with captopril was started. The aim of the captopril treatment was primarily to avoid the rise in arterial blood pressure that is normally associated with the natural progression of diabetic nephropathy and secondarily to reduce mean arterial blood pressure by 5 mmHg. Initially, all treated patients received 12.5 mg captopril before breakfast and dinner. This treatment was adjusted in accordance with the results of trimonthly blood pressure recordings. The highest dose of captopril used was 50 mg b.i.d.

Five patients were excluded during the study: one appeared upon reexamination to have a rapidly progressing cortical cataract (control), three required retinal photocoagulation treatment for macular edema (one control) or for proliferative retinopathy (one control and one captopril-treated subject), and one (control) failed to appear for follow-up. The clinical and demographic data of the three patients who were excluded after having received retinal photocoagulation treatment were not different from those of the rest of the patient population. Their permeabilities at entry were 5.8, 11.2, and 15.4×10^{-7} cm/s (mean of two eyes), respectively.

At baseline, 13 of the 15 patients who completed the study had <10 retinal hemorrages and red spots and <5 soft and hard exudates within the temporal vascular arcades of each eye. The two remaining patients (one in each group) had no lesions near the foveola but >10 and <20 hemorrages and red spots and <5 exudates per eye within the temporal vascular arcades. The two groups did not differ with respect to the severity of retinopathy. Visual acuity was 6/6 in all but one patient, who had 6/9 in both eyes. No signs or symptoms were found of other eye disease than diabetic retinopathy. The study design was approved by the local medical ethics committee and informed consent was obtained from all patients (all legal requirements governing consent were met).

Methods

All investigations were carried out between 1:30 and 3:30 p.m., the patients being at rest between the injection of fluorescein and vitreous fluorometry. Investigations every 6 months included determination of blood pressure and best corrected visual acuity (Snellen), slit-lamp biomicroscopy, ophthalmoscopy, fundus photography, and fluorescein angiography (Canon CF-60Z, Kawasaki, Japan; Kodachrome ISO 200, Rochester, N.Y. USA; Ilford HP5, ISO 400, Moberley, Ches., UK). Vitreous fluorometry was carried out at 12 and 18 months (instrument failure and repair made vitreous fluorometry unavailable at 6 months).

Arterial blood pressure was measured every 3rd month with a Hawksley random zero manometer (cuff, 25×12 cm) that was placed on the right arm after the patient had been resting supine for at least 10 min. The dose of captopril was adjusted accordingly. Diastolic blood pressure was recorded at the disappearance of the Korotkoff sounds (phase V). Mean arterial blood pressure was calculated as diastolic pressure plus one-third of the blood pressure amplitude. Blood glucose was measured by a color reagent strip read by a Reflomat reflectometer (Boehringer-Mannheim, Ingelheim, FRG). Stable hemoglobin A_{1c} (HbA_{1c}) was measured at each investigation (normal range, 4.1%–6.1% of total hemoglobin) [22].

Vitreous fluorometry was undertaken in conjunction with the injection of fluorescein (14 mg/kg) for fluorescein angiography. Injection, blood sampling, and blood sample analysis were done as previously described [16]. Ocular fluorescence was measured along the optical axis of the eye using an automated ocular fluorometer (Fluorotron, Coherent, Palo Alto, Calif., USA) before and 60–70 min after fluorescein injection. The fluorescence measured is a sum of the contribution of fluorescein and its metabolite fluorescein glucuronide. At the excitation and detection bands of the fluorometer, the molar fluorescence of fluorescein glucuronide is only one-fifth that of fluorescein or less, depending on the spectral transmittance of the lens. Overall fluorescence was expressed in fluorescein units. Lens transmittance was determined from the lens fluorescence curve as described by Zeimer and Noth [34].

The free plasma concentrations of fluorescein and fluorescein glucuronide in plasma were determined by plasma ultrafiltration and high-pressure liquid chromatography [16]. Overall ultrafiltrate fluorescence in equivalent fluorescein concentration units was calculated assuming a fluorescence intensity ratio of fluorescein glucuronide to fluorescein of 0.11, in accordance with the characteristics of equipment previously used by us for plasma analysis in vitreous fluorometry [17].

A simplified permeability index was calculated by dividing the posterior vitreous fluorescence curve integral from 2 to 8 mm in front of the retina by the logarithmically interpolated free plasma fluorescence curve integral from injection to measurement of vitreous fluorescence [12, 18]. It is assumed that the transport properties through the blood-retina barrier are the same for fluorescein and fluorescein glucuronide.

It is further assumed that the vitreous fluorescence measured is attributable to fluorescein only, although fluorescein glucuronide also appears to enter the vitreous [15, 19]. At 60 min after injection and with the fluorometer used, the contribution of fluorescein glucuronide to vitreous fluorescence is probably $<10\%$. Provided that plasma decay concentrations of fluorescein and fluorescein glucuronide do not change significantly during the study, the ratio of the two dyes in the vitreous probably remains unchanged. Thus, the lack of separate data on fluorescein glucuronide and fluorescein in the vitreous has no significant effect on the results.

Pupillary dilatation was achieved by the administration of tropicamide 0.5% and phenylephrine hydrochloride 10% as eyedrops.

The color fundus photographs were quantitated by a masked observer according to the following principle: only the macula was assessed, i.e., the area within the temporal vascular arcades, since only this area of the retina contributes to the fluorescein leakage measured by axial posterior vitreous fluorometry [3]. Hemorrages, red spots and soft and hard exudates were counted. The angiograms of the same area were evaluated and classified according to the degree of fluorescein leakage: no leakage, moderate spotty leakage, intense spotty leakage, intense diffuse leakage, and leakage from proliferations. The progression of morphological changes was evaluated by the observer, who was given the fundus photographs and retinal angiograms obtained for each patient at entry and after 18 months but was unaware of their chronological order. The observer was then asked to rank the pictures according to the severity of retinopathy.

Statistical analysis

The statistical analysis evaluated the relative change in permeability (mean of the two eyes), blood pressure, blood glucose, and HbA_{1c} from the initiation of the study to reexamination at 12 and 18 months. For blood-retina barrier permeability, variance increases with the mean change in permeability; therefore, the results were weighted by logarithmic transformation of the permeability. The changes in the two patient groups were compared using Student's *t*-test (double-sided) for significance.

Results

The two patient groups were well matched with respect to sex, age, duration of diabetes, metabolic control (Table 1), blood pressure (Table 2), and blood-retina barrier permeability (Table 3). Treated patients received on average 26±5 mg captopril (mean±SD) at 6 months, 40±15 mg at 12 months, and 51±18 mg at 18 months.

Table 1. Baseline clinical data of insulin-dependent diabetic patients

	Patient number	Sex	Age (years)	Duration (years)	HbA_{1c} (%)	Insulin dose (IU kg^{-1} $24\ h^{-1}$)
Treatment	1	M	27	26	10.5	0.97
	2	M	43	19	7.8	0.56
	3	M	23	19	10.6	0.48
	4	M	23	13	9.1	0.87
	5	M	22	19	7.4	0.83
	6	F	22	9	12.1	0.98
	7	M	36	15	9.1	0.50
	8	M	36	16	9.2	0.67
	9	F	27	12	10.1	0.83
Mean ±SD		2 F/7 M	29 ±8	16 ±5	9.5 ±1.5	0.74 ±0.20
Control	11	M	36	19	8.4	0.50
	12	M	38	24	9.5	0.86
	13	M	37	24	8.9	0.72
	14	M	37	22	11.0	0.64
	15	M	28	15	7.6	0.67
	16	F	25	14	7.7	0.81
Mean ±SD		1 F/5 M	32 ±5	20 ±4	8.8 ±1.3	0.70 ±0.13

Table 2. Arterial blood pressure with and without captopril in insulin-dependent diabetic patients with nephropathy and background retinopathy

	Patient number	Baseline (mmHg)	6 months (mmHg)	12 months (mmHg)	18 months (mmHg)
Treatment	1	124/74	123/67	122/72	134/71
	2	113/74	116/80	125/78	134/87
	3	112/77	116/74	112/81	106/73
	4	130/77	119/76	112/76	120/81
	5	127/60	128/71	123/75	116/63
	6	115/78	111/70	106/75	106/71
	7	136/84	141/70	128/71	141/72
	8	139/86	124/84	131/86	134/89
	9	132/80	126/64	134/69	126/63
Mean SD		125/77 10/7	123/73 9/6	121/76 10/5	124/74 13/9
Control	11	131/88	134/90	140/94	140/93
	12	146/83	148/85	150/80	138/78
	13	121/79	125/82	131/82	121/75
	14	114/70	116/73	123/77	124/78
	15	136/83	143/85	130/80	127/78
	16	126/82	119/75	131/81	142/74
Mean SD		129/81 11/6	131/82 13/7	134/82 9/6	132/79 9/7

Table 3. Blood-retina barrier permeability (P 10^{-7} cm/s) with and without captopril treatment in normotensive insulin-dependent diabetic patients with nephropathy and background nephropathy

	Patient number	P_0	$P_{1\text{-year}}$	$P_{1.5\text{-year}}$	$P_{1\text{-year}}/P_0$	$P_{1.5\text{-year}}/P_0$
Treatment	1	1.66	1.94	2.33	1.17	1.40
	2	2.11	1.33	2.05	0.63	0.97
	3	5.47	4.06	5.85	0.74	1.07
	4	2.33	2.28	3.44	0.98	1.48
	5	1.26	0.57	0.98	0.45	0.78
	6	1.92	1.52	1.48	0.79	0.77
	7	14.4	13.6	14.3	0.94	0.99
	8	3.31	3.31	3.76	1.00	1.14
	9	4.65	5.49	3.95	1.18	0.85
Mean ±SD		4.12 ±4.11	3.79 ±3.98	4.24 ±4.05	0.88 ±0.24	1.04 ±0.25
Control	11	3.51	7.42	7.82	2.11	2.23
	12	2.71	4.27	3.98	1.58	1.47
	13	1.16	1.69	2.65	1.46	2.28
	14	1.10	0.65	1.19	0.59	1.08
	15	7.10	6.79	7.54	0.96	1.06
	16	4.08	7.13	10.1	1.75	2.48
Mean ±SD		3.28 ±2.23	4.66 ±2.94	5.55 ±3.46	1.41 ±0.55	1.77 ±0.64

P_0, permeability (mean of two eyes) before captopril treatment; $P_{1\text{-year}}$ and $P_{1.5\text{-year}}$, permeabilities after 12 and 18 months' treatment. The relative change in permeability with time was significantly higher in the control group than in the captopril-treated group after both 12 months ($P<0.05$, double-sided, log-transformed) and 18 months ($P<0.01$)

In patients receiving captopril, the permeability of the blood-retina barrier remained practically unchanged, being $4.1\pm4.1\times10^{7}$ cm/s at the onset of treatment and $3.8\pm4.0\times10^{-7}$ cm/s and $4.2\pm4.1\times10^{-7}$ cm/s after 12 and 18 months' treatment, respectively (Table 3, Fig. 1). In the control group the permeability increased from $3.3\pm2.2\times10^{-7}$ cm/s at the initiation of the study to $4.7\pm2.9\times10^{-7}$ cm/s at 12 months and $5.6\pm3.5\times10^{-7}$ cm/s at 18 months. The change in permeability in the control group was significantly higher than that in the treated group at both 12 months ($P<0.05$) and 18 months ($P<0.01$). For individual patients, no systematic correlation was found between the change in permeability and the change in mean arterial blood pressure.

The fundus photographs and retinal angiograms did not demonstrate any systematic tendency towards worsening or improvement over the period of observation in either of the patient groups. Visual acuity remained unchanged throughout the study. No signs or symptoms of eye disease other than diabetic retinopathy were found.

Arterial blood pressure remained nearly unchanged in both groups (Fig. 1). Arterial hypertension (sustained diastolic blood pressure ≥95 mmHg) did not develop in any of the patients during the study. The average mean arterial blood pressure in the captopril-treated group was 125±10/77±7 mmHg at entry and 124±13/74±9 mmHg after 18 months (Table 2), whereas in the

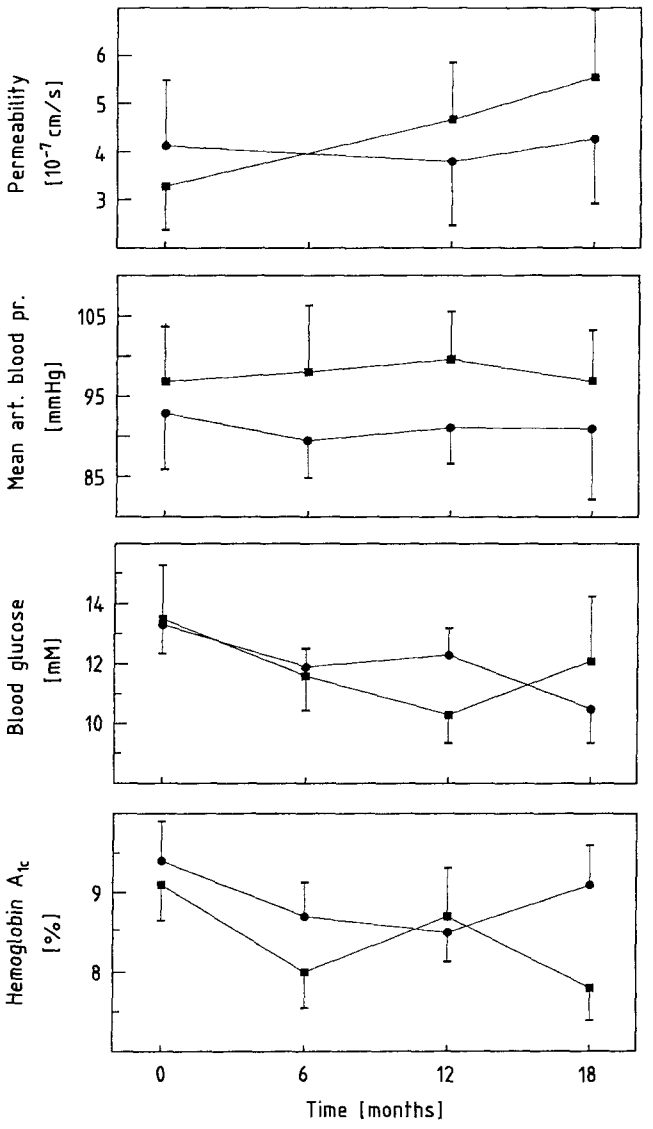

Fig. 1. Results of a prospective trial of angiotensin-converting enzyme inhibition by captopril in normotensive patients with insulin-dependent diabetes and diabetic nephropathy. Mean values and standard errors of the mean (*bars*) from the initiation of treatment through 18 months are shown for blood-retina barrier permeability, mean arterial blood pressure (*mean art. blood pr.*), blood glucose concentration, and hemoglobin A_{1c} concentration in control (*squares*) and captopril-treated (*circles*) groups. The relative increase in permeability was significantly higher in the control group than in the captopril-treated group. No other significant differences were found between the two groups

control group the values were $129 \pm 11/81 \pm 6$ mmHg prior to treatment and $132 \pm 9/79 \pm 7$ mmHg after 18 months. These changes were not statistically significant.

As reflected by blood glucose and hemoglobin A_{1c} (HbA_{1c}) levels, metabolic control did not change significantly during the study, although a trend towards improved control was noted in both patient groups (Fig. 1).

Lens autofluorescence and lens transmittance did not change significantly in either group during the study, nor did the plasma concentration curve integrals for fluorescein and fluorescein glucuronide. Individual variations in plasma curve integrals were smaller than $\pm 15\%$.

Discussion

We found that over a period of 18 months, blood-retina barrier permeability to fluorescein in normotensive insulin-dependent diabetic patients with nephropathy and background retinopathy was stabilized by angiotensin-converting enzyme inhibition with captopril. In contrast, a marked progression was found in an untreated control group. Thus, captopril treatment appears to arrest the progression of blood-retina barrier leakage over a period of at least 18 months in such patients. Hemoglobin A_{1c} (HbA_{1c}) and blood glucose concentrations tended to improve in both groups during the study. Thus, a difference in metabolic control cannot explain the difference observed in the progression of fluorescein leakage.

It should be mentioned that the inhibition of angiotensin-converting enzyme arrests the progressive rise in albuminuria in normotensive insulin-dependent diabetic patients with incipient or overt nephropathy [20, 28]. A reduction in glomerular capillary hydraulic pressure has been suggested as being the most likely mechanism involved. This has been supported by direct measurements of glomerular capillary pressure before and during angiotensin-converting enzyme inhibition in normotensive streptozotocin-treated diabetic rats [1, 33]. Direct measurements have also demonstrated capillary hypertension in renal and extrarenal tissues of normotensive streptozotocin-treated diabetic rats [6, 8, 11].

Autoregulation of the retinal blood flow is impaired in diabetic background retinopathy and is nearly completely lacking in proliferative diabetic retinopathy [30]. Impaired autoregulation facilitates downstream transmission of systemic blood pressure to the retinal microcirculation, with ensuing capillary hypertension and, eventually, even structural damage to the capillary wall. Our own previous studies have shown that the reduction in permeability per millimeter of mercury reduction in blood pressure is 5 times higher in hypertensive diabetic patients with nephropathy than in non-diabetic hypertensive patients [13, 29]. Impaired autoregulation may thus explain the damaging effect of hypertension in diabetic retinopathy [9, 32] and the beneficial effect of captopril treatment on the permeability of the blood-retina barrier.

Theoretically, the change in leakage may be cuased solely by a change in transcapillary hydrostatic pressure, but structural changes that increase the permeability-surface area product may also occur secondarily to the change in hydrostatic pressure, e.g., by widening of endothelial intercellular clefts or damage to the endothelial cell body [23]. It is important to recognize that we do not know whether an increase in blood pressure has an instantaneous or a protracted effect on blood-retina barrier permeability. Further studies are needed to show whether the degree of fluorescein leakage is determined by the blood pressure level during the examination or if it is a function of the blood pressure integral over a longer period preceding the examination.

Recently, non-hemodynamic effects of angiotensin I-converting enzyme inhibition have been discovered in the eye, providing evidence that angiotensin II possesses

angiogenic activity [4] and that an ocular renin-angiotensin system exists [7, 31]. Thus, captopril may also influence blood-retina barrier leakage through an anti-angiogenic mechanism.

Our data do not reveal whether captopril treatment can completely halt the progression of blood-retina barrier leakage. We do not know whether hypotensive treatment prevents or merely postpones the progression of diabetic retinopathy and the accompanying deterioration of vision. It can be concluded, however, that the rate of increase in blood-retina barrier leakage of fluorescein in normotensive insulin-dependent diabetic patients with nephropathy and background retinopathy can be decreased over a period of at least 18 months by angiotensin-converting enzyme inhibition with captopril. Further investigations should attempt to evaluate the long-term value of this treatment in larger groups of patients and to compare angiotensin-converting enzyme inhibition with other hypotensive agents.

Acknowledgements. The authors thank Bente Mertz and Hans-Henrik Petersen for their technical assistance.

References

1. Anderson S, Rennke HG, Garcia DL, Brenner BM, Riley SL, Sandstrom DJ (1989) Short and long term effects of antihypertensive therapy in the diabetic rat. Kidney Int 36:526–536
2. Cunha-Vaz JG, Abreu JR, Campos AJ, Figo GM (1975) Early breakdown of the blood-retinal barrier in diabetes. Br J Ophthalmol 59:649–656
3. Dalgaard P, Barker VA, Lund-Andersen H (1989) Vitreous fluorophotometry: mathematical analysis of the effect of peripheral leakage on axial scans. Invest Ophthalmol Vis Sci 30:1522–1526
4. Fernandez LA, Twickler J, Mead A (1985) Neovascularization produced by angiotensin II. J Lab Clin Med 105:141–145
5. Hommel E, Parving H-H, Mathiesen E, Edsberg B, Damkjær Nielsen M, Giese J (1986) Effect of captopril on kidney function in insulin-dependent diabetic patients with nephropathy. Br Med J 293:467–470
6. Hostetter TH, Troy JL, Brenner BM (1981) Glomerular hemodynamics in experimental diabetes. Kidney Int 19:410–415
7. Igic R, Kojovic V (1980) Angiotensin I converting enzyme (kinase II) in ocular tissues. Exp Eye Res 30:299–303
8. Jensen PK, Steven K, Blæhr H, Christiansen JS, Parving H-H (1986) Effects of indomethacin on glomerular hemodynamics in experimental diabetes. Kidney Int 29:490–495
9. Knowler WC, Bennett PA, Ballantine EJ (1980) Increased incidence of retinopathy in diabetics with elevated blood pressure. N Engl J Med 302:645–650
10. Kohner EM, McLeod D, Marshall J (1982) Diabetic eye disease. In: Keen H, Jarrett J (eds) Complications of diabetes. Arnold, London, pp 19–108
11. Korthuis RJ, Pitts VH, Granger DN (1987) Intestinal capillary filtration in experimental diabetes mellitus. Am J Physiol 253:G20–G25
12. Krogsaa B, Lund-Andersen H, Mehlsen J, Sestoft L, Larsen J (1981) The blood-retinal barrier permeability in diabetic patients. Acta Ophthalmol 59:689–694
13. Krogsaa B, Lund-Andersen H, Parving H-H, Bjældager P (1983) The blood-retinal barrier permeability in essential hypertension. Acta Ophthalmol 61:541–544
14. Krogsaa B, Lund-Andersen H, Mehlsen J, Sestoft L (1987) Blood-retinal barrier permeability versus diabetes duration and retinal morphology in insulin-dependent diabetic patients. Acta Ophthalmol 65:686–692
15. Larsen M, Dalgaard P, Lund-Andersen H (1987) Differential spectrofluorophotometry in the human vitreous body. Noninvasive assessment of the visual system, technical digest. Optical Society of America, Washington, DC, pp 144–147
16. Larsen M, Loft S, Hommel E, Lund-Andersen H (1988) Fluorescein and fluorescein glucuronide in plasma after intravenous injection of fluorescein. Acta Ophthalmol 66:427–432
17. Lund-Andersen H, Krogsaa B, Jensen PK (1982) Fluorescein in human plasma in vivo. Acta Ophthalmol 60:709–716
18. Lund-Andersen H, Krogsaa B, LaCour M, Larsen J (1985) Quantitative vitreous fluorophotometry applying a mathematical model of the eye. Invest Ophthalmol Vis Sci 26:698–710
19. Lund-Andersen H, Larsen M, Dalgaard P, Olsen W (1987) Fluorescein and fluorescein glucuronide in the vitreous body of diabetic patients. Graefe's Arch Clin Exp Ophthalmol 225:173–176
20. Marre M, Chatellier G. Leblanc H, Guyenne T-T, Ménard J, Passa P (1988) Prevention of diabetic nephropathy with enalapril in normotensive diabetics with microalbuminuria. Br Med J 297:1092–1095
21. Mogensen CE (1982) Long term antihypertensive treatment inhibiting progression of diabetic nephropathy. Br Med J 285:685–688
22. Mortensen HB (1980) Quantitative determination of haemoglobin A_{1c} by thin layer isoelectric focusing. J Chromatogr 182:325–333
23. Olesen S-P (1989) An electrophysiological study of microvascular permeability and its modulation by chemical mediators. Acta Physiol Scand [Suppl] 136:[Suppl] 579
24. Parving H-H, Hommel E (1989) Prognosis in diabetic nephropathy. Br Med J 299:230–233
25. Parving H-H, Andersen AR, Smidt UM, Svendsen PA (1983) Early aggressive antihypertensive treatment reduces rate of decline in kidney function in diabetic nephropathy. Lancet I:1175–1179
26. Parving H-H, Andersen AR, Smidt UM, Hommel E, Mathiesen ER, Svendsen PA (1987) Effect of antihypertensive treatment on kidney function in diabetic nephropathy. Br Med J 294:1443–1447
27. Parving H-H, Hommel E, Smidt UM (1988) Protection of kidney function and decrease in albuminuria by captopril in insulin-dependent diabetics with nephropathy. Br Med J 297:1086–1091
28. Parving H-H, Hommel E, Nielsen MD, Giese J (1989) Effect of captopril on blood pressure and kidney function in normotensive insulin-dependent diabetics with nephropathy. Br Med J 299:533–536
29. Parving H-H, Larsen M, Hommel E, Lund-Andersen H (1989) Effect of antihypertensive treatment on blood-retinal barrier permeability to fluorescein in hypertensive type 1 (insulin-dependent) diabetic patients with background retinopathy. Diabetologia 32:440–444
30. Sinclair SH, Grunwald JE, Riva C, Braunstein SL, Nichols CW, Schwartz S (1982) Retinal vascular autoregulation in diabetes mellitus. Ophthalmology 89:748–750
31. Sramek SJ, Wallow IHL, Day RP, Ehrlich EN (1988) Ocular renin-angiotensin: immunohistochemical evidence for the presence of prorenin in eye tissue. Invest Ophthalmol Vis Sci 29:1749–1752
32. West KM, Erdreich LJ, Stober JA (1980) A detailed study of risk factors for retinopathy and nephropathy in diabetes. Diabetes 29:501–508
33. Zatz R, Dunn BR, Meyer TW, Anderson S, Rennke HG, Brenner BM (1986) Prevention of diabetic glomerulopathy by pharmacological amelioration of glomerular capillary hypertension. J Clin Invest 77:1925–1930
34. Zeimer RC, Noth JM (1984) A new method of measuring in vivo the lens transmittance, and study of lens scatter, fluorescence and transmittance. Ophthalmic Res 16:246–255