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Impaired Autoregulation of the Retinal Vasculature and Microalbuminuria in Diabetes Mellitus

*LUMINA P. LANIGAN, †CHARLES V. CLARK, ‡JAFFAR ALLAWI,
*DAVID W. HILL, ‡HARRY KEEN
London

Summary

The relationship between microalbuminuria and retinal vessel responses to sustained handgrip contraction was studied in a group of 20 diabetic patients. The diabetics were divided into two groups based on their albumin excretion rates (AER): Group 1 (AER≤10 mcg/min) consisted of ten diabetic patients, mean age 55.8 ± 3.9 years (mean±SEM); five IDDM and five NIDDM. Group 2 (AER>10 mcg/min) comprised ten diabetic patients: mean age 56.8 ± 3.04 years; six IDDM and four NIDDM. Both groups were similar in that there were no significant differences between mean age, type of diabetes, mean duration of diabetes, glycaemic control or mean resting blood pressures. Group 2 diabetics had a higher incidence of autonomic dysfunction than Group 1, based on the results of four standard tests of autonomic nerve function. There were significantly decreased retinal vessel responses to sustained handgrip contraction in Group 2 diabetics (mean arteriolar constriction 0.1 ± 0.32%, and mean venule constriction 1.0% ± 0.99%) compared with Group 1 diabetics (mean arteriolar constriction 6.9 ± 1.69%, and mean venule constriction 4.2 ± 0.05%). Retinopathy was slightly worse in Group 2.

The implications of the association of microalbuminuria (AER>10 mcg/min) and loss of retinal vessel reactivity to sustained handgrip contraction are discussed.

Retinal vessel responses to sustained isometric muscle contraction have recently been quantified.[1] The changes in vessel calibre probably reflect an autoregulatory response to the simultaneous rise in systemic blood pressure. By contrast, the diabetic retinal circulation shows impaired autoregulation with complete loss occurring in proliferative retinopathy.[2]

An association between proliferative retinopathy and proteinuria is recognised in diabetic patients.[3-6] Functional haemodynamic changes have been proposed as aetiological factors in the development of these complications.[7,8] As a direct corollary, one may postulate a relationship between proteinuria and impaired retinal autoregulation in patients with diabetes mellitus.

We therefore studied the relationship between microalbuminuria and retinal vessel responses to sustained isometric muscle contraction in a group of diabetic patients.

Patients and Methods

Twenty diabetic patients (mean ± standard error of the mean (SEM)), (18 male, mean age: 56.3 ± 2.4 years; range 34 to 73 years) were included in the study following informed

From: *Research Department of Ophthalmology, Royal College of Surgeons of England, †Moorfields Eye Hospital and ‡Guy's Hospital, London.

Correspondence to: L. P. Lanigan FRCSE, Moorfields Eye Hospital, City Road, London EC1V 2PD.

consent and Ethical Committee approval. The eleven insulin dependent diabetics and nine non-insulin dependent diabetics were subdivided into two groups: based on the results of albumin excretion rates (AER). The AER were determined using a modified immunoassay technique (with single antibody assay and polyethylene glycoprecipitation) to measure albumin concentration.[9] Excretion rates were calculated from one or more timed overnight samples of urine collection. The upper limit of normal for AER from overnight samples was set at 10 mcg/min[10] and patients with such values were included in Group 1. Diabetics with AER greater than ten mcg/min were defined as Group 2.

Group 1 (AER≤10 mcgm/min) consisted of ten diabetic patients: mean age 55.8 ± 3.9 years, range 34–71 years, five IDDM and five NIDDM. *Group 2* comprised ten diabetic patients: mean age 56.8 ± 2.04 years, range 41 to 73 years, six IDDM and four NIDDM.

The mean duration of diabetes mellitus was 13 ± 2.86 years (range 2 to 25 years) and 10.3 ± 2.61 years (range one to 29 years) for Groups 1 and 2 respectively.

Long-term control of diabetes was assessed by glycosylated haemoglobin estimation in all subjects. Diabetics with autonomic nerve dysfunction were identified by the following methods:

(a) Diastolic blood pressure rise of less than or equal to 10 mmHg in response to 33% maximum sustained handgrip contraction.
(b) Immediate heart-rate response to standing 30:15 ratio less than or equal to 1.00.
(c) A decrease in systolic blood pressure in response to standing from the supine position of greater than or equal to 30 mmHg.
(d) Heart-rate variation in response to a Valsalva ratio of less than 1.21. The degree of autonomic dysfunction was classified as early, definite and severe, according to standard criteria.[11]

Retinal vessel responses to systemic autonomic stimulation

The protocol was similar to that described previously.[1] Each patient was studied seated at the fundus camera with one pupil dilated (whichever was preferred by the patient) with G. Tropicamide 1% and G. Pheneylephrine 10%.

Three baseline blood pressures were taken from the non-exercising arm using a sphygmomanometer with an automatic inflatable cuff (COPAL UA 231). The subject was instructed to perform three maximum handgrip contractions with the dominant arm to establish their maximum voluntary contraction (MVC). The subject then performed a sustained handgrip contraction at 33% MVC for 2–2.5 minutes; three BP measurements were taken at 0.5, 1.5 and 2.5 minutes during handgrip contraction and three phases of fundus photographs (each consisting of five replications) were taken at 1, 2 and 2.5 minutes. On release of the handgrip a final BP reading

Table I *Clinical features of Groups 1 and 2 diabetics*

	Group 1	*Group 2*
	AER ≤10 mcg/min n=10	*AER >10 mcg/min n=10*
Sex M:F	9:1	9:1
Age (years)	55.8 ± 3.87	56.8 ± 3.1
Duration of DM (years)	13 ± 1.27	10.3 ± 2.6
Systolic BP	145 ± 5.8	151 ± 3.7
Diastolic BP	85 ± 3.3	85 ± 3.0
Retinopathy (No)	7	7
HbA1%	9.1 ± 0.8	8.4 ± 0.6
Aut. Dysfunction (No)	3	7
Type of DM	5 IDDM	6 NIDDM
Ret. artery change %	−6.9 ± 1.69	−0.1 ± 0.32
Ret. venule change %	−4.2 ± 0.55	−0.99 ± 0.99
Diast. BP rise to HG	+23 ± 2.9	+23 ± 4.3

mean ± SEM.

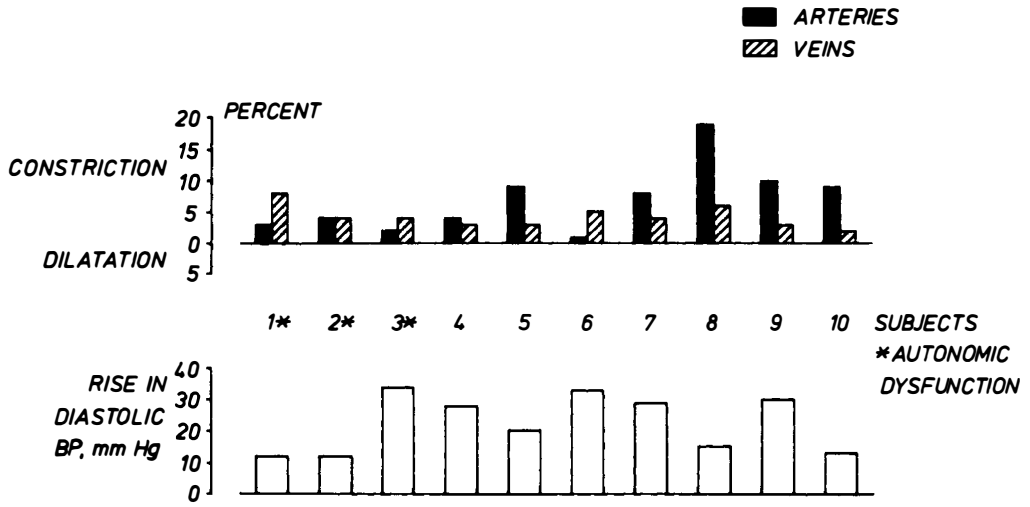

Fig. 1. *Individual mean retinal vessel and blood pressure responses during handgrip contraction for Group 1 (AER≤10 mcg/min).*

and single phase of fundus photographs were taken at five minutes. All diabetic patients maintained a 33% maximum voluntary contraction for 2.5 minutes.

Analysis

All films were analysed using the Quantimet 800 Image analyser (Cambridge Instruments) a technique established in this department.[12] Ten to 18 suitable vessel sites were selected in each patient comprising approximately equal numbers of arterioles and venules nominally within the calibre range (64–174 μm) calculated on the basis of the Gullstrand Schematic Eye. Vessel calibres at these sites were measured and the means, standard error of the means (SEM) and one way analysis of variance (ANOV) for each site within replications and between the phases were calculated. Percentage change in mean retinal vessel calibre between phase 1 and phase 4 (at 2.5 min handgrip) were calculated for each

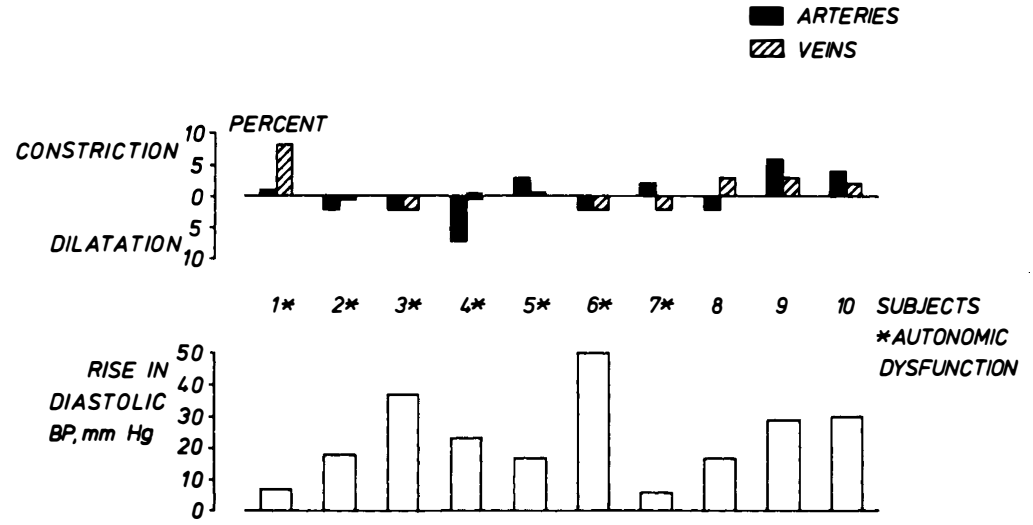

Fig. 2 *Individual mean retinal vessel and blood pressure responses during handgrip contraction for Group 2 (AER>10 mcg/min).*

Table II *Blood pressure and mean retinal vessel responses and autonomic status for Group 1 diabetics: AER ≤10 mcg/min*

Subj. No.	Age	Sex	Type DM	DM	Dur. resting BP	Auton. status	Retino. grade	AER mcg/min	Rise in DBP	Retinal vessel calibre change Art. %	Ven. %
1.	67	M	NIDDM	25	130/76	D	2	1.6	+12	−3	−8
2.	56	F	NIDDM	6	182/93	D	2	8.5	+12	−4	−4
3.	42	M	IDDM	25	142/80	D	3	7.5	+34	−2	−4
4.	58	M	NIDDM	4	153/82	N	0	6.3	+28	−4	−3
5.	60	M	NIDDM	2	126/63	N	0	9.5	+20	−9	−3
6.	67	M	IDDM	25	142/95	N	2	9.5	+33	−1	−5
7.	60	M	IDDM	14	161/99	N	0	0.3	+29	−8	−4
8.	71	M	NIDDM	7	147/84	N	1	4.2	+15	−19	−6
9.	43	M	IDDM	9	145/90	N	1	2.6	+30	−10	−3
10.	34	M	IDDM	13	118/88	N	3	6.4	+13	−9	−2

subject; significance was assessed by the student t-test for paired data (two tailed).

Linear regression analysis was applied to assess any correlation between microalbuminuria and mean retinal arteriolar responses.

Results

The two diabetic groups were very similar in all respects except retinopathy and autonomic status; Table I.

(1) Retinal vessel responses

Mean retinal vessel responses to sustained handgrip were significantly greater in Group 1 than Group 2; mean arteriolar constriction ($p<0.02$) and mean venule constriction ($p<0.02$). In Group 1 (AER≤10 mcgm/min), there was a mean arteriolar constriction of $6.9 \pm 1.69\%$ ($p<0.01$) and mean venule constriction of $4.2 \pm 0.05\%$ ($p<0.001$). Group 2 (AER>10 mcgm/min) showed a mean arteriolar constriction of $0.1 \pm 0.32\%$ and mean venule cosntriction of $1.0 \pm 0.99\%$. The individual mean retinal vessel rsponses are shown in Figures 1 and 2.

(2) Blood pressure responses

There were no significant differences in the mean rise in diastolic blood pressure during sustained handgrip contraction between the two groups: Group 1 $+22.6 \pm 2.0$ mmHg, range 12–34; Group 2 $+23.4 \pm 4.29$ mmHg, range 6–50 mmHg.

There was no correlation between the blood pressure responses and the retinal vessel responses in either group.

(3) Autonomic status (Tables II and III)

Three diabetics in Group 1 had definite autonomic dysfunction based on autonomic nerve function tests, while in Group 2 (AER>10 mcg/min) three had definite autonomic dysfunction and four early dysfunction.

Table III *Blood pressure and mean retinal vessel responses and autonomic status for Group 2 diabetics: AER ≤10 mcg/min*

Subj. No.	Age	Sex	Type DM	DM	Dur. resting BP	Auton. status	Retino. grade	AER mcg/min	Rise in DBP	Retinal vessel calibre change Art. %	Ven. %
1.	54	M	IDDM	29	151/86	E	1	22.6	+7	−1	−8
2.	60	M	NIDDM	5	150/95	D	2	11.7	+18	+2	+0.3
3.	49	M	NIDDM	9	145/95	E	0	22.3	+37	+2	+2
4.	71	M	NIDDM	12	169/80	D	2	19.5	+23	+7	0
5.	56	M	IDDM	1	166/96	E	0	13.9	+17	−3	−0.2
6.	41	M	IDDM	9	138/78	E	1	14.4	+50	+2	+2
7.	51	M	IDDM	13	138/76	D	2	69.7	+6	−2	+2
8.	73	M	IDDM	6	164/67	N	1	13.3	+17	+2	−3
9.	55	F	IDDM	17	148/88	N	1	10.8	+29	−6	−3
10.	58	M	NIDDM	2	139/87	N	0	25.0	+30	−4	−2

Table IV *Severity of retinopathy in the two diabetic groups*

Retinopathy Grade	*Group 1 (AER ≤10 mcg/min)*	*Group 2 (AER >10 mcg/min)*
0 . . . no retinopathy	*3*	*3*
1 . . . mild background	*2*	*4*
3 . . . severe background	*3*	*3*
4 . . . proliferative	*2*	*0*

(4) Glycaemic control

There was no difference in the degree of glycaemic control between the two groups as assessed by HbA1 values: Group 1 9.09 ± 0.83%, and Group 2 8.38 ± 0.56%.

(5) Retinopathy

Retinopathy was assessed by opthalmoscopy and inspection of the fundus photographs. The degree of retinopathy was slightly worse in Group 2 compared to Group 1 (Table IV). Retinopathy was graded as follows:

0 . . . . no retinopathy
1 . . . . mild background (<haemorhages)
2 . . . . severe background (>10 haemorhages ± exudates)
3 . . . . proliferative retinopathy.

(6) Relationship between microalbuminuria and retinal vessel responses

Subject no.7 in Group 2 had an AER of 69.7 mcg/min and was a complete outlier compared to the rest of the AER values in this group. Excluding this subject from the linear regression analysis, there was a significant correlation between loss of retinal artery responses and microalbuminuria ($r=0.579$; $p<0.001$), (Fig. 3).

Discussion

The present study demonstrates significantly decreased retinal vessel responses to systemic autonomic nerve stimulation in diabetic patients with microalbuminuria. The groups studied were reasonably equivalent, with no significant differences in mean age, type of

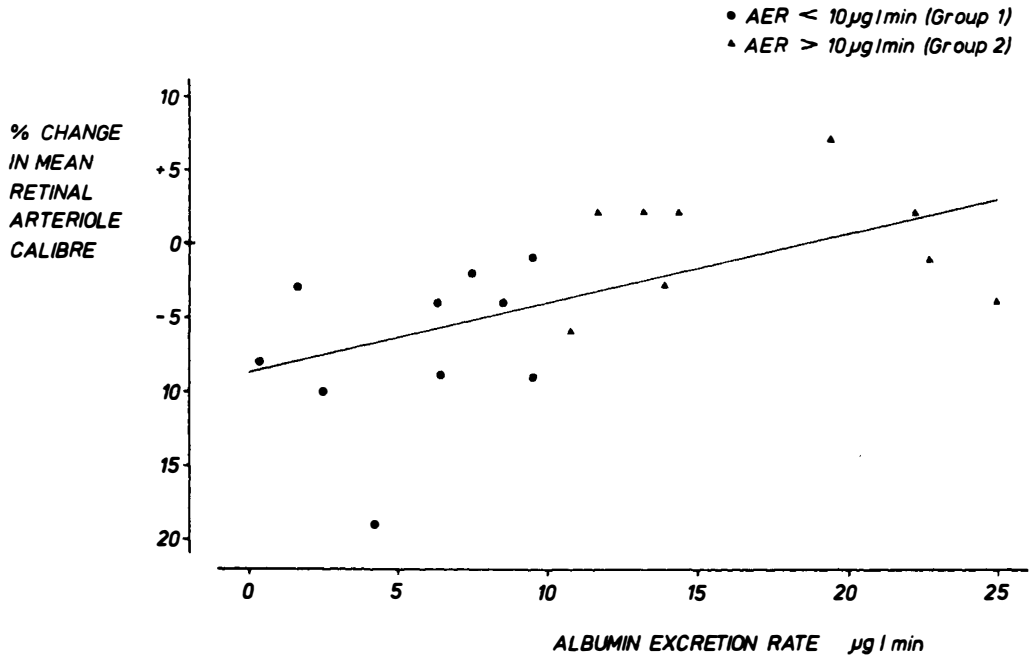

Fig. 3 *Correlation between mean retinal artery responses during handgrip contraction and AER.*

diabetes, mean duration of diabetes, glycaemic control or mean resting blood pressures.

Significant retinal vessel constriction occurs in normal subjects during systemic autonomic stimulation.[1] The vessel constriction probably represents an autoregulatory response to the elevation in systemic blood pressure during sustained handgrip contraction. The present study has shown a significant loss of retinal vessel reactivity to sustained handgrip contraction in diabetics with microalbuminuria (AER>10 mcg/min). Excluding subject no.7 in Group 2, there is a significant correlation between retinal vessel responses and microalbuminuria, confirming an association between these diabetic complications.

There was a higher incidence of autonomic dysfunction in Group 2 (seven diabetics, of which three had definite autonomic neuropathy and four mild autonomic dysfunction) compared with Group 1 (three diabetics had definite autonomic dysfunction). Autonomic neuropathy has previously been shown to affect renal function by reducing splanchnic vascular resistance with consequent increase in renal blood flow[13] and urinary sodium excretion.[14] The higher incidence of autonomic dysfunction in Group 2, may be an important factor related to the increased AER in this group, although the association of autonomic dysfunction and microalbuminuria may equally merely reflect an advanced stage in the diabetic microvascular disease, as patients with diabetic autonomic neuropathy are also at a higher risk of developing abnormal renal function.

The degree of retinopathy, however, was actually slightly worse in Group 1 compared to Group 2 (Table IV), although the difference between the groups was not significant. This may reflect the small size of the group studied and the patchy nature of diabetic vascular disease. Sinclair *et al.*[2] have demonstrated an inverse relationship between retinal vessel autoregulation and diabetic retinopathy, with complete loss of autoregulation occurring in proliferative retinopathy. However in the present study, the group with maximum loss of retinal vessel response (ie impaired autoregulation) (AER>10 mcg/min; Group 2) showed less severe retinopathy. This apparent paradox was also present in the study by Osei *et al.*,[15] reporting abnormal retinal artery responses to cold pressor testing in patients with no clinical retinopathy. Furthermore 50% of the diabetics with microalbuminuria studied by Barnett *et al.*,[4] did not have any retinopathy.

It has been proposed that diabetics with higher glomerular filtration rates early in their disease course are more likely to develop nephropathy suggesting an association between early haemodynamic changes and late glomerulopathy.[16] Haemodynamic changes have also been implicated in the development and/or progression of diabetic retinopathy.[17-19] Ipsilateral carotid artery stenosis and renal artery stenosis afford protection from retinopathy and diabetic glomerulosclerosis respectively.[20,21] It is noteworthy that nephropathy has been reported in at least 47% of diabetics with advanced proliferative retinopathy[5] and, conversely, Deckert *et al.*[22] have shown that at some stage during the development of nephropathy, retinopathy is an almost inevitable concomitant feature.

Microalbuminuria is both an early predictor of diabetic nephropathy[16,23] and has been proposed as the most effective non-ocular indicator of visual loss in diabetes.[5] The observed association between retinal vessel reactivity and microalbuminuria may be a manifestation of coincidental natural history, however it may equally support the hypothesis of a causal relationship between haemodynamic changes and diabetic nephropathy. Impaired autoregulation of the retinal vasculature may represent an early prognostic indicator of the alteration in haemodynamics proposed as a significant factor in the pathogenesis of nephropathy and retinopathy.

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References

[1] Lanigan LP, Clark CV, Hill DW: Retinal circulation responses to systemic autonomic nerve stimulation. *Eye,* 1988, **2:** 415–7.

[2] Sinclair SH, Grunwald JE, Riva CE, Braunstein

SN, Nichols CW, Schwartz SS: Retinal vessel autoregulation in diabetes. *Ophthalmology* 1982, **89(7):** 748–50.

[3] Jerneld B and Algvere P: Relationship of duration and onset of diabetes to prevalence of diabetic retinopathy. *Am J Ophthalmol* 1986, **102:** 431–7.

[4] Barnett AH, Dallinger K, Jennings P, Fletcher J, Odugbesan O: Microalbuminuria and diabetic retinopathy. *Lancet* 1985, **1:** 53–4.

[5] Rand LI, Prudhomme GJ, Ederer F, *et al.*, and the Diabetic Retinopathy Study Research Group: Factors influencing the development of visual loss in advanced diabetic retinopathy. *Invest Ophthalmol Vis Sci.* 1985, **26:** 983–991

[6] Jerneld B, Algvere P: Proteinuria and blood glucose levels in a population with diabetic retinopathy. *Am J Ophthalmol* 1987, **104:** 283–9.

[7] Hostetter TH, Rennke HG, Brenner BM: The case for intrarenal hypertension in the initiation and progression of diabetic and other glomerulopathies. *Am J Med* 1982, **72:** 375–80.

[8] Stefansson ES, Landers EB, Wolbarst ML: The role of oxygen and vasodilatation in diabetic nephropathy. In: Friedman EA. L'Esperance FA eds. Diabetic-renal syndrome. 2nd ed. New York, Grune and Stratton 1982, 117–150.

[9] Keen H and Chlouverakis K: An immunoassay for urinary albumin at low concentrations. *Lancet* 1963, **2:** 913–6.

[10] Jarret RJ, Viberti C, Argyropoulos A, Hill RD, Mahmud D, Murrells JJ: Microalbuminuria predicts mortality in non-insulin dependent diabetics. *Diabetic Medicine* 1984, **1:** 17–19.

[11] Ewing DJ and Clarke BF: Autonomic neuropathy: Its diagnosis and prognosis. In Clinics in Endocrinology and Metabolism. Watkins PJ, ed. WB Saunders Company, London 1986, **15(4):** 855–88.

[12] Hill DW and Crabtree A: Vascular calibres. *Tr Ophthalmol Soc UK* 1984, **104:** 107.

[13] Hilsted J: Pathophysiology in diabetic autonomic neuropathy, cardiovascular, hormonal and metabolic studies. *Diabetes* 1982, **31:** 730–7.

[14] Bell GM, Reed W, Ewing DJ, *et al.*: Abnormal urinary sodium excretion in diabetics with autonomic neuropathy (Abstract). British Diabetic Association, Spring meeting Oxford, March 1985.

[15] Osei K, Fields PG, Cataland S, Craig EL, George JM, O'Dorsio TM: Abnormal retinal artery responses to stress in patients with Type 1 diabetes. *Am J Med* 1985, **78:** 595–601.

[16] Mogensen CE and Christensen CK: Predicting diabetic nephropathy in insulin dependent diabetics. *New Eng J Med* 1984, **311(2):** 89–93.

[17] Dorf A, Knowler WC , Ballintine EJ: Retinal artery presure and systemic blood pressure are associated with diabetic retinopathy. *Diabetes* 1979, **28:** 412.

[18] Knowler WC, Bennet PH, Ballintine EJ: Increased incidence of retinopathy in diabetics with increased blood pressure. *N Eng Med J* 1980, **302:** 645–50.

[19] Parving HH, Viberti GC, Keen H, Christensen JS, Larsen NS: Haemodynamic factors in the genesis of diabetic microangiopathy.

[20] Gray AJ and Rosenbaum A: Retinal artery pressure in asymmetrical and diabetic retinopathy. *Arch Opthalmol* 1966, **75:** 758–61.

[21] Berkman J and Rifkin H: Unilateral nodular diabetic glomerulosclerosis (Kimmelsiel-Wilson): report of a case. *Metabolism* 1973, **22:** 715–21.

[22] Deckert T, Poulson JE, Larsen M: Prognosis of diabetes with diabetes onset before the age of 31. *Diabetologia* 1978, **4:** 463–77.

[23] Viberti GC, Jarret RJ; Mahmud V, Hill RD, Arvyropoulos A, Keen H: Microalbuminuria as a predictor of clinical nephropathy in insulin dependent diabetics. *Lancet* 1982, **1:** 1430–2.