Virchows Arch (2001) 438:618–623
DOI 10.1007/s004280100396

ORIGINAL ARTICLE

Christian Gulmann · Ruth Østerby
Hans-Jacob Bangstad · Susanne Rudberg

The juxtaglomerular apparatus in young type-1 diabetic patients with microalbuminuria

Effect of antihypertensive treatment

Received: 15 November 2000 / Accepted: 20 December 2000 / Published online: 1 March 2001

Abstract *Background*: Our goal was to investigate the effect of antihypertensive drugs on the juxtaglomerular apparatus (JGA) in young type-1 diabetic patients with microalbuminuria. *Methods*: Twelve patients were allocated to treatment with either an angiotensin-converting enzyme inhibitor (group 1, six subjects) or a beta-receptor blocker (group 2, six subjects). A comparable group of nine patients without antihypertensive treatment provided reference values (group 3, nine subjects). Renal biopsies were taken at baseline and after a median of 40 months (groups 1 and 2) and 30 months (group 3). Using light microscopy with 1-µm serial sections of the plastic-embedded biopsies, volumes of the JGA and glomerulus and areas of the macula densa and lumina of the afferent and efferent arterioles were obtained. *Results*: A significant decrease of the volume of the JGA (P=0.026) and of the volume of the JGA relative to that of its corresponding glomerulus (P=0.0005) was noted in the reference group only. Negative correlations existed between the increase in the luminal area of the afferent arteriole and mean diastolic blood pressure in the study period in group 1 (P=0.024) and group 2 (P=0.032). *Conclusions*: Our results showed that a decrease in the size of the JGA is offset by antihypertensives. The negative correlation between the change in the luminal area of the afferent arteriole and mean diastolic blood pressure in groups 1 and 2 suggest that renal protection in antihypertensive treatment may be through a better constriction of the afferent arteriole protecting the glomerulus from systemic blood pressure.

Keywords Angiotensin-converting enzyme inhibitors · Beta-receptor blockers · Juxtaglomerular apparatus pathology · Microalbuminuria · Type-1 diabetes · Stereology

C. Gulmann (✉)
Department of Histopathology, St. James's Hospital,
Dublin 8, Ireland
e-mail: christian.gulmann@ireland.com
Tel.: +353-1-4162993, Fax: +353-1-4103466

C. Gulmann · R. Østerby
Electron Microscopy Laboratory,
Institute of Experimental Clinical Research and
Institute of Pathology, Aarhus Kommunehospital, Denmark

H.-J. Bangstad
Department of Paediatrics, Ullevål University Hospital,
Oslo, Norway

S. Rudberg
Department of Women and Child Health, Paediatric Unit,
Karolinska Institutet, Stockholm, Sweden

Introduction

Diabetes mellitus (DM) is frequently associated with nephropathy, but details about the possible mechanisms are not clear. Several studies indicate the involvement of the juxtaglomerular apparatus (JGA) in the development and progression of diabetic nephropathy [1, 3, 7, 9, 22], because both of the JGA's main functions (synthesis and secretion of renin and direct control of glomerular hemodynamics via the afferent and efferent arterioles) have been reported as abnormal. Increased perfusion and glomerular filtration rate (GFR) are common features in early stages of type-1 DM [22], and renin activity has been reported as abnormal [1, 3, 9]. Using quantitative methods, we have previously shown that the JGA is significantly enlarged in the early phase of microalbuminuria in type-1 diabetic patients [7].

Antihypertensive treatment has been shown to have a beneficial effect on the progression of albuminuria in patients with type-1 DM and microalbuminuria [4, 6, 11, 19]. However, lowering of the albumin excretion rate (AER) by antihypertensive treatment does not necessarily reflect a reversion or inhibition of progression of the renal structural abnormalities, although we have recently reported that microalbuminuric type-1 DM patients included in the present series showed lack of progression in glomerulopathy with antihypertensive treatment [18]. However, the mechanisms of the beneficial effects of antihypertensives are unclear.

Antihypertensive drugs, especially angiotensin converting enzyme (ACE) inhibitors would be expected to

profoundly influence the JGA. Various studies in non-diabetic rabbits [16] have shown an increase in JGA size during antihypertensive treatment. So far, no data exist on the natural history of the structure of the JGA in diabetes, although, in some reports, sclerosis of the JGA was suggested in later stages of diabetic renal disease [17, 20]. No previous investigations have dealt with the possible effects of antihypertensive treatment in diabetes.

Considering the pivotal role of the JGA in regulation of glomerular flow and systemic blood pressure the region seems to be of great importance during antihypertensive treatment. The present study was, therefore, performed to obtain quantitative data on the JGA in young type-1 DM patients in the microalbuminuric phase of the diabetic nephropathy before and after treatment with either an ACE inhibitor or a beta blocker and to compare them with a group that did not receive antihypertensive treatment.

Subjects and methods

Subjects

Baseline kidney biopsies were available from 18 young type-1 DM patients who have had diabetes for more than 5 years, controlled at three departments of paediatrics in Stockholm. All patients were over 15 years old and had a prepubertal onset of diabetes. The AER was within the range defined as microalbuminuria: 15–200 µg/min in at least two out of three timed overnight urine samples collected consecutively in the last year before the biopsy was taken. Microalbuminuria had been present for a mean duration of 2 years. None of the patients had received antihypertensive drugs or a low protein or low salt diet prior to inclusion in the study. The patients were randomly allocated to treatment with either an ACE inhibitor (enalapril, 20 mg/day; group 1) or a beta blocker (metoprolol, 100 mg/day, group 2). Five patients dropped out before the follow-up biopsy due to causes unrelated to their disease and, in one case, the biopsy material was insufficient for present measurements. The final follow-up material consisted of six patients in each of the groups.

Informed consent had been obtained from all subjects, and the biopsies were approved by the ethics committee. However, the ethics committee did not permit renal biopsies in an untreated reference group. Therefore, a previously studied group of microalbuminuric type-1 DM patients with similar age, duration of DM, GFR, blood pressure and level of microalbuminuria was used (reference group, group 3). These patients were part of a previous study in Oslo, Norway, completed immediately before the antihypertensive treatment trial, comparing conventional (2–5 daily) insulin injections with intensified insulin treatment (continuous subcutaneous insulin infusion) [2]. All patients in the present study received conventional insulin treatment (two or multiple daily insulin injections).

Table 1 presents clinical data. Blood pressures were obtained using an automatic devise (Dinamap, Critikon, Johnson-Johnson, Tampa, Fla.) in groups 1 and 2 and a conventional sphygmomanometer in group 3. GFR was measured using continuous insulin clearance. Timed overnight AER was obtained using an immunoturbidimetric method [21]. Haemoglobin (Hb)A_{1C} was analysed using high-pressure liquid chromatography. During the treatment period, HbA_{1C}, blood pressure and timed overnight AER were determined every second or third month.

Methods

Ultrasound-guided percutaneous kidney biopsies were obtained using an automated biopsy devise. They were taken at baseline and after a period of 40 months (range 35–50 months) in groups 1 and 2 and after 30 months (range 25–33 months) in group 3. The tissue was fixed in 2% glutaraldehyde in buffer and delivered to the laboratory in Aarhus, where further processing was carried out. The embedding medium for baseline and follow-up biopsies was epon in groups 1 and 2 and vestopal in group 3.

The blocks were sectioned systematically at 1 µm. Examination levels were every fifth or tenth section. The average distance, T, between the levels was determined using a technique described in a previous work [14]. All parameters except for the mesangial volume fraction and basement membrane thickness were obtained using light microscopy.

The glomerulus was defined as the minimal circumscribed polygon enclosing the capillary tuft [12]. Every new glomerulus

Table 1 Clinical data. Median (range). Clinical values at baseline and during follow-up. Only albumin excretion rate (AER) in groups 1 and 2 are not mean values during follow-up, because they fell significantly during the first 12 months. Here, the mean of the last three measurements made prior to the follow-up biopsy is used. Age and diabetes duration are shown at baseline. *Hb* haemoglobin; *GFR* glomerular filtration rate

	Group 1		Group 2		Group 3 (controls)	
	Baseline	Follow-up	Baseline	Follow-up	Baseline	Follow-up
n (Gender)	6 (5 Female/ 1male)		6 (3 Female/ 3 male)		9 (5 Female/ 4 male)	
Age (years)	18 (15–20)		20 (18–23)		19 (17–29)	
Diabetes duration (years)	10 (6–15)		12.5 (9–16)		12 (8–13)	
Blood pressure (mmHg)	122.5 (105–135)/ 77.5 (70–95)	120 (112–131)/ 71 (60–79)	122.5 (110–140)/ 81.5 (65–95)	128.5 (116–135)/ 74 (67–83)	124 (115–150)/ 85 (76–98)	125 (113–145) /82 (76–95)[a]
HbA_{1C} (%)	8.9 (6.4–12.6)	9 (7.2–11.2)	10 (7.2–11.8)	8.5 (4.7–10.6)	9 (7.9–12.2)	8.9 (7.9–12.4)
AER (µg/min)	31.5 (23–160)	11 (8–14)[b]	29 (19–41)	5 (2–12)[c]	33 (18–194)	23 (7–347)
GFR (ml/min)	110.5 (88–151)	113 (89.8–153)	121 (95–138)	118.5 (106–148)	128 (101–209)	143 (107–184)
Interval, baseline to follow-up (months)	42 (35–46)		37.5 (36–54)		31 (25–33)	

[a] Mean diastolic blood pressure was lower in group 3 than in groups 1 (P=0.0047) and 2 (P=0.0095)
[b] AER fell significantly in groups 1 and 2 (P=0.028 in both cases)

that appeared was used, making sampling independent of size. At 292× magnification, the areas of glomerular profiles were determined using point counting at 10 µm between levels. The glomular volume, V(glomerulus), was then calculated using Cavalieri's principle [12]. If some levels of the glomerulus were missing, V(glomerulus) was obtained using the maximal profile area method [12], assuming spherical glomeruli.

The vascular pole area, A(VP), was calculated by measuring at the linear distance of the vascular pole (i.e. the area of the glomerulus at the vascular pole not surrounded by Bowman's capsule) at the level of reflection of Bowman's capsule. An approximate estimate of A(VP) was calculated as the sum of lengths on all of the sections through the A(VP), multiplied by the mean distance between the levels. The following parameters were obtained from measurements at 5-µm intervals between levels. The microscopic image was projected onto a computer screen at a total magnification of 1440×. The methods have previously been described in detail [7, 14].

An operational definition of the JGA was used in this study, namely the lacis cell field plus the part of the wall of the juxtaglomerular arterioles adjacent to the lacis cells (Fig. 1), thereby measuring a structure that could be clearly identified on any section, independent of sectioning angle, taking advantage of the possibility to follow the region in sequential sections [JGA volume, V(JGA)]. The limit towards the glomerulus was at the level of reflection of the Bowman's capsule. V(JGA) was estimated using Cavalieri's method [12] for every new JGA that appeared in the tissue. V(JGA), as a percentage of glomerular volume, V(JGA)/V(glomerulus)%, was found for each nephron, and the mean value for individual biopsies was calculated. A mean of 10 (range 5–17) JGA were studied per biopsy.

The area of the macula densa, A(macula densa), was defined as the projected, plane (i.e. without curvature) interface between the macula densa and the lacis cells and the juxtaglomerular arterioles. An approximate estimate was obtained as the sum of lengths on all of the sections through macula densa, multiplied by the mean distance between the levels.

The arterioles were identified as afferent or efferent either from their appearance on the section or by following their course in the serial sections, either up to larger arteries or to capillaries [area of the arteriolar lumina; A(afferent) and A(efferent)]. The lumina were measured at the level of reflection of Bowman's capsule (Fig. 1). For each pair of arterioles belonging to the same nephron, the ratio of the areas, A(afferent)/A(efferent), was calculated. The mesangial volume fraction, V_V(mesangium/glomerulus), and basement membrane thickness, BMT, previously published [18], were estimated by means of electron microscopy using standard stereological methods [12].

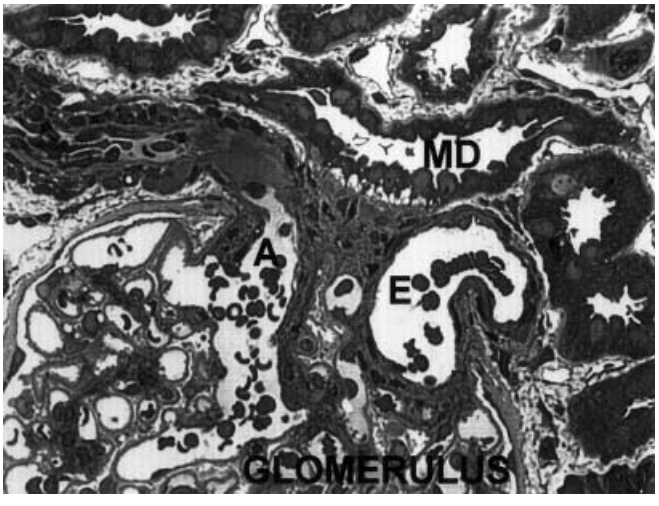

Fig. 1 ×210. Section (1-µm) showing a profile of the juxtaglomerular apparatus: afferent arteriole (*A*), efferent arteriole (*E*), and macula densa (*M*). The juxtaglomerular apparatus (JGA) was measured as follows: The lacis cells (between the macula densa and the arterioles) and the part of the arteriolar walls bordering these. The level of reflection of the Bowman's capsule served as the border towards the glomerulus. The vascular pole area and the luminal areas of the arterioles were also measured here

Statistical analysis

Statistical significance was defined as $P<0.05$. To test changes within a group from baseline to follow-up, the Students' paired *t*-test was used. When testing differences among groups, the Kruskal–Wallis test was used and, if positive, the Student's *t*-test was used to test differences between the individual groups using a Bonferoni correction (significance level $P/3=0.0167$). Due to the variation in time interval between baseline and follow-up biopsy, for calculations, the follow-up values were standardised to 24 months, assuming a linear progression of lesions. Correlations between variables were tested with least squares regression. Two variables were considered significantly correlated if $P<0.05$; the correlation coefficient, *r*, is also given.

Results

The results are shown in Table 1, Table 2, Fig. 2, Fig. 3, and Fig. 4. AER decreased in groups 1 and 2 ($P=0.028$ in either case), and all were normoalbuminuric at termination of the study. At baseline, all subjects were normotensive, and the blood pressure did not change significantly within any of the groups. However, in groups 1 and 2, the mean diastolic blood pressure throughout the study period was significantly lower than in group 3 ($P=0.0018$ vs group 1 and $P=0.0088$ vs group 2). HbA_{1C} and GFR did not change in any of the groups.

Structural results

At baseline, the A(macula densa) was significantly larger in group *3* than in group 1 ($P=0.0015$). No other differ-

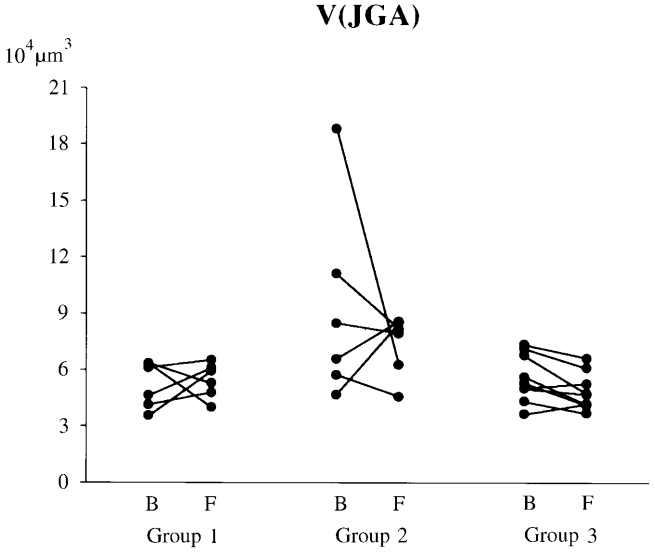

Fig. 2 Mean juxtaglomerular apparatus (JGA) volume in patients at baseline and follow-up

Table 2 Results. Median (range). *JGA* juxtaglomerular apparatus; *V(JGA)* JGA volume; *V (glomerulus)* glomerular volume; *A(VP)* vascular pole area; *A(efferent)* area of the efferent arteriole; *A(afferent)* area of the afferent arteriole; *A(macula densa)* macula densa area

	Group 1		Group 2		Group 3 (controls)	
	Baseline	Follow-up	Baseline	Follow-up	Baseline	Follow-up
V(JGA) 10^4 µm^3	5.53 (3.52–6.33)	5.58 (3.98–6.49)	7.52 (4.66–18.8)	8.04 (4.56–8.56)	5.28 (3.62–7.33)	4.66 (3.66–6.59)[a]
V(JGA)/V (glomerulus) %	1.65 (1.28–2.46)	1.83 (1.65–2.78)	2.04 (1.73–4.21)	2.06 (1.87–2.68)	2.40 (1.86–3.14)	1.98 (1.28–2.7)[b]
A(macula densa) µm^2	1169 (959–1671)	1409 (1294–1708)	1811 (1073–2028)	2120 (1523–2369)	1743 (1200–2053)[c]	1736 (1264–1896)
A(afferent) µm^2	433 (214–655)	327 (241–497)	417 (318–601)	376 (339–815)	425 (273–595)	392 (268–747)
A(efferent) µm^2	163 (68–224)	172 (82–337)	231 (171–490)	197 (124–241)[d]	253 (122–337)	191 (128–362)
A(afferent)/A(efferent)	3.62 (2.47–6.29)	2.72 (2.31–5.8)	2.62 (1.04–4.06)	2.9 (1.69–5.62)	2.19 (1.11–3.4)	2.52 (1.42–3.02)
V(glomerulus) 10^4 µm^3	271 (209–379)	271 (218–325)	336 (275–569)	315 (236–409)	244 (161–487)	283 (203–543)
A(VP) µm^2	2326 (1171–3270)	2250 (1603–3664)	2455 (2421–3563)	2877 (2399–4157)	2397 (1919–4031)	2993 (2328–5401)

[a] V(JGA) fell significantly during the study period (P=0.02)
[b] V(JGA)/V(glomerulus) fell significantly during the study period (P=0.0077)
[c] A(macula densa) was significantly higher in group 3 than in group 1 at baseline (P=0.0032)
[d] A(efferent) decreased significantly during the study period (P=0.046)

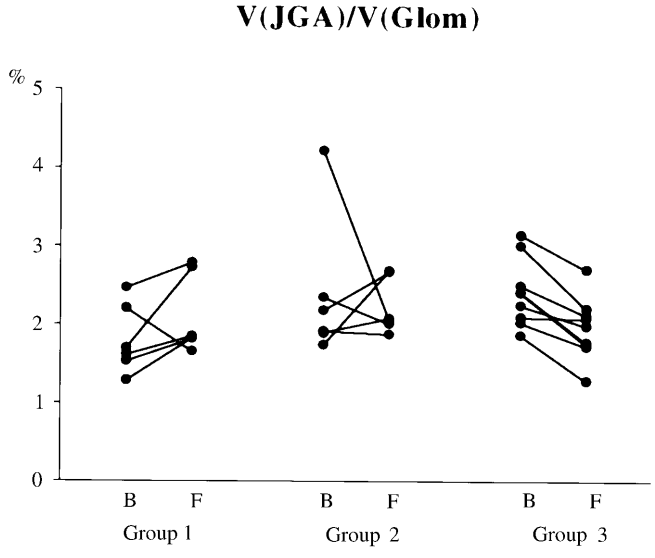

Fig. 3 Juxtaglomerular apparatus (JGA) volume relative to that of its corresponding glomerulus. Mean values in each patient at baseline and at follow-up

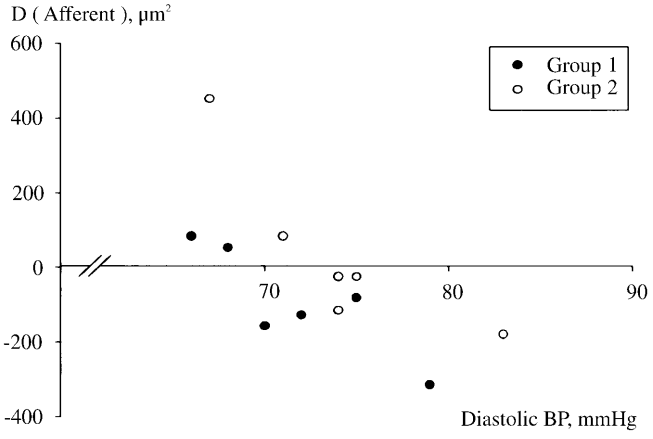

Fig. 4 Change in *A* (afferent arteriole), i.e. the area of the lumen of the afferent arteriole at follow-up minus that at baseline, against mean diastolic blood pressure throughout the study. Significant negative correlations were noted in groups 1 and 2

ences in structural parameters existed at baseline. In groups 1 and 2, no structural changes were noted between baseline and follow-up. In the reference group (group 3), there was a significant decrease in V(JGA) and in the ratio V(JGA)/V(glomerulus; P=0.026 and P=0.0005, respectively). No such trend was noted in groups 1 and 2.

There was no change in glomerular volume in groups 1 and 2, whereas an increment existed in group 3 (P=0.04). A(VP) did not change in any of the groups (Table 2) [15]. The coefficient of variation in V(JGA) within biopsies was overall 0.15–0.58 (mean 0.27), and the coefficient of error was 0.05–0.21 (mean 0.09). There were no differences between the groups.

With all patients pooled at baseline, strong positive correlations existed between the A(VP) and the V(JGA) (P<0.000; r=0.92) and the A(macula densa; P=0.022; r=0.50). Also, a correlation between V(JGA) and V(glomerulus) was seen (P=0.001; r=0.63). These correlations were also seen when the groups were regarded separately. No correlations were noted between glomerulopathy parameters (BMT and mesangial matrix volume fraction) and those pertaining to the JGA at baseline or when changes were considered.

No correlations were noted between the structural parameters describing the JGA and clinical parameters [age, duration of diabetes, body mass index (BMI), GFR, AER, HbA_{1C} and blood pressure] at baseline or at follow-up. In groups 1 and 2 but not in group 3, negative correlations were noted between the changes over time in A(afferent) and the mean diastolic blood pressure throughout the study period (Fig. 4), P=0.024; r=–0.87 in group 1 and P=0.032; r=–0.85 in group 2.

Discussion

Antihypertensive treatment has clinically been shown to decrease the rate of renal functional decline in microalbuminuric type-1 diabetic patients (as measured by the level of microalbuminuria). However, only few studies have dealt with the changes in structural parameters in humans. We have previously shown a tendency towards retardation of progression in standard glomerulopathy parameters in our series of patients treated with antihypertensives and no differences between beta blockers and ACE inhibitors [18]. We have also described a retardation of glomerular growth in patients treated with antihypertensive drugs relative to untreated patients and a tendency to increment in the vascular pole area in untreated patients [15]. Structural changes of the wall of afferent arterioles progressed slightly in the ACE-I treated group [8].

The actual mechanisms for the supposed beneficial effects of antihypertensives and the involvement of the JGA are unknown. We have previously shown the JGA to be enlarged in young microalbuminuric type-1 DM patients [7] (equal to baseline values for the present groups 1 and 2). This may well be a morphological counterpart of the known functional aberrations [9, 10] (although possible functional implications can not be proven from the observed enlargement).

This study shows a slight but significant decrease in the size of the JGA over time in the reference group, i.e. reflecting the natural course in diabetic patients at this stage of disease. The decrease was only slight, but this may well be due to the relatively short follow-up period (3 years). More long-term studies are needed to confirm our findings. As the V(glomerulus) increased in this group, the ratio between the V(JGA) and of that of its corresponding glomerulus was highly significantly decreased. Neither of these changes existed in the patients treated with antihypertensives. The exact mechanism of change in JGA size is not apparent from this study (because cell count or measurement of cell/matrix ratio were not performed) and could be due to hyperplasia/hypertrophy with later atrophy or due to changes in the extracellular matrix. If there is early JGA hyperplasia/hypertrophy in nephropathy with subsequent atrophy, it certainly explains some of the equivocal studies of activity of the renin angiotensin system in diabetes. Some studies showed hyperfunction in the early stages of DM characterised by hyperfiltration [23], other studies indicated normal function [1, 3, 5] and studies in overt nephropathy showed hypofunction [9].

A negative correlation existed between the change in the A(afferent) at entry into the glomerulus and the mean diastolic blood pressure over the study period in the treated groups but not in the untreated one (Fig. 4). All patients were normotensive at baseline, and no significant changes in diastolic blood pressure were noted from baseline to follow-up in any of the groups. However, the mean diastolic blood pressure over the study period was significantly lower in groups 1 and 2 than in the control group. These findings indicate that only in patients treated with antihypertensive drugs does a high mean diastolic blood pressure (within the limits of normotension) cause the afferent arteriole to constrict, as seen in the larger decrement in its area in these patients. This may be an important clue to the beneficial effects of antihypertensives in microalbuminuria. Although no major impact on blood pressure is achieved, treatment with antihypertensives enables the afferent arteriole to more effectively constrict in response to high blood pressure, thereby protecting the glomerulus. The reason for this can only be speculated here. Previous studies have shown a significant matrix accumulation in afferent and efferent arterioles in microalbuminuric type-1 DM patients [13]. One could therefore speculate that a decrease in matrix in the arteriolar wall during antihypertensive treatment (as is seen in the glomerulus [18]) renders the wall less rigid. However, we have recently shown that there was a lack of reversion of matrix accumulation in the arterioles during antihypertensive treatment in groups 1 and 2 [8]. Although patients without antihypertensive treatment were not included in that study, it seems unlikely that the present findings can be explained from a purely mechanical theory (i.e. rigidity of the arteriolar wall based on matrix volume fraction). Another possibility is a direct effect on the smooth muscle cells within the vascular wall.

The absence of correlation between A(afferent) and blood pressure at follow-up may be due to the small number of patients studied here. As seen previously, and also noted here, there is a large variation in the A(afferent). It may be that a cross-sectional study would fail to detect a correlation and that only when individual changes were studied they become clear. One effect of ACE inhibitors is said to be dilatation of the efferent arteriole. Although non-significant, a tendency towards an increment in luminal area was noted in group 1 (ACE inhibitor treatment) as opposed to the decrease in luminal area in groups 2 and 3.

It can be speculated that a hollow structure (such as an arteriole) is unlikely to remain stable during processing. Also, a biopsy reflects the situation only at the moment it is taken. However, in this study, baseline and follow-up biopsies were processed similarly, and the extensive and unbiased sampling within each biopsy ensured that a mean of ten nephrons were studied per biopsy. Finally, surrounding tissue would stabilise the arteriolar wall, particularly at the point where they were studied here (at the entrance or exit from the glomerulus).

An optimal control group was not available. Preparations and measurements were not done at the same time, and the embedding medium was different between the

groups. The groups were well-matched for all of the clinical parameters, and the same clinical and laboratory techniques were used. While comparisons between groups may be viewed upon with some caution, changes observed within groups are not affected by these conditions. The intra-biopsy variation in JGA size was high. However, with the extensive sampling (median ten JGA per biopsy) the coefficients of error were acceptable, indicating adequate sampling.

Variations in JGA size between patients were also high. One patient in group 2 had a very large mean V(JGA) at baseline, which decreased considerably in size (Fig. 2 and Fig. 3). It is interesting that this patient did not differ clinically from the others in the group. Also, within groups 1 and 2, patients with increasing JGA sizes (three patients in group 1 and two patients in group 2) did not differ clinically from the other patients. The reason for these structural differences are unclear but may well be due to small groups. It should be noted that in all three groups, the V(JGA) at baseline was nearly doubled relative to non-diabetic subjects [7]. This is highly pathological, and variations within the groups would be expected to be high. Also, the treatment regime in each case was decided randomly (i.e. independent of JGA size at baseline).

In conclusion, the JGA, which in the early phase of microalbuminuria is enlarged compared with non-diabetic individuals [7], significantly decreases in size over a period of a few years in subjects not treated with antihypertensives. This is in contrast with the continued glomerular growth in these patients. Also, negative correlations existed between the changes in the A(afferent) and mean diastolic blood pressure in patients treated with antihypertensive drugs, indicating better glomerular protection and perhaps explaining the beneficial effects of antihypertensives in microalbuminuric type-1 diabetic patients.

Acknowledgements Ms. Birthe Iversen, Ms. Lone Lysgaard, Ms. Birtha Saugbjerg, Ms. Karin Schultz and Ms Gun-Marie Taube are thanked for their excellent technical assistance. The study was supported by the Danish Diabetes Association, the Danish Medical Research Council, the Aaarhus University Research Foundation, the Novo Nordic Research Fund, the Swedish Diabetes Association, the Swedish Diabetes Foundation, the First of May Flower Campaign for Health, the Swedish Medical Association, the Research Funds of Karolinska Institute, the Aage Louis-Hansens Foundation and the Norwegian Diabetes Association.

References

1. Anderson S, Jung FF, Ingelfinger JR (1993) Renal renin-angiotensin system in diabetes: functional, immunohistochemical, and molecular biological correlations. Am J Physiol 265:F477–F486
2. Bangstad H-J, Østerby R, Dahl-Jørgensen K, Berg KJ, Hartmann A, Hanssen KF (1994) Improvement of blood glucose control in IDDM patients retards the progression of morphological changes in early diabetic nephropathy. Diabetologia 37:483–490
3. Björck S (1990) The renin angiotensin system in diabetes mellitus. A physiological and therapeutic study. Scand J Urol Nephrol [Suppl 1] 26:1–51
4. Björck S, Mulec H, Johnsen SA, Norden G, Aurell M (1992) Renal protective effect of enalapril in diabetic nephropathy. BMJ 304:339–342
5. Carvalho-Braga D, Almeida R, Azevedo M, Amaral I, Medina J, Hargreaves M (1991) Glomerular hyperfiltration in insulin-dependent diabetes mellitus: no evidence for enhanced activity of the renin-angiotensin-aldosterone system. J Diabetes Complications 5:126
6. The EUCLID study group (1997) Randomised placebo-controlled trial of lisinopril in normotensive patients with insulin-dependent diabetes and normoalbuminuria or microalbuminuria. Lancet 349:1787–1792
7. Gulmann C, Rudberg S, Nyberg G, Østerby R (1998) Enlargement of the JGA in insulin-dependent diabetes mellitus patients with microalbuminuria. Virchows Arch 433:63–67
8. Gulmann C, Rudberg S, Østerby R (1999) Renal arterioles in patients with type I diabetes and microalbuminuria before and after treatment with antihypertensive drugs. Virchows Arch 434:523–528
9. Hsueh WA, Anderson PW (1993) Systemic hypertension and the renin-angiotensin system in diabetic vascular complications. Am J Cardiol 72:14H–21H
10. Jensen PK, Kristensen KS, Rasch R, Persson AEG (1988) Decreased sensitivity of the tubuloglomerular feedback mechanism in experimental diabetic rats. In: Persson AEG, Boberg U (eds) The juxtaglomerular apparatus. Elsevier, Amsterdam, pp 333–338
11. Mathiesen ER, Hommel E, Giese J, Parving H-H (1991) Efficacy of captopril postponing nephropathy in normotensive insulin-dependent diabetics with microalbuminuria. BMJ 330: 81–87
12. Østerby R (1995) Research methodologies related to renal complications: structural changes. In: Mogensen CE, Standl E (eds) Research methodologies in human diabetes, part 2. Walter de Gruyter and Co., Berlin, New York, pp 289–309
13. Østerby R, Bangstad HJ, Nyberg G, Walker JD, Viberti G (1995) A quantitative ultrastructural study of juxtaglomerular arterioles in IDDM patients with micro- and normoalbuminuria. Diabetologia 38:1320–1327
14. Østerby R, Asplund J, Bangstad HJ, Nyberg G, Rudberg S, Viberti G, Walker JD (1997) Glomerular volume and the vascular pole area in patients with insulin-dependent diabetes mellitus. Virchows Arch 431:351–357
15. Østerby R, Bangstad H-J, Rudberg S (2001) Follow-up study of glomerular dimensions and cortical interstitium in microalbuminuric type-1 diabetic patients with or without antihypertensive treatment. Nephrol Dial Transplant (in press)
16. Overturf ML, Sybers HD, Druilhet RE, Smith SA, Kirkendall WM (1982) Capoten-induced juxtaglomerular hyperplasia in rabbits. Res Commun Chem Pathol Pharmacol 36:169–172
17. Paulsen EP, Burke BA, Vernier RL, Mallare MJ, Innes DJ Jr, Sturgill BC (1994) Juxtaglomerular body abnormalities in youth-onset diabetic subjects. Kidney Int 45:1132–1139
18. Rudberg S, Østerby R, Bangstad HJ, Dahlquist G, Persson B (1999) Effect of angiotensin converting enzyme inhibitor or beta blocker on glomerular structural changes in young microalbuminuric patients with type I (insulin-dependent) diabetes mellitus. Diabetologia 42:589–595
19. Sawicki PT, for the Diabetes Teaching and Treatment Programmes Working Group (1997) Stabilization of glomerular filtration rate over 2 years in patients with diabetic nephropathy under intensified therapy regimens. Nephrol Dial Transplant 12:1890–1899
20. Schindler AM, Sommers SC (1966) Diabetic sclerosis of the renal juxtaglomerular apparatus. Lab Invest 15:877–884
21. Teppo AM (1982) Immunoturbidimetry of albumin and immunoglobulin G in urine. Clin Chem 28:1359–1361
22. Viberti G, Walker JD (1991) Natural history and pathogenesis of diabetic nephropathy. J Diabetes Complications 5:72–75
23. Wiseman MJ, Drury PL, Keen H, Viberti GC (1984) Plasma renin activity in insulin-dependent diabetics with raised glomerular filtration rate. Clin Endocrinol (Oxf) 21:409–414