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Quantitative ultrastructural study of afferent and efferent arterioles in IgA glomerulonephritis and benign nephrosclerosis

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Abstract Arteriolosclerosis frequently occurs in IgA nephritis (IgAN), and it is the hallmark of benign nephrosclerosis (BNS). The quantitative ultrastructure of juxtaglomerular arterioles is not known in these disorders. We examined afferent and efferent arterioles in renal biopsies from 25 adult patients with IgAN (hypertension at biopsy: 14 patients) and 9 patients with BNS. Six age-matched living renal transplant donors acted as controls. A systematic independent sample of profiles was obtained in thin sections taken at predetermined levels. The thickness of the media (myomedial cells plus the matrix) and the thickness of the medial matrix were estimated stereologically. From these estimates, the matrix/myomedia ratio was calculated. In IgAN with normotension or hypertension, the afferent media and its compartments did not exhibit significant thickening compared with the controls, whereas in BNS the afferent media and its layers were markedly and significantly thickened. The efferent media in IgAN and BNS displayed mild and significant thickening, with significant thickening of the matrix in BNS and IgAN with normotension. The matrix/myomedia ratio was not altered significantly in any group. The results indicate that the afferent arterioles are not the main sites of IgAN-related arteriolosclerosis, that arteriolosclerosis in IgAN and arteriolosclerosis in BNS are different lesions, and that increased efferent arteriolar thickness, demonstrated here for the first time in IgAN and BNS, might be a manifestation of angiotensin II-mediated autoregulatory efferent vasoconstriction exerted to maintain the glomerular filtration pressure.

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Introduction

Hyaline arteriolosclerosis, the hallmark of benign nephrosclerosis (BNS) [22, 30], is a nonspecific lesion. It is also observed in diabetic nephropathy and chronic cyclosporin nephropathy and in the ageing kidney. It is of interest that among glomerulonephritides [22], arteriolosclerosis is frequently encountered in IgA nephritis (IgAN) [6, 9, 10, 14, 21, 22, 26, 37, 41, 52], even in normotensive young adult patients [9, 14, 21, 31, 35, 41, 52], and contributes to the progression of IgAN [14, 32]. The association between IgAN-related arteriolosclerosis and hypertension-induced arteriolosclerosis is not known. In a recent ultrastructural quantitative study [44], afferent and efferent arterioles from patients with insulin-dependent diabetes mellitus were examined stereologically, and an arteriolar accumulation of extracellular material was observed in the early phase of diabetic nephropathy. We adopted that method [44] in the present investigation to analyse the afferent and efferent arterioles in renal biopsy samples from 25 adult patients with IgAN and 9 patients with BNS. In IgAN, normotensive and hypertensive patients were distinguished on the basis of the prebiopsy blood pressure. Renal biopsy specimens from living kidney transplant donors served as healthy controls. We set out to answer the following questions: does hypertension at biopsy influence the afferent arteriolar parameters in IgAN? is there any difference between IgAN-related arteriolosclerosis and BNS-associated hyaline arteriolosclerosis? and what efferent arteriolar changes exist in IgAN and BNS?

Materials and methods

Cases with primary IgAN or BNS were selected from the percutaneous renal biopsy material collected in Szeged between 1979 and

Table 1 The series (*BNS* benign nephrosclerosis, *IgAN* IgA nephritis, *RR–* normotensives, *RR+* hypertensives)

	Healthy	BNS	IgAN RR–	IgAN RR+
n	6	9	11	14
Gender	2 F, 4 M	5 F, 4 M	6 F, 5 M	3 F, 11 M
Age, median (range)[a]	43 (26–55)	36 (18–51)	34 (22–50)	38 (19–56)
18–30 years	1	3	4	4
31–40 years	1	3	3	4
41–50 years	3	1	4	4
Above 50 years	1	2	0	2

[a] No significant difference among groups in terms of age

Table 2 Clinical variables at the time of renal biopsy

	BNS		IgAN RR–		IgAN RR+	
	Median (range)	*n*	Median (range)	*n*	Median (range)	*n*
Systolic blood pressure (mm Hg)	155 (143.5–190)	9	130 (110–140)	11	150 (140–217)	14
Diastolic blood pressure (mm Hg)	100 (92–120)	9	85 (75–90)	11	100 (90–135)	14
Daily urine protein excretion (g)	0.9 (0.2–8.2)	9	2.3 (0.5–7.3)	11	1.3 (0.2–5.1)	14
Creatinine clearance (ml/s)	1.63 (0.63–1.86)	5	1.48 (0.52–2.38)	10	1.06 (0.18–2.73)	10
Serum creatinine (μmol/l)	97 (69–251)	9	88 (52–144)	11	112 (82–337)	14
Serum total cholesterol (mmol/l)	5.3 (4,7–9)	9	5.4 (4–10)	7	6.6 (3.4–9)	12
Serum triglycerides (mmol/l)	1.8 (1.1–7.6)	9	2.1 (1.75–2.4)	5	2.2 (0.6–5.8)	11
Serum albumin (g/l)	3.5 (2.8–4.1)	3	3.5 (2.8–4.5)	5	3.7 (3.3–4)	11
Duration of disease (months)	24 (2–120)	9	24 (6–168)	11	12 (6–72)	13

1992, with the provisos that the renal cortical tissue samples were originally examined by light microscopy, immunofluorescence (IgG, IgA, IgM, C3 and fibrinogen) and electron microscopy, the slides stained for light microscopy contained at least ten glomerular profiles, advanced glomerular sclerosis was not present, and the patients did not have diabetes or an impaired glucose tolerance at the time of the biopsy. The diagnosis of BNS was made if the biopsy findings disclosed hyaline arteriolosclerosis in the absence of glomerular disease, the patient had elevated blood pressure, imaging techniques revealed normally positioned kidneys without scarring or signs of obstructive nephropathy, and the search for a cause of secondary hypertension proved negative. There were 25 cases with IgAN and 7 cases with BNS that fulfilled these criteria. Two cases with BNS from the renal biopsy material from Ljubljana, which also fulfilled the selection criteria, were included in the BNS group. Tissue specimens for electron microscopy were fixed in 3% buffered glutaraldehyde, postfixed in 1% osmium tetroxide, and subsequently embedded in Durcupan ACM in Szeged, or in Epon 812 in Ljubljana.

The clinical features of IgAN and BNS are summarized in Tables 1 and 2. In IgAN, two groups were established on the basis of the mean blood pressure values [29] measured on the 1st and 3rd days of hospitalization: hypertensives (values above 140/90 mm Hg: 14 patients) and normotensives (values below or at 140/90 mm Hg: 11 patients). In 2 men, the average of the two readings was below 140/90 mm Hg, but they had an elevated blood pressure on the 1st day (150/90 and 140/100 mm Hg, respectively). These patients were included in the normotensive group. In BNS, the biopsies were performed to diagnose or exclude glomerular disease. Prior to biopsy, 6 hypertensive IgAN patients and 8 BNS patients were treated with various combinations of antihypertensive drugs for 1–5 months. The group of healthy individuals (controls) consisted of 6 normotensive living transplant donors from whom renal biopsy specimens were taken (Table 1). Clinical examination in these persons prior to the donation disclosed normal blood pressure, normal renal function and no diabetes. The patients were Swedish and the biopsy procedure was performed in Göteborg, Sweden. The tissue samples were mailed in 2% buffered glutaraldehyde to the Department of Pathology, University of Aarhus, Aarhus, Denmark. After postfixation in 1% osmium tetroxide, the blocks were subsequently embedded in Vestopal. All the patients reported on here are Caucasians.

The changes in IgAN [1, 2, 11, 12, 14, 15, 26, 33, 39] were scored semiquantitatively by two independent observers (J.O. and B.I.), without any knowledge of the clinical and ultrastructural quantitative data. The glomerular score (0–12) was obtained by determining the percentage of glomeruli totally sclerosed, the percentage of glomeruli with crescents, the percentage of glomeruli with segmental lesions (adhesions and/or subendothelial hyalinosis and/or sclerosis) and the degree of mesangial matrix and cell proliferation. Subendothelial hyalinosis was regarded as a sign of hyperperfusion injury. The tubulointerstitial score (0–12) reflected the extent of interstitial fibrosis, the extent of interstitial infiltrates and the extent of tubular atrophy. The vascular score in small arteries and arterioles (0–2) was adopted from [14]: 0, vessel media with two smooth muscle cell layers, and little or no hyaline material in the vessel walls; 1, vessel media with two to three smooth muscle cell layers, and hyaline material present in the vessel walls focally; and 2, vessel media with three or more smooth muscle cell layers, with widespread hyaline material in the vessel walls.

Trimmed blocks were available for the present study in most cases. The methodology for sampling of arteriolar profiles has been published recently [44]. In brief, the blocks were sectioned serially, starting with a baseline section (0 level). From this 0 level, 1-μm-thick sections were cut, picked up and numbered consecutively, and stained for light microscopy to identify arteriolar profiles as afferent or efferent by following their course through the serial sections. Adjacent to thin sections, a sketch of all arteriolar profiles was made on semithin sections used as reference for electron microscopy. Every 50 μm from the baseline level, thin sections were prepared, covering the full extent of the semithin sections. From the thin sections, an independent, systematic sample was obtained by photographing all arteriolar profiles present in the sections. The full extent of the arterioles was photographed, photomontages being made when necessary. The negatives were photographically enlarged to ×6550. The actual magnification of the print was calculated by simultaneous photographing of a calibrating grid with 2160 lines/mm. The number of arteriolar profiles obtained in each group is shown in Table 3. The groups with IgAN with normotension and with BNS contained 1 patient with one efferent profile and 1 patient with two efferent profiles, respectively. These patients were omitted from the calculation of efferent arterioles.

The tunica media of the arteriole extends from the external aspect of the endothelial cytoplasm to the surrounding interstitial tis-

Table 3 Number of arteriolar profiles studied by electron microscopy

	Controls	BNS	IgAN RR–	IgAN RR+
Afferent profile, mean (range)	22 (11–28)	13 (3–24)	15 (4–36)	15 (3–34)
Efferent profile, mean (range)	26 (5–44)	11 (2–19)[a]	7 (1–14)[a]	13 (3–25)

[a] Cases with only one efferent profile and two efferent profiles available, respectively, were omitted from calculations of efferent arterioles

sue. It consists of the myomedial cells and the extracellular matrix. The matrix is composed of the basal lamina material between the myomedial cells, the subendothelial basement membrane, the external basal lamina, the insudated hyaline material, the collagen fibres and other matrix substances and, on occasion, the elastic elements and immune deposits [16, 21, 22, 24, 35, 50, 52].

A transparent square grid with 9 points and 136 mm testline length per unit was placed with an independent position on the prints. The sum of points hitting the smooth muscle cells and the matrix over all profiles per biopsy served for estimation of their volume fractions, the media being used as reference space. The sum of intersections between grid lines and the external basal lamina of the myomedial cells was used to calculate the surface density of the arteriolar circumference. From these data, the average thickness of the media and the theoretical average thickness of the matrix of the media (the thickness of the matrix components spread in an even layer on the arteriolar circumference, Fig. 1) were computed [20]. From the values for the media and matrix, the thickness of the myomedia and the matrix/media ratio were calculated.

The sampling of profiles and the measurements were done by Zs.R., without any knowledge of the clinical or light microscopical data of the patients.

The Mann-Whitney U-test was used to examine the differences between the stereological variables in normotensive IgAN, hypertensive IgAN and BNS versus the controls, and between normotensive and hypertensive IgAN versus BNS. The difference between the histological scores for hypertensive IgAN against normotensive IgAN was analysed with Student's unpaired *t*-test. The level of significance was 0.05. Linear regression analysis was applied to explore the link between the stereological data and the clinical variables listed in Table 2.

Results

In IgAN, there was no significant difference in light microscopical severity between normotensives and hypertensives. Segmental glomerular lesions and hyalinosis in small arteries and arterioles were present in 24 and 23 patients, respectively. Hyperperfusion injury was observed in 9 patients. In BNS, the severity of hyaline arteriolosclerosis in 5 patients exceeded the vascular score of

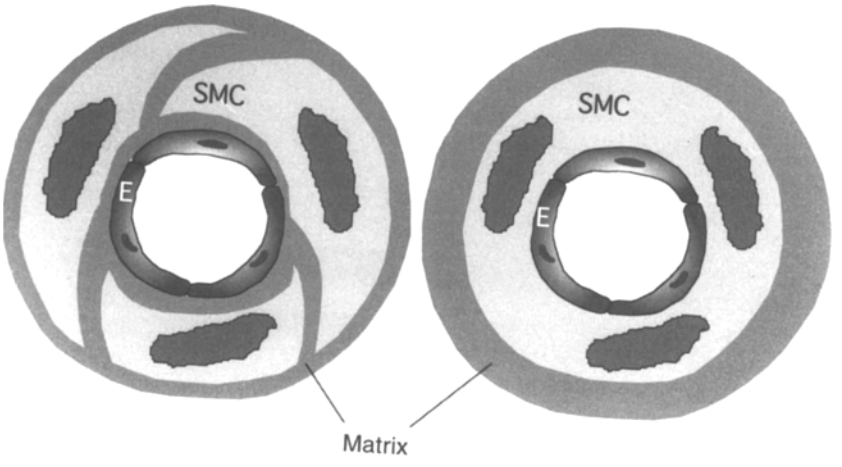

Fig. 1 Theoretical thickness of arteriolar matrix. The matrix is spread in an even layer on the arteriolar circumference (*right*). *SMC* smooth muscle cell, *E* endothelium

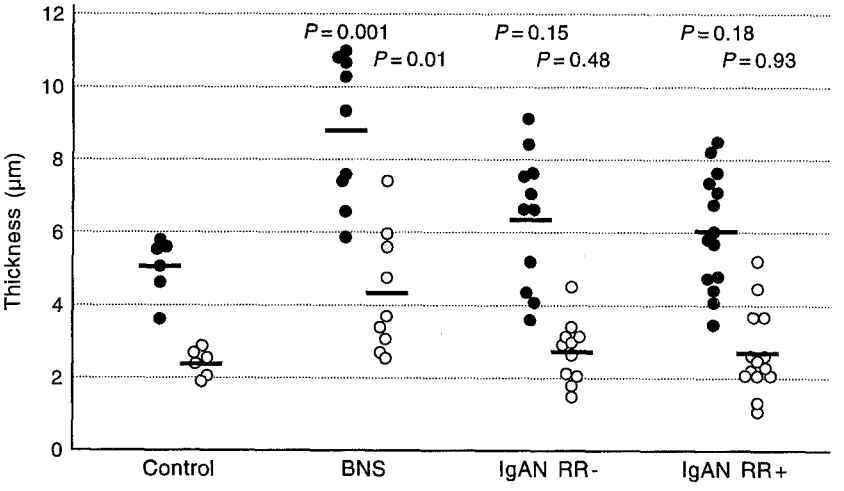

Fig. 2 Estimated media (●) and matrix (○) thickness in afferent arterioles. *BNS* benign nephrosclerosis, *IgAN* IgA nephritis, RR– normotensives, *RR+* hypertensives

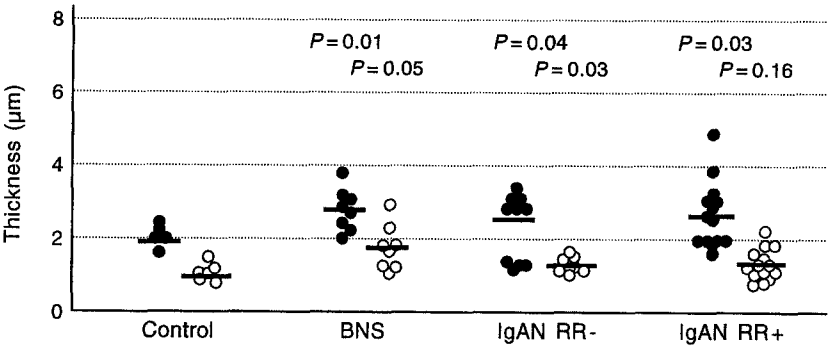

Fig. 3 Estimated media (●) and matrix (○) thickness in efferent arterioles

Table 4 Sterological estimates (mean±SD) in the study groups (*Vv* volume fraction; *T* thickness, *p vs control* $P<0.05$, versus controls)

	Controls	BNS	*P* vs control	IgAN RR−	*P* vs control	IgAN RR+	*P* vs control
Afferent							
Vv (matrix/media)	0.46±0.08	0.46±0.08	0.93	0.41±0.07	0.22	0.43±0.12	0.65
Media T (μm)	5±0.8	8.8±2	0.001	6.3±1.8	0.15	6.1±1.6	0.18
Matrix T (μm)	2.3±0.3	4.3±1.7	0.01	2.6±0.8	0.48	2.6±1.1	0.93
Matrix T/myomedia T	0.8±0.1	1.1±0.9	0.46	0.7±0.2	0.26	0.7±0.3	0.65
Efferent							
Vv (matrix/media)	0.48±0.04	0.48±0.08	0.93	0.48±0.07	0.92	0.45±0.10	0.54
Media T (μm)	1.8±0.3	2.7±0.5	0.01	2.4±0.6	0.04	2.5±0.9	0.03
Matrix T (μm)	0.9±0.1	1.5±0.6	0.05	1.1±0.2	0.03	1.2±0.4	0.16
Matrix T/myomedia T	1.2±0.6	1.5±0.8	0.53	0.9±0.3	0.38	1.1±0.9	0.86

2 in IgAN. In 2 patients the severity of the lesions was comparable to the vascular score of 2, and in 2 patients the lesions would have been scored as 1. Four patients displayed hyperperfusion injury.

In IgAN, as opposed to the controls, there was a non significant thickening of the afferent media and its layers. The thickness of the afferent media was in the "normal range" in 4 normotensives and 5 hypertensives (Figs. 2, 3, Table 4). Of these patients, 6 had an average vascular score of 1.5 and a global score of 12.5, pointing to pronounced histopathological expression of IgAN. The efferent media and its compartments exhibited increased thickness, which was significant for the media in both groups, and for the matrix in the normotensives. The thickness of the efferent media was in the "normal range" in 4 normotensives and 6 hypertensives. These patients had marked lesions of IgAN (average vascular score: 1.2, global score: 10.1). In BNS versus the controls, a marked and significant thickening was found in the afferent media and its compartments. In the efferent profiles, a significant thickening of the media was observed, whereas the increase in the matrix thickness was at the cut-off point of the *P*-value.

The afferent arteriolar profiles in BNS were significantly thicker than those in IgAN with normotension ($P=0.01$ for the media), and in IgAN with hypertension ($P=0.002$ for the media). The quantitative status of the efferent arteriolar profiles in BNS did not differ significantly from those seen in IgAN with normotension or hypertension. The matrix/myomedia ratios revealed that the thickenings in any group proportionately involved the matrix and the muscular coat.

No correlation was found between morphological and clinical variables.

Discussion

The present study provides the first ultrastructural quantitative data on the glomerular arterioles in IgAN and BNS. Interpretation of the findings is difficult, however, since haemodynamic data on the glomerular microcirculation in humans are few. Further, the relatively low number of profiles, which were frequently sectioned tangentionally due to the tortouosity or arterioles, did not make it possible to calculate such resistance vessel parameters as the luminal diameter or media cross-sectional area. Because of these limitations, our conclusions should be treated with caution. In this discussion, we deal first with the efferent arterioles, which have an important role in the adaptive haemodynamic changes in the glomeruli, as they maintain the filtration pressure [4, 18, 47, 51].

The efferent media in IgAN exhibited a mild, albeit significant, thickening in both the normotensive and the hypertensive patients, this involving the proportionate thickening of the matrix and the myomedia. In a rat model of IgAN, an increased synthesis of glomerular thromboxane was observed, which was not counterbalanced by an increased synthesis of prostaglandin E2, resulting in mesangial cell contraction, vasoconstriction of efferent arterioles, and the development of microhaematuria [17]. The situation in the human kidney seems different. A weak immunohistochemical reactivity of

thromboxane synthase was found in the podocytes, while the mesangial cells were negative. Thromboxane synthase immunoreactivity was not increased in two cases of IgAN investigated [42]. However, mesangial cells in IgAN have an increased expression of alpha smooth muscle actin [3, 19], indicating enhanced contractile properties. It is likely therefore that, as in the rat model of IgAN, the mesangial cells do contract, probably because of the direct contractile effect of immune aggregates [13]. In the present study, segmental glomerular lesions were observed in all but 1 patient. These lesions play an important part in the progression of IgAN [33]. We hypothesize that the mesangial contraction, together with the narrowing of the glomerular capillaries by mesangial cell proliferation, segmental sclerosis and, on occasion, by crescents, reduces the glomerular filtration surface area, leading to a decrease in the filtration pressure. Readjustment of the filtration pressure may be achieved by efferent arteriolar vasoconstriction mediated by the local autoregulatory action of angiotensin II [27]. The action might be manifested morphologically by a thickening of the efferent arterioles, the finding of the present study. Recently, the angiotensin-converting enzyme inhibitors have been found to have beneficial effects in stabilizing the creatinine clearance and improving proteinuria in IgAN [8]. The protective effects may be related to the action of these drugs in reducing glomerular capillary hypertension [47], by amelioriating the vasospasm of the efferent arterioles. The data of therapy indirectly suggest that the efferent arteriolar thickening demonstrated by us may be linked with the action of angiotensin II.

Extraglomerular vascular hyalinosis, indicating microvessel disease, was observed in 23 patients. The microvasculopathy, however, tended to preserve the afferent profiles, since the stereological estimations demonstrated a non-significant increase in the thickness of the media in the patients overall, and "normal" medial thicknesses were measured ultrastructurally in 6 patients with marked light microscopical vascular changes. In an earlier study on extraglomerular vascular immune deposits in 425 patients with IgAN, the deposits occurred in small interlobular arteries in 52% of the cases, in arterioles in 16% of the cases, and in both sites in 17% of the cases [52]. The results of the previous and the present study indicate that the small interlobular arteries rather than the afferent arterioles are the main sites of IgAN-related arteriolosclerosis.

The pathomechanism of the microvasculopathy is not clear. It might be a feature of the glomerular disease itself [14, 32], or it might be part of a hyperperfusion injury [5, 40]. We consider it to be mainly the result of haemodynamic maladaptive damage by the autoregulatory action of angiotensin II. Angiotensin II generally constricts efferent arterioles more than afferent arterioles [45]. The relative decrease in the afferent arteriolar resistance might protect the afferent arterioles from the development of marked microvasculopathy, and this is probably why the measured increase in thickness of the media in our randomly selected patients was not significant. The interpretation of the afferent arteriolar findings relies on the studies in rats with haemodynamic adaptation [7, 25] or diabetic hyperfiltration [43], in which a decrease in the afferent arteriolar resistance was observed.

Systemic hypertension aggravates the progression of IgAN [31]. In this respect a surprising finding in the present study was that hypertension at biopsy was not associated with enhanced quantitative change when compared with the normotensives. The reason for this observation is unclear. Factors may be the relatively short duration of the hypertensive period (median: 12 months) and mild hypertensive values (median: 150/100 mm Hg.

Although we have no laboratory data as to whether our BNS patients had high-renin or low-renin hypertension, we assume that the renin-angiotensin system was in operation. The suspicion is strong in 8 patients in whom severe vascular changes and/or hyperperfusion injury of the glomeruli indicated hyperreninaemia or intrarenal haemodynamic adaptation. The efferent arterioles displayed a significant media thickening versus the controls, which proportionately involved the myomedia and the matrix. The thickening might be due to a vasospasm of the efferent arterioles, mediated by angiotensin II [18, 27]. This role of angiotensin II is presumed on the basis of the observation that patients with renovascular hypertension had increased efferent arteriolar resistance [34]. In uncomplicated essential hypertension the efferent arteriolar resistance was not elevated [34], and therefore the efferent arteriolar thickening demonstrated in the present study may be confined on the small subgroup of hypertensive patients requiring renal biopsy to exclude glomerular disease [28, 38].

Previous light microscopical studies on afferent arterioles [23, 47, 49] described thickening of the arteriolar wall. The present study confirmed and extended that observation by demonstrating that the thickening proportionately involved the matrix and the myomedia. The proportionate thickening is surprising, since hyalinosis of the interlobular arteries and afferent arterioles is regarded as the leading feature of BNS. In the light of the present study, it seems likely that the thickening of afferent smooth muscle cells can be overlooked on light microscopy. Our study does not answer the question of whether the increased myomedia thickness in BNS is due to the growth of the vessels or not. Observations on human resistance vessels indicate that hypertension is mainly associated with vessel wall remodelling (rearrangement of the same amount of material around a smaller lumen) rather than growth [36, 46]. The increase in wall thickness in BNS versus IgAN was significant, demonstrating that arteriolosclerosis in IgAN and hyaline arteriolosclerosis in BNS are different lesions.

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References

1. Alamartine E, Sabatier JC, Berthoux FC (1990) Comparison of pathological lesions on repeated renal biopsies in 73 patients with primary IgA glomerulonephritis: value of quantitative scoring and approach to final prognosis. Clin Nephrol 34: 45–50
2. Alamartine E, Sabatier JC, Guerin C, Berliet JM, Berthoux F (1991) Prognostic factors in mesangial IgA glomerulonephritis: an extensive study with univariate and multivariate analyses. Am J Kidney Dis 18:12–19
3. Alpers CE, Hudkins KL, Gown AM, Johnson RJ (1992) Enhanced expression of "muscle specific" actin in glomerulonephritis. Kidney Int 41:1134–1142
4. Anderson S, Rennke HG, Brenner BM (1986) Therapeutic advantage of converting enzyme inhibitors in arresting progressive renal disease associated with systemic hypertension in the rat. J Clin Invest 77:1993–2000
5. Baldwin DS, Neugarten J (1987) Hypertension and renal diseases. Am J Kidney Dis 10:186–191
6. Bogenschütz O, Bohle A, Batz C, Wehrmann M, Pressler H, Kendziorra H, Gartner HV (1990) IgA nephritis: on the importance of morphological and clinical parameters in the long term. Prognosis of 239 patients. Am J Nephrol 10:137–147
7. Brenner BM (1985) Nephron adaptation to renal injury or ablation. Am J Physiol 249 [Renal Fluid Electrolyte Physiol 18]: F324–F337
8. Cattran DC, Greenwood C, Ritchie S (1994) Long-term benefits of angiotensin-converting enzyme inhibitor therapy in patients with severe immunoglobulin A nephropathy: a comparison to patients receiving treatment with antihypertensive agents and to patients receiving no therapy. Am J Kidney Dis 23:247–254
9. Clarkson AR, Seymour AE, Thompson AJ, Haynes WDG, Chan YL, Jackson B (1977) IgA nephropathy: a syndrome of uniform morphology, diverse clinical features and uncertain prognosis. Clin Nephrol 8:459–471
10. D'Amico G, Imbasciati E, Barbiano di Belgioioso G, Bertoli S, Fogazzi G, Ferrario F, Fellin G, Ragni A, Colasanti G, Minetti L, Ponticelli C (1985) Idiopathic IgA mesangial nephropathy. Medicine 64:49–60
11. D'Amico G, Minetti L, Ponticelli C, Fellin G, Ferrario F, Barbiano di Belgioioso G, Imbasciati E, Ragni A, Bertoli S, Fogazzi G, Duca G (1986) Prognostic indicators in idiopathic IgA mesangial nephropathy. QJM [N Ser] 59:363–378
12. Donadio JV, Bergstrahl EJ, Offord KP, Holley KE, Spencer DC, the Mayo Nephrology Collaborative Group (1994) Clinical and histopathologic associations with impaired renal function in IgA nephropathy. Clin Nephrol 41:65–71
13. Emancipator SN (1994) IgA nephropathy: morphologic expression and pathogenesis. Am J Kidney Dis 23:451–462
14. Feiner HD, Cabili S, Baldwin DS, Schacht RG, Gallo GR (1982) Intrarenal vascular sclerosis in IgA nephropathy. Clin Nephrol 18:183–192
15. Gallo GR, Katafuchi R, Neelakantappa K, Baldwin DS (1988) Prognostic pathologic markers in IgA nephropathy. Am J Kidney Dis 12:362–365
16. Gamble CN (1986) The pathogenesis of hyaline arteriolosclerosis. Am J Pathol 122:410–420
17. Gesualdo L, Emancipator SN, Kesselheim C, Lamm ME (1992) Glomerular hemodynamics and eicosanoid synthesis in a rat model of IgA nephropathy. Kidney Int 42:106–114
18. Gomez RA, Norwood VF (1995) Developmental consequences of the renin-angiotensin system. Am J Kidney Dis 26:409–431
19. Goumenos DS, Brown CB, Shortland J, El Nahas AM (1994) Myofibroblasts, predictors of progression of mesangial IgA Nephorpathy? Nephrol Dial Transplant 9:1418–1425
20. Gundersen HJ, Bendtsen TF, Korbo L, Marcussen N, Moller A, Nielsen K, Nyengaard JR, Pakkenberg B, Sorensen FB, Vesterby A, West MJ (1988) Some new, simple and efficient stereological methods and their use in pathological research and diagnosis. APMIS 96:379–394
21. Hara M, Honda K, Matsuya S, Endo Y, Hara S, Suzuku Y (1988) The juxtaglomerular apparatus in IgA nephropathy: an analysis of the transport and fate of IgA deposits at the glomerular hilus. Virchows Arch [A] 413:431–443
22. Helmchen U, Wenzel UO (1994) Benign and malignant nephrosclerosis and renovascular disease. In: Tisher CC, Brenner BM (eds) Renal pathology: with clinical and functional correlations. Lippincott, Philadelphia, pp 1201–1211
23. Heptinstall RH (1954) Renal biopsies in hypertension. Br Heart J 16:133–140
24. Heptinstall RH (1992) Essential hypertension. Pathology of the kidney. Little, Brown, & G, Boston, pp 951–1028
25. Hostetter TH, Olson JL, Rennke HG, Venkatachalam MA, Brenner BM (1981) Hyperfiltration in remnant nephrons: a potentially adverse response to renal ablation. Am J Physiol 241 [Renal Fluid Electrolyte Physiol 10]:F85–F93
26. Ibels LS, Györy AZ (1994) IgA nephropathy: analysis of the natural history, important factors in the progression of renal disease, and a review of the literature. Medicine 73:79–102
27. Ichikawa I, Harris RC (1991) Angiotensin actions in the kidney: renewed insight into the old hormone. Kidney Int 40: 583–596
28. Innes A, Johnston PA, Morgan AG, Davison AM, Burden RP (1993) Clinical features of benign hypertensive nephrosclerosis at time of renal biopsy. Q J Med 86:271–275
29. Joint National Committee on Detection, Evaluation, and Treatment of high blood Pressure (1993) Fifth Report (JNC V). Arch Intern Med 153:154–183
30. Katafuchi R, Takebayashi S (1987) Morphometrical and functional correlations in benign nephrosclerosis. Clin Nephrol 28: 238–243
31. Katafuchi R, Takebayashi S, Taguchi T (1988) Hypertension-related aggravation of IgA nephropathy: a statistical approach. Clin Nephrol 30:261–269
32. Katafuchi R, Vamvakas E, Neelakantappa K, Baldwin DS, Gallo GR (1990) Microvascular disease and the progression of IgA nephropathy. Am J Kidney Dis 15:72–79
33. Katafuchi R, Oh Y, Hori K, Komota T, Yanase T, Ikeda K, Omura T, Fujimi S (1994) An important role of glomerular segmental lesions on progression of IgA nephropathy: a multivariate analysis. Clin Nephrol 41:191–198
34. Kimura G, London GM, Safar ME, Kuramochi M, Omae T (1991) Glomerular hypertension in renovascular hypertensive patients. Kidney Int 39:966–972
35. Mágori A, Ormos J, Sonkodi S, Túri S, Zombori J, Iványi B, Kemény É (1984) Arteriolar lesions in human renal biopsy material with special regard to the ultrastructural changes in the basal lamina network of the vascular wall. Ultrastruct Pathol 6:185–198
36. Mulvany MJ (1995) Resistance vessel growth and remodelling: cause or consequence in cardiovascular disease. J Hum Hypertens 9:479–485
37. Mustonen J, Pasternack A, Helin H, Nikkila M (1985) Clinicopathologic correlations in a series of 143 patients with IgA glomerulonephritis. Am J Nephrol 5:150–157
38. Narvate J, Prive M, Saba SR, Ramirez G (1987) Proteinuria in hypertension. Am J Kidney Dis 10:408–416
30. Neelakantappa K, Gallo GR, Baldwin DS (1988) Proteinuria in IgA nephropathy. Kidney Int 33:716–721
40. Neugarten J, Feiner HD, Schacht RG, Gallo GR, Baldwin DS (1982) Aggravation of experimental glomerulonephritis by superimposed clip hypertension. Kidney Int 22:257–263
41. Nicholls KM, Fairley KF, Dowling JP, Kincaid-Smith P (1984) The clinical course of mesangial IgA associated nephropathy in adults. QJM [N Ser] 53:227–249
42. Nüsing R, Fehr PM, Gudat F, Kemeny E, Mihatsch MJ, Ullrich V (1994) The localization of thromboxane synthase in normal and pathological kidney tissue using a monoclonal antibody Tü 300. Virchows Arch 424:69–74
43. Ohishi K, Okwueze MI, Vari RC, Carmines PK (1994) Juxtamedullary microvascular dysfunction during the hyperfiltration stage of diabetes mellitus. Am J Physiol 267 [Renal Fluid Electrolyte Physiol 36]:F99–F105

44. Osterby R, Bangstad HJ, Nyberg G, Walker JD, Viberti GC (1995) A quantitative ultrastructural study of juxtaglomerular arterioles in IDDM patients with micro- and normoalbuminuria. Diabetologia 38:1320–1327
45. Preston RA, Singer I, Epstein M (1996) Renal parenchymal hypertension. Arch Intern Med 156:602–611
46. Short D (1966) The vascular fault in chronic hypertension. Lancet 1:1302–1304
47. Simons JL, Provoost AB, Anderson S, Rennke HG, Troy JL, Brenner BM (1994) Modulation of glomerular hypertension defines susceptibility to progressive glomerular injury. Kidney Int 46:396–404
48. Sommers SC, Melamed J (1990) Renal pathology in essential hypertension. Am J Hypertens 3:583–587
49. Tracy RE (1970) Quantitative measures of the severity of hypertensive nephrosclerosis. Am J Epidemiol 91:25–31
50. Valenzuela R, Gogate PA, Deodhar SD, Gifford RW (1980) Hyaline arteriolar nephrosclerosis. Lab Invest 43:530–534
51. Yoshida Y, Kawamura T, Ikoma M, Fogo A, Ichikawa I (1989) Effects of antihypertensive drugs on glomerular morphology. Kidney Int 36:626–635
52. Zidar N, Ferluga D, Volavsek M, Vizjak A, Luzar S, Kveder R (1992) Renal extraglomerular vascular immune deposits in IgA glomerulonephritis. Kidney Int 1444–1449