Virchows Archiv A Pathol Anat (1992) 420:127–129

Virchows Archiv A
Pathological Anatomy and Histopathology

Comparison of size of juxtamedullary and outer cortical glomeruli in normal adult kidney

K.M. Newbold, A. Sandison, and A.J. Howie

Department of Pathology, University of Birmingham, Birmingham B15 2TT, UK

Received August 21, 1991 / Received after revision September 23, 1991 / Accepted September 25, 1991

Summary. Abnormally large glomeruli are susceptible to hyperfiltration-associated sclerosis. We used an established morphometric method to test the general belief that juxtamedullary glomeruli are larger than those in the outer cortex, in a population with no clinical or pathological evidence of renal disease. Overall, juxtamedullary glomeruli were significantly larger, but this varied according to the amount of global glomerulosclerosis present. Global sclerosis increased with age, particularly in the outer cortex, and the ratio of juxtamedullary to outer cortical glomerular size showed a positive correlation with overall, and outer cortical, global sclerosis. Thus in the truly normal adult kidney, juxtamedullary glomeruli are not significantly larger than outer cortical glomeruli. However, global sclerosis increases with age and is most marked in the outer cortex, and this leads to compensatory enlargement of predominantly the juxtamedullary glomeruli. These findings suggest that in single kidneys, or in conditions characterised by ischaemic glomerulosclerosis such as hypertension, morphological changes related to hyperfiltration may appear first, and therefore become most severe, in juxtamedullary glomeruli.

Key words: Glomerular size – Kidney size – Renal morphometry – Global glomerulosclerosis

Introduction

The main determinant of glomerular size is body size, measured by the body surface area (BSA) (Kasiske and Umen 1986; Newbold et al. 1989). Studies of kidneys in humans (Bhathena et al. 1985; Newbold and Howie 1990a; Newbold et al. 1990) and animals (Yoshida et al. 1989; MacKay et al. 1990) suggest that loss of renal tissue, or of individual glomeruli, results in compensatory enlargement of unaffected glomeruli so that total filtration area maintains a constant relationship with BSA. It is increasingly apparent that glomerular size is an important factor in the initiation and progression of glomerular disease. There is evidence that abnormal enlargement confers greater susceptibility to glomerulosclerosis (Bhathena et al. 1985; Yoshida et al. 1989; MacKay et al. 1990; Newbold and Howie 1990a), and may be a predictor of poor outcome in some types of disease (Fogo et al. 1990).

There is a general belief that in normal kidneys, juxtamedullary (JM) glomeruli are larger than those in outer cortical (OC) areas (Elias and Hennig 1967; Hanberg-Sorensen 1972; Hurley and Drummond 1974; McLachlan et al. 1977). This is certainly true in the neonatal period, since glomeruli in the outermost cortex are still forming from metanephric blastema while those in the JM region are fully developed and therefore larger. However, to our knowledge there has been no systematic assessment of relative glomerular size in either normal or diseased adult kidneys. If it is true that JM glomeruli are larger, there is a possibility that they are more likely to become sclerosed. In view of this, we used a well-established morphometric method to compare relative glomerular size in outer and juxtamedullary cortex in a population with no clinical or pathological evidence of renal disease.

Materials and Methods

Routinely taken random sections of kidney from 41 consecutive hospital necropsies were selected from the files of the Department of Pathology, University of Birmingham (mean age 61 years, range 22–92; 27 males). Selection was made on the basis that the post mortem or subsequent histology report gave no indication of clinical or pathological evidence of renal disease, or of systemic disease that could have affected the kidney. Kidneys showing visible cortical scarring, either diffuse or focal, were not studied. The height and weight of the patient, as measured at necropsy, and the weight of one kidney, were noted.

A fine marker pen was used to outline on each coverslip an OC and JM zone of equal width. The midpoints between the cortico-medullary junction at the base of medullary pyramids and the

Offprint requests to: A.J. Howie

cortical surface were marked. A line was drawn through these points, parallel with the cortical surface, to define an OC zone. Further lines were then drawn around the medullary pyramids, parallel to the cortico-medullary junction and also passing through the midpoints, to define a JM zone. Any cortex falling outside these two zones was blanked out.

Glomerular cross-sectional area was measured in OC and JM zones on each slide using a method previously described (Newbold et al. 1989). Briefly, the microscopic image was projected onto the monitor screen of a Leitz Imagan semi-automatic image analyser, and a random starting point found using random number tables and the Vernier scale on the microscope. Using a digitiser tablet, a traced outline of Bowman's capsule was made of 50 glomeruli in each zone, by following a series of parallel rows perpendicular to the cortical surface. Globally sclerosed glomeruli were not measured. A separate observer evaluated the proportion of globally sclerosed glomeruli within each zone in each case by simple counting of all glomeruli.

The mean glomerular cross-sectional area for OC and JM zones in each case was calculated by taking the mean of the largest 12 measurements (Newbold et al. 1989). Similarly, an overall mean glomerular size for each kidney was derived by taking the mean of the largest 25 measurements out of the total of 100 made for both regions combined. The BSA was calculated for each case from the height and weight measurements using the formula of DuBois and DuBois (1916):

$$BSA(m^2) = \text{weight (kg)}^{0.425} \times \text{height (cm)}^{0.725} \times 0.007184.$$

It was not known if any patient had significantly changed weight during their terminal illness, but such changes in weight would have relatively little effect on the calculated BSA.

The mean OC and JM glomerular areas of all 41 cases were then calculated, together with the mean JM to OC glomerular area ratio. The correlation between BSA and kidney weight, and between kidney weight and overall glomerular area, was determined by Pearson's correlation coefficient. Mean OC and JM glomerular areas were compared using Student's t-test and the relationships between age, global sclerosis and JM to OC area ratio were tested using Pearson's correlation coefficient.

Results

The raw data for each of the 41 cases are shown in Table 1. The overall mean glomerular cross-sectional area for all 41 cases was 3.53 $\mu m^2 \times 10^4$, and overall global sclerosis 5%. Mean OC glomerular area was 3.41 $\mu m^2 \times 10^4$, and global sclerosis 6%, while figures for the JM zone were 3.62 $\mu m^2 \times 10^4$ and 3% respectively. The mean JM to OC glomerular area ratio was 1.07 (range 0.81–1.38).

There was a significant difference between OC and JM glomerular area ($t = 3.18$, $P < 0.01$). The JM to OC area ratio showed a positive correlation with overall global sclerosis ($r = 0.39$, $P = 0.01$) and with OC global sclerosis ($r = 0.37$, $P = 0.02$), but not with global sclerosis in the JM zone. There was a positive correlation between age and overall global sclerosis ($r = 0.50$, $P = 0.001$) and age and OC global sclerosis ($r = 0.46$, $P = 0.003$). The correlation between age and JM to OC area ratio was not significant ($r = 0.27$, $P = 0.09$).

There was a positive correlation between BSA and kidney weight ($r = 0.42$, $P = 0.007$), and kidney weight and overall glomerular area ($r = 0.38$, $P = 0.01$).

Table 1. Clinical details, weight of one kidney, and overall outer cortical (OC), and juxtamedullary (JM) glomerular area and percentage of global sclerosis in 41 patients

Age, sex	BSA (m^2)	Kidney weight (g)	*Glomerular area* ($\mu m^2 \times 10^4$)			*Global sclerosis* (%)		
			OC	JM	Overall	OC	JM	Overall
22,M	2.14	190	2.59	2.81	2.72	0	0	0
23,M	1.73	183	3.01	3.28	3.09	0	0	0
25,M	1.75	160	3.89	4.21	4.09	1	2	1
25,F	1.64	155	2.73	2.92	2.81	0	0	0
26,M	1.70	200	4.10	3.34	3.81	0	0	0
40,M	2.28	163	3.81	3.82	3.80	1	0	1
43,F	1.87	160	3.25	3.39	3.30	0	0	0
43,F	1.49	230	4.38	4.54	4.51	0	0	0
48,F	1.82	190	3.04	2.88	2.94	0	0	0
49,F	1.62	210	2.87	3.23	3.06	0	0	0
52,M	1.83	175	4.45	3.92	4.21	6	2	4
56,M	1.62	140	3.23	2.97	3.13	3	1	2
56,M	1.98	275	3.51	4.55	4.07	0	0	0
57,F	1.62	105	2.60	2.96	2.83	7	0	4
57,M	1.85	123	4.08	4.17	4.12	0	0	0
60,M	1.53	120	3.44	3.32	3.28	2	5	4
62,M	1.97	200	2.98	3.43	3.17	0	0	0
63,M	1.56	145	3.97	3.96	3.76	0	1	1
64,F	1.71	150	3.89	3.87	3.83	11	8	9
65,M	1.78	240	3.78	4.13	4.00	2	4	3
66,F	1.42	80	3.06	3.10	3.06	10	3	7
66,M	1.68	160	3.36	3.75	3.53	1	0	1
67,M	1.77	127	4.14	4.25	4.15	19	4	11
68,M	1.42	135	2.81	3.04	2.92	7	5	6
68,F	–	95	2.67	3.57	3.19	32	2	21
70,M	1.62	150	4.35	4.05	4.18	7	3	5
70,F	1.56	120	3.81	3.68	3.73	25	9	19
71,F	1.59	138	2.70	3.11	2.99	5	1	3
71,M	1.48	133	3.68	4.43	4.09	14	13	14
72,F	1.21	140	2.85	3.58	3.31	4	1	3
73,M	1.75	145	4.07	4.12	4.08	7	9	8
74,M	1.66	205	4.28	5.89	5.47	20	5	16
75,M	1.69	163	3.52	3.61	3.56	3	5	4
78,M	1.78	102	3.47	3.96	3.74	4	5	5
78,F	1.47	127	3.96	3.72	3.81	7	4	6
79,M	1.55	90	2.78	3.11	2.88	2	4	3
81,M	2.06	135	3.51	3.03	3.32	8	2	5
81,M	1.73	120	3.56	3.67	3.62	0	0	0
86,F	1.33	85	2.52	3.34	3.05	25	19	23
89,M	1.68	105	3.00	3.16	3.08	8	3	6
92,M	1.45	105	2.08	2.68	2.45	8	2	6

BSA, Body surface area

Discussion

The mean overall glomerular area for the 41 cases, and the presence of positive correlations between BSA and kidney weight, and kidney weight and overall glomerular area, confirm that the cases used conform to the normal range as assessed in previous studies (Newbold et al. 1989). It can be argued that a mean rate of global sclerosis of 5% suggests that the kidneys were not truly normal, and it is likely that this figure reflects the age of the patients in this necropsy population. It should be stressed again that we avoided obviously scarred kidneys in this study. We found a positive correlation between age and both overall, and outer cortical, global sclerosis and others have shown that global sclerosis increases with age (Elias and Hennig 1967; Holtenberg et al. 1974; Kaplan et al. 1975; Kappel and Olsen 1980; Kasiske 1987), even in the absence of significant peripheral vas-

cular disease. This may be an important factor in the interpretation of the results.

The overall JM to OC area ratio was very close to unity, but within this group of apparently normal kidneys, the ratio showed a positive correlation with the degree of overall, and outer cortical, global sclerosis. Thus in a truly normal kidney, that is, one in which global sclerosis is not present, the JM to OC ratio is probably one. Global sclerosis was greater in the OC area and this probably relates to the anatomy of the blood supply, and adjacent non-sclerosed glomeruli may well be ischaemic to a lesser degree. We have previously shown that where global sclerosis occurs, there is compensatory hypertrophy in intact glomeruli (Newbold and Howie 1990a). This study suggests that compensatory hypertrophy is most marked in the JM area when global sclerosis is greater in the outer cortex, perhaps because relative ischaemia prevents significant enlargement of OC glomeruli.

There is no doubt that in early childhood the JM glomeruli are larger, since these are fully formed at birth while outermost glomeruli are incompletely developed. During enlargement of the kidney throughout childhood this difference will become less marked as the outermost glomeruli develop and enlarge, so that in the truly normal kidney of early adulthood there is no significant difference in the size of OC and JM glomeruli. As ageing occurs, with or without significant ischaemia, global sclerosis affecting mainly OC glomeruli leads to compensatory enlargement affecting mainly the JM glomeruli. Since most renal biopsies are taken from children or adults with renal impairment, it is not surprising that there is a general view that JM glomeruli are relatively large.

The size of glomeruli is highly relevant to the pathogenesis of glomerular disease (Yoshida et al. 1989; Fogo et al. 1990; MacKay et al. 1990; Newbold and Howie 1990a; Newbold et al. 1990). The greatest enlargement occurs in single kidneys, where it is associated with hyperfiltration (Malt 1969; Fleck and Braunlich 1984) and characteristic segmental (Newbold and Howie 1990b) and global sclerosis, which ultimately results in renal functional impairment (Fleck and Braunlich 1984; Bhathena et al. 1985). Glomerular hyperfiltration also occurs in acromegaly where it is not accompanied by glomerular enlargement (Hutchins and Kutchemeshgi 1973; Newbold et al. 1989), and in this situation segmental or global sclerosis, or functional impairment, do not occur. Thus the presence of glomerular hypertrophy is of central importance in the progression of glomerular disease, since it implies loss of glomeruli elsewhere or the existence of proliferative glomerular disease, and an increased susceptibility to hyperfiltration-related damage. The findings of this study suggest that in single kidneys, or in conditions such as hypertension that are characterised by ischaemic glomerulosclerosis, morphological changes related to hyperfiltration may appear first, and therefore become most severe, in JM glomeruli.

References

Bhathena DB, Julian BA, McMorrow RG, Bachter RW (1985) Focal sclerosis of hypertrophied glomeruli in solitary functioning kidneys of humans. Am J Kidney Dis 5:226–232

DuBois D, DuBois EF (1916) Clinical calorimetry. Arch Intern Med 17:863–871

Elias H, Hennig A (1967) Stereology of the human renal glomerulus. In: Weibel ER, Elias H (eds) Quantitative methods in morphology. Springer, Berlin Heidelberg New York, pp 130–166

Fleck C, Braunlich H (1984) Kidney function after unilateral nephrectomy. Exp Pathol 25:3–18

Fogo A, Hawkins EP, Berry PL, Glick AD, Chiang ML, MacDonell RC, Ichikawa I (1990) Glomerular hypertrophy in minimal change disease predicts subsequent progression to focal glomerular sclerosis. Kidney Int 38:115–123

Hanberg-Sorensen F (1972) Quantitative studies of the renal corpuscles. 1. Intraglomerular, interglomerular and interfocal variation in the normal kidney. Acta Pathol Microbiol Scand 80:115–124

Holtenberg NK, Adams DF, Solomon HS, Rashid A, Abrams HL, Merrill JP (1974) Senescence and the renal vasculature in normal man. Circ Res 34:309–316

Hurley RM, Drummond KN (1974) Glomerular enlargement in primary renal disease. Arch Pathol 97:389–391

Hutchins GM, Kutchemeshgi AD (1973) Renal glomerular enlargement in chronic passive congestion. Johns Hopkins Med J 132:292–300

Kaplan C, Pasternack B, Shah H, Gallo G (1975) Age-related incidence of sclerotic glomeruli in human kidneys. Am J Physiol 80:227–234

Kappel B, Olsen S (1980) Cortical interstitial tissue and sclerosed glomeruli in the normal human kidney, related to age and sex. A quantitative study. Virchows Arch [A] 387:271–277

Kasiske BL (1987) Relationship between vascular disease and age-associated changes in the human kidney. Kidney Int 31:1153–1159

Kasiske BL, Umen AJ (1986) The influence of age, sex, race, and body habitus on kidney weight in humans. Arch Pathol Lab Med 110:55–60

MacKay K, Striker LJ, Stauffer JW, Agodoa LY, Striker GE (1990) Relationship of glomerular hypertrophy and sclerosis: studies in SV40 transgenic mice. Kidney Int 37:741–748

Malt RA (1969) Compensatory growth of the kidney. N Engl J Med 280:1446–1459

McLachlan MSF, Guthrie JC, Anderson CK, Fulker MJ (1977) Vascular and glomerular changes in the ageing kidney. J Pathol 121:65–78

Newbold KM, Howie AJ (1990a) Determinants of glomerular cross-sectional area. J Pathol 162:329–332

Newbold KM, Howie AJ (1990b) Analysis of the position of segmental lesions in glomeruli in vasculitic-type glomerulonephritis and other disorders. J Pathol 162:149–155

Newbold KM, Howie AJ, Girling AJ, Kizaki T, Bryan RL, Carey MP (1989) A simple method for assessment of glomerular size and its use in the study of kidneys in acromegaly and compensatory renal enlargement. J Pathol 158:139–146

Newbold KM, Howie AJ, Koram A, Adu D, Michael J (1990) Assessment of glomerular size in renal biopsies including minimal change nephropathy and single kidneys. J Pathol 160:255–258

Yoshida Y, Fogo A, Ichikawa I (1989) Glomerular hemodynamic changes vs hypertrophy in experimental glomerular sclerosis. Kidney Int 35:654–660