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Genetic renal disease

Original article

Chronology of renal scarring in males with Alport syndrome

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Abstract. We investigated the onset of renal scarring in 62 males (aged 4–26 years) with Alport syndrome by measuring cortical interstitial volume fraction [Vv (interstitium/cortex)] and percentage global glomerular sclerosis in kidney biopsies. Male pediatric ($n = 9$) and adult ($n = 7$) donor kidneys served as controls. Creatinine clearance at the time of biopsy was available for 43 Alport patients. A statistically insignificant correlation between age and Vv (interstitium/cortex) was observed in normal subjects ($r = +0.47$, slope = 0.0009, $P = 0.07$). In the Alport patients, age was significantly correlated with Vv (interstitium/cortex ($r = +0.49$, slope = 0.01, $P = 0.001$) and global glomerular sclerosis ($r = +0.41$, $P = 0.01$), and inversely correlated with creatinine clearance ($r = –0.33$, $P = 0.04$). Creatinine clearance was inversely correlated with Vv (interstitium/cortex) ($r = –0.78$, $P = 0.001$) and global glomerular sclerosis ($r = –0.74$, $P = 0.001$). The correlation with creatinine clearance was especially strong for Vv (interstitium/cortex) values above the normal range, i.e., > 0.2 ($r = –0.82$, $P = 0.001$), and was absent for Vv (interstitium/cortex) < 0.2 ($r = –0.119$, $P = 0.55$). Creatinine clearance values less than 80 ml/min per 1.73 m^2 occurred more frequently in patients with Vv (interstitium/cortex) values > 0.2 ($P < 0.0001$) and in patients with $> 10\%$ globally sclerosed glomeruli ($P < 0.001$). Patients $\leq$ or > 10 years of age differed in Vv (interstitium/cortex) [0.13 ± 0.09 (mean $\pm$ SD) vs. 0.24 ± 0.026, $P < 0.001$], the frequency of Vv (interstitium/cortex) > 0.2 (3/32 vs. 15/31, $P < 0.0001$), the frequency of $> 10\%$ globally sclerosed glomeruli (3/33 vs. 11/30, $P < 0.05$), mean creatinine clearance (113 ± 7 vs. 84 ± 10 ml/min per 1.73 m^2, $P = 0.057$), and the frequency of creatinine clearance < 80 ml/min per 1.73 m^2 (1/20 vs. 11/23, $P < 0.01$). Thus, reduced creatinine clearance in males with Alport syndrome is associated with Vv (interstitium/cortex) > 0.2 and $> 10\%$ globally sclerosed glomeruli. These are frequently detectable in the 2nd decade. We hypothesize that most Alport males will require intervention during the 1st decade for optimal preservation of kidney function.

Key words: Alport syndrome – Renal scarring – Cortical interstitial volume fraction – Global glomerular sclerosis

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Introduction

Alport syndrome, an inherited cause of renal failure, results from mutations in genes encoding type IV collagen, the major collagenous constituent of basement membranes. X-linked dominant Alport syndrome, due to mutations in *COL4A5*, the gene encoding the α5 chain of type IV collagen, is the most common form of the disease [1]. Autosomal recessive Alport syndrome is caused by mutations in *COL4A3* or *COL4A4*, encoding the α3(IV) or α4(IV) chains, respectively [2–5]. Autosomal dominant Alport syndrome has also been recognized by pedigree analysis, but these mutations have yet to be identified [6].

The clinical course of Alport syndrome is well established: the disease progresses inexorably to renal failure, usually during the first 2–3 decades of life, in male patients with X-linked dominant disease, and in patients of either gender with autosomal recessive disease [7, 8]. While there is no proven treatment for Alport syndrome other than renal transplantation, both inhibition of angiotensin II formation or action and specific gene therapy have been suggested as potentially effective interventions [9, 10]. Whatever intervention may eventually undergo clinical testing, it would be useful to know when renal scarring becomes detectable, assuming that intervention initiated before scarring appears will have the greatest long-term benefit, and whether serial measurement of glomerular filtration rate (GFR) could serve as a reliable surrogate for recurrent examination of histological changes in renal biopsy material. Although investigators have described the progression of renal

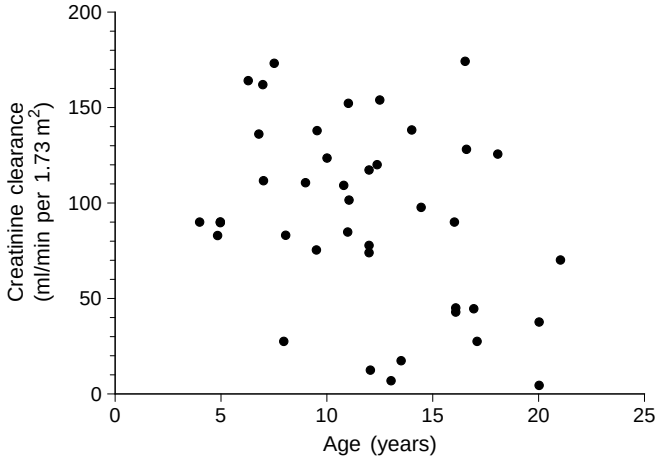

Fig. 1. Creatinine clearance versus age in males with Alport syndrome ($r = -0.33$, $P = 0.04$)

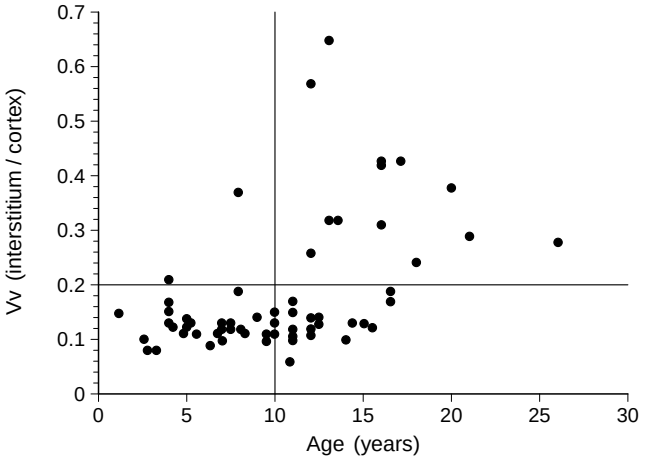

Fig. 2. Cortical interstitial volume fraction [*Vv (interstitium/cortex)*] versus age in males with Alport syndrome ($r = +0.49$, $P = 0.001$). The *solid horizontal line* indicates a Vv (interstitium/cortex) value of 0.2, while the *vertical line* denotes age 10 years

changes in Alport syndrome with age [7, 8, 11], to date there has been no large-scale effort to correlate age, quantifiable measures of renal scarring, and GFR. Therefore we undertook a study designed to describe the chronology of renal scarring in Alport syndrome and to assess the utility of creatinine clearance as an indirect marker of renal scarring in this disease. Cortical interstitial volume fraction [Vv (interstitium/cortex)] and global glomerular sclerosis were measured as markers of renal scarring, because of our previous observation in a small group of Alport patients that these parameters were inversely correlated with creatinine clearance [12].

Patients and methods

Patients. This study included 62 males with Alport syndrome from whom diagnostic renal biopsy material was available at Hôpital Necker-Enfants Malades in Paris (France) or at the University of Minnesota in Minneapolis (USA). The patients ranged in age from 4 to 26 years at the time of biopsy. Each patient had only a single renal biopsy. At the time of biopsy, 20 patients had isolated hematuria and 41 had hematuria and proteinuria (range 0.3–10 g/24 h); for 1 patient, information regarding protein excretion at the time of biopsy was not available. The diagnosis of Alport syndrome required hematuria and at least two of the following: sensorineural deafness, diffuse glomerular basement membrane (GBM) lamination, or a positive family history of end-stage renal disease. Four patients are known or strongly suspected to have autosomal recessive disease and 58 patients have X-linked Alport syndrome based on family history, molecular genetics, and/or immunohistochemistry. Fifty-six patients are white, 4 are north African, 1 is black, and 1 is Indian. Creatinine clearance at the time of biopsy, normalized for body surface area, was available for 43 patients. Fourteen of these patients were described in a previous report [12].

Structural analysis. Vv (interstitium/cortex) was measured on periodic acid-Schiff-stained light microscopic sections at an approximate magnification of X300 by point-counting images projected onto a grid on a white surface with a projection microscope [13]. The entire cortical tissue available on one section from each patient was evaluated, without knowledge of the patient's clinical status or creatinine clearance. Fine points were counted to determine the number of points falling on the interstitium (P_I), defined as points falling other than on glomeruli, tubules, and vessels larger than one tubular diameter. Coarse points were counted to determine points falling on the renal cortex (P_C). A median of 1,656 coarse points (range 527–4,176) and 215 fine points (range 53–1,214) were enumerated. As each coarse point defined four fine points, Vv (interstitium/cortex) = $P_I/P_C \times 4$ ($\mu m^3/\mu m^3$). Normal values for Vv (interstitium/cortex) in adult males ($n = 7$) were determined previously [13]. Pediatric male norms for Vv (interstitium/cortex) were established for the present study using 9 cadaveric kidneys donated for transplantation. These donors were 3–15 years of age.

Glomeruli exhibiting replacement of the capillary tufts by dense scar or extensive closure of capillary loops with wrinkling of the GBMs, minimal residual luminal space, and marked periglomerular fibrosis were considered globally sclerosed [14]. The number of globally sclerosed glomeruli was expressed as a percentage of the total number of glomeruli in the biopsy specimen. Focal segmental glomerulosclerosis (FSGS) lesions were not included in this definition. FSGS lesions cannot be accurately quantitated without performing careful analysis of serially sectioned biopsy material [15], which was not available due to the retrospective nature of this study. Creatinine clearance was measured using standard laboratory techniques, and normalized to body surface area (1.73 m^2).

Statistical analysis. Data are expressed as mean plus or minus standard deviation. Relationships between age, creatinine clearance, Vv (interstitium/cortex), and global glomerular sclerosis were examined by simple linear regression, using the Statworks program on a Macintosh personal computer. Comparisons of Vv (interstitium/cortex), global glomerular sclerosis, and creatinine clearance in patients $\leq$ or >10 years of age were made by chi-squared and Mann-Whitney tests. These tests were also used to compare creatinine clearance in patients with Vv (interstitium/cortex) values $\leq$ or >0.20 (above and below the upper limit of normal). All patients were included in analysis of the relationships between age and Vv (interstitium/cortex) and between age and global glomerular sclerosis. Only patients in whom creatinine clearance was measured at the time of biopsy were included in the analyses of the relationships of this variable with age and with renal stuctural parameters.

Results

Vv (interstitium/cortex) in normal subjects was 0.13 ± 0.03. A slight increase in Vv (interstitium/cortex) with age was observed in normal subjects, although this trend did not

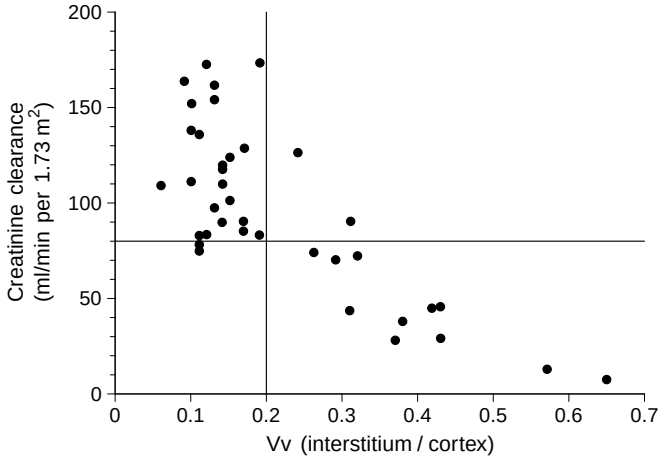

Fig. 3. Creatinine clearance versus Vv (interstitium/cortex) in males with Alport syndrome ($r = -0.78$, $P = 0.001$). The *solid horizontal line* indicates a creatinine clearance value of 80 ml/min per 1.73 m², while the *vertical line* denotes a Vv (interstitium/cortex) value of 0.2

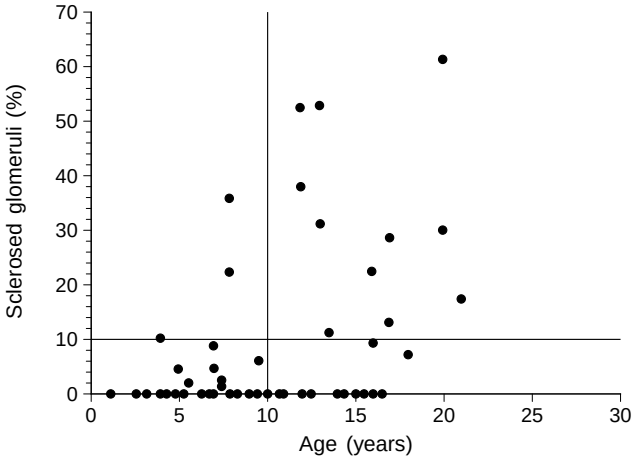

Fig. 4. Percentage glomerular sclerosis versus age in males with Alport syndrome ($r = +0.41$, $P = 0.01$). The *solid horizontal line* indicates 10% glomerular sclerosis, while the *vertical line* denotes age 10 years

Table 1. Cortical interstitial volume fraction [Vv (interstitium/cortex)], global glomerular sclerosis, and creatinine clearance in Alport males ≤ or >10 years of age

	≤10 years (n = 33)	10–26 years (n = 29)	P
Vv (interstitium/cortex)	0.13 ± 0.05[a]	0.24 ± 0.02	<0.001
Vv (interstitium/cortex) >0.2	2/33	17/29	<0.0001
Globally sclerosed glomeruli (%)	3.1 ± 7.6[a]	13.1 ± 19	0.17
>10 globally sclerosed glomeruli	2/33	11/29	<0.05
Creatinine clearance (ml/min per 1.73 m²)	113 ± 31*	84 ± 50	0.057
Creatinine clearance <80 ml/min per 1.73 m²	1/20	11/23	<0.01

[a] Mean ± SD

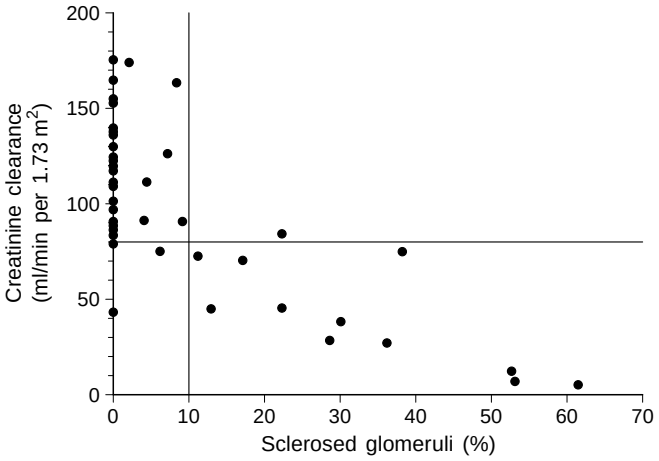

Fig. 5. Creatinine clearance versus percentage glomerular sclerosis in males with Alport syndrome ($r = -0.74$, $P = 0.001$). The *solid horizontal line* indicates a creatinine clearance value of 80 ml/min per 1.73 m², while the *vertical line* indicates 10% glomerular sclerosis

reach statistical significance ($r = +0.47$, slope = 0.0009, $P = 0.07$). The values for subjects ≤15 years of age (0.12 ± 0.02, $n = 9$) and those >15 years (0.14 ± 0.03) were not significantly different ($P < 0.17$, $n = 7$), indicating the absence of an important pubertal influence on Vv (interstitium/cortex).

Creatinine clearance in males with Alport syndrome showed an inverse relationship with age ($r = -0.33$, $P = 0.04$, Fig. 1), while Vv (interstitium/cortex) was directly related to age ($r = +0.49$, slope = 0.011, $P = 0.001$, Fig. 2). A strong inverse relationship between (Vv interstitium/cortex) and creatinine clearance was also observed ($r = -0.78$, $P = 0.001$, Fig. 3).

Inspection of Fig. 2 describing the relationship between age and Vv (interstitium/cortex) in Alport patients indicated that substantial expansion of the renal cortical interstitium is unusual during the 1st decade of life, but is often discernable during the subsequent decade. We therefore compared Vv (interstitium/cortex) and creatinine clearance in patients ≤ or >10 years of age (Table 1). Vv (interstitium/cortex) was greater in patients >10 years of age than those ≤10 years ($P < 0.001$). Increased Vv (interstitium/cortex) values (greater than 2 SD above the normal mean) were observed more often in patients >10 years of age ($P < 0.0001$). The mean creatinine clearance was greater in patients ≤10 years of age ($P = 0.057$). Patients >10 years of age were more likely to exhibit a creatinine clearance of <80 ml/min per 1.73 m², which was chosen as the threshold for renal insufficiency ($P < 0.01$) [16].

The data presented in Fig. 3 indicate a wide range of creatinine clearance measurements for patients with Vv (interstitium/cortex) values in the normal range (<0.2) and a nearly linear relationship between creatinine clearance and Vv (interstitium/cortex) when the latter values exceeded 0.2. In fact, there was no correlation between creatinine clearance and Vv (interstitium/cortex) in patients with Vv (interstitium/cortex) <0.2 ($r = -0.119$, $P = 0.55$), while there was a very strong inverse relationship between

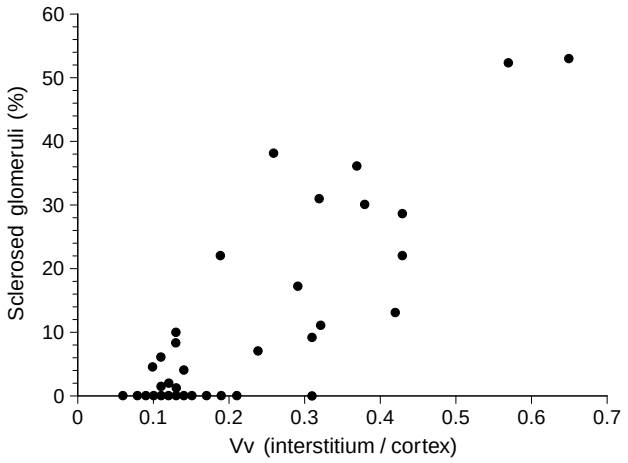

Fig. 6. Percentage glomerular sclerosis versus Vv (interstitium/cortex) in males with Alport syndrome (r = +0.84, P = 0.001)

creatinine clearance and Vv (interstitium/cortex) in patients with Vv (interstitium/cortex) >0.2 (r = –0.82, P = 0.01). The creatinine clearance in patients with Vv (interstitium/cortex) <0.2 (117 ± 6 ml/min per 1.73 m^2) was significantly higher than the creatinine clearance in patients with Vv (interstitium/cortex) >0.2 (52 ± 9 ml/min per 1.73 m^2, $P < 0.001$).

Age in Alport males was directly related to the percentage of globally sclerosed glomeruli (r = +0.41, P = 0.01, Fig. 4). Patients ≤ 10 years of age exhibited less global glomerular sclerosis than those >10 years of age, but this difference was not statistically significant ($P < 0.17$, Table 1). Global glomerular sclerosis showed a strong inverse correlation with creatinine clearance (r = –0.74, P = 0.001, Fig. 5). There was no correlation between global glomerular sclerosis and creatinine clearance when the percentage of sclerotic glomeruli was in the normal range, i.e., $\leq 10\%$ [13] (r = 0.006, P = 0.97), but there was a strong inverse correlation when the percentage of sclerotic glomeruli was $>10\%$ (r = –0.75, P = 0.005). Vv (interstitium/cortex) and global glomerular sclerosis were highly correlated (r = +0.84, P = 0.001, Fig. 6).

The majority of subjects with $\geq 10\%$ globally sclerosed glomeruli had creatinine clearances less than 80 ml/min per 1.73 m^2 (Fig. 5). Creatinine clearance was less than 80 ml/min per 1.73 m^2 in 3 of 31 subjects with less then 10% sclerosed glomeruli, compared with 11 of 12 subjects with greater than 10% sclerosed glomeruli ($P < 0.001$). The mean creatinine clearance (42 ± 27.5 ml/min per 1.73 m^2) was lower in subjects with $>10\%$ sclerosed glomeruli than in those with $<10\%$ sclerosed glomeruli (114.6 ± 32.6 ml/min per 1.73 m^2, $P < 0.001$). Alport males ≥ 10 years of age were more likely to exhibit $>10\%$ global glomerular sclerosis ($P < 0.05$, Table 1).

Discussion

Alport syndrome occurs as a consequence of mutation at one of three genetic loci that encode type IV collagen chains, *COL4A3* [α3(IV)], *COL4A4* [α4(IV)], or *COL4A5* [α5(IV)] [17]. These mutations are thought to impair formation and/or stability of collagen networks comprising these chains, so that these networks are absent from basement membranes or substantially reduced in quantity. Deficiency or dysfunction of a type IV collagen network(s) is a plausible explanation for certain characteristic features of Alport syndrome, such as the attenuation of GBMs seen in young Alport males [11], presumably accounting for their hematuria, and the lens capsule thinning that is associated with anterior lenticonus [18]. However, the progression of the Alport nephropathy to renal failure is much less readily explained. Alport males typically have normal renal function during the 1st decade of life, despite the abnormal composition of their GBMs. This situation changes dramatically during the 2nd and 3rd decades, when Alport males characteristically develop uremia. Although the abnormalities of type IV collagen in Alport basement membranes initiate processes that eventually result in renal failure, these processes and their natural history have not been precisely characterized. Certain of these processes may be specific to Alport syndrome, requiring specific interventions, while others may be common to chronic renal disease and, perhaps, remediable with non-specific therapies.

Progressive expansion of the renal interstitium is a common feature of advanced glomerular disease, and appears to be closely related to progressive deterioration of renal function [13, 19–22]. In a previous study of a small group of male and female Alport patients, we found a strong inverse correlation between renal Vv (interstitium/cortex) and creatinine clearance [12]. The present study confirms this relationship in much larger group of Alport males, and demonstrates the correlation of interstitial expansion with age: only 2 of 33 Alport patients exhibited increased values for Vv (interstitium/cortex) during the 1st decade of life, while Vv (interstitium/cortex) was increased in many patients during the 2nd decade.

A trend toward a slight increase in Vv (interstitium/cortex) with age was observed in normal male subjects, although this was not statistically significant, perhaps due in part to the small number of age-matched individuals available for study. However, the slope of the increase in Vv (interstitium/cortex) was 12-fold greater in Alport males than in controls. Consequently, the marked increase in Vv (interstitium/cortex) that is seen with increasing age in Alport males can only to a minor degree be explained by normal renal maturation or growth. Thus, renal interstitial expansion is characteristic of the 2nd decade of life in Alport males, and is tightly associated with progressive deterioration in GFR.

The rate of progression to end-stage renal disease in males with Alport syndrome varies from family to family [23]. This may account in part for the relatively weak relationship between age and creatinine clearance in the present study. It is also possible that creatinine clearance overestimated GFR in some patients [24]. Creatinine clearance was well preserved during the 1st decade of life in these Alport patients, but diminished values were frequently observed after 10 years of age. Creatinine clearance reflects, in part, the severity of cortical interstitial expan-

sion, as indicated by the strong inverse correlation between the parameters. However, 2 patients with Vv (interstitium/cortex) values >0.2 had creatinine clearances ≥ 90 ml/min per 1.73 m^2. Moreover, when Vv (interstitium/cortex) was <0.2, there was no correlation between this structural parameter and creatinine clearance, which showed a wide scattering of values. This phenomenon was not noted in our original description of structural-functional relationships in Alport syndrome [12], because only a small number of patients with Vv (interstitium/cortex) values within the normal range were available for analysis. In that study, in order to explain why GFRs were significantly lower for any degree of glomerular or interstitial structural change in Alport patients compared with patients with diabetic nephropathy or mesangiocapillary glomerulonephritis, we hypothesized that the hydraulic conductivity of the glomerular capillary wall might be reduced in Alport patients because of the abnormal matrix composition of the GBM [12]. Variations in hydraulic conductivity may also account for the new observation of diverse creatinine clearance values in Alport males with normal Vv (interstitium/cortex).

The findings of this study have important implications for the design of interventions aimed at altering the natural history of the Alport nephropathy. First, it appears that a normal creatinine clearance in Alport patients is strongly suggestive of normal or minimally increased cortical interstitial volume and few or no globally sclerotic glomeruli. Since increase in Vv (interstitium/cortex) is so highly correlated with reduction in GFR in Alport syndrome, it is reasonable to suppose that serial determination of creatinine clearance, or other measures of GFR, will accurately reflect interstitial responses to an intervention. Second, a Vv (interstitium/cortex) of 0.2 can be viewed as a threshold that corresponds to the onset of the progressive decline in glomerular filtration in Alport syndrome. Similarly, glomerular filtration is rarely impaired in Alport males with less than 10% global glomerular sclerosis. As these levels of renal scarring are rarely reached during the first 10 years of life, for many Alport males this period may represent a "window of opportunity" during which the maximal benefit from any intervention may be derived. However, it is recognized that renal injury may have been initiated during this interval that will eventually result in later renal scarring regardless of the intervention.

In summary, because of the absence of quantitative information on the chronology of renal scarring in Alport syndrome, we evaluated renal biopsies in a large cohort of patients ranging in age from 4 to 26 years. Interstitial volume fraction and percentage glomerular sclerosis, both inversely related to creatinine clearance, were uncommon in the 1st decade but observed frequently thereafter. Thus, glomerular scarring and interstitial fibrosis typically become detectable during the 2nd decade of life in Alport males. Creatinine clearance appears to be a good surrogate measure of interstitial expansion and glomerular sclerosis in Alport syndrome. Delaying intervention until there is reduction in creatinine clearance may produce suboptimal results, because important structural changes may already have occurred. Prevention of decline in GFR is an acceptable endpoint for therapeutic efficacy in Alport syndrome, although concomitant structural studies would expand our understanding of this important disorder.

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Workshop

Early renal development: a key to the understanding of adult disease?

9–11 September 1998

Stockholm, Sweden

The VIIth Workshop on Developmental Nephrology in association with the XIth Congress of the International Pediatric Nephrology Association (London, 12–16 September 1998) will be held in Stockholm, Sweden, 9–11 September 1998. The workshop will focus on molecular mechanisms regulating early kidney maturation with the hypothesis that some adult diseases may have their roots in fetal or early postnatal life. It will consist of poster sessions and 5 sessions with invited speakers as follows:

- Angiogenesis
- Nephrogenesis: from stem cell to mature nephron
- Apoptosis: a double-edged sword
- Regulatory systems
- Molecular mechanisms of water and electrolyte homeostasis

Speakers include: G. Germino (Baltimore), K. Tryggvasson (Stockholm), R. Lifton (Yale), R. Thakker (London)

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