AJH 2002; 15:53S–56S

Effect of Hypertension on the Progression of Chronic Renal Failure in Children

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This article reviews the current state of knowledge concerning the vicious cycle of hypertension and progressive loss of renal function in renal disease, as well as the renoprotective potential of antihypertensive treatment, with a specific focus on children and adolescents. Deficient arteriolar autoregulation renders damaged kidneys particularly sensitive to systemic high blood pressure (BP). Intraglomerular hypertension promotes proteinuria, which further activates the renin-angiotensin system (RAS). Angiotensin II, apart from its vasoconstrictor effects, induces local proinflammatory and profibrotic signaling molecules resulting in renal scarring. The activity of the scarring process with the resultant loss of functional renal mass appears to be modulated, in part, by a polymorphism in the angiotensin converting enzyme (ACE) gene. Clinical studies in adults have demonstrated convincingly the high risk of progression of chronic renal failure (CRF) associated with high BP, the benefit of lowering BP to even the low normal range, and the specific benefit of drugs that inhibit the RAS on the progression of CRF. In children, even moderately elevated BP and moderate proteinuria have been shown to be significant risk factors for progression and CRF. The optimal target BP for children with CRF is currently being determined in a multinational, randomized, prospective trial. Am J Hypertens 2002;15:53S–56S © 2002 American Journal of Hypertension, Ltd.

Key Words: Chronic renal failure, hypertension, pediatric.

Chronic renal disease is associated with high blood pressure (BP), and hypertension has more recently received additional attention for its close correlation to the progressive loss of renal function. This is of particular interest in pediatric nephrology, as severe hypertension in children predominantly affects patients with renal diseases. In contrast to the cardiovascular sequelae of childhood-onset essential hypertension, such as left ventricular hypertrophy and vascular damage, which may not become clinically relevant before adulthood, rapid progression of renal insufficiency may result in end stage renal insufficiency during childhood.

This article reviews the actual knowledge on causes and effects in the vicious cycle of hypertension and progressive loss of renal function, as well as the renoprotective potential of antihypertensive treatment, with special attention to the pediatric age group.

Why Hyertension Is So Bad for Damaged Kidneys

Healthy kidneys protect their glomerular tufts from the effects of systemic BP variability by judicious adaptation of their afferent arteriolar tone, leading to a stable filtration pressure over a wide range of systemic BP (Fig. 1). This autoregulation is thought to be deficient in chronic renal failure (CRF),[1] and the correlation of glomerular filtration rate (GFR) and proteinuria to systemic BP in humans with nephropathies strongly supports this view.[2] In addition, systemic or local angiotensin II induces constriction, especially of the efferent arteriole, thereby further increasing the intraglomerular pressure.[3]

Intraglomerular hypertension induces fluid shear stress, hyperfiltration, and proteinuria.[4,5] The proteinuria becomes part of a vicious cycle by further activating the local renin-angiotensin system (RAS). Angiotensin II,

Received October 15, 2001. Accepted October 16, 2001.

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This work was presented at the International Pediatric Hypertension Association (IPHA) meeting on May 19, 2001, and was supported by a travel grant from IPHA.

0895-7061/02/$22.00
PII S0895-7061(01)02296-8

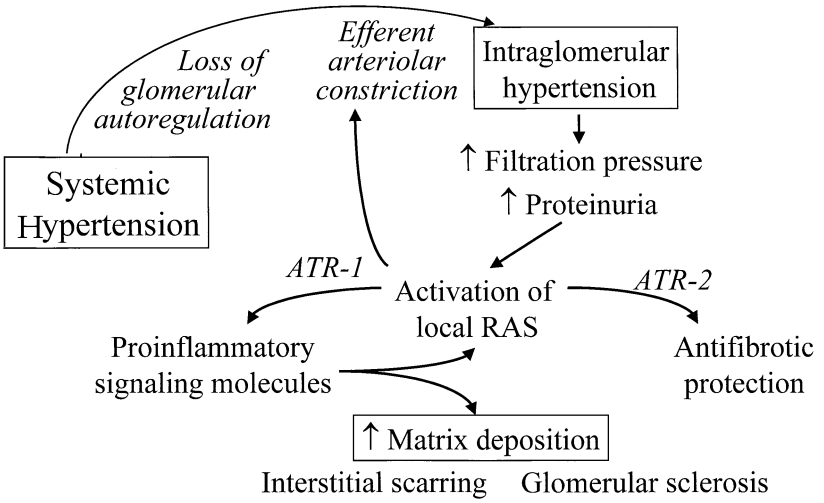

FIG. 1. Pathophysiology consequences of hypertension in damaged kidneys. ATR-1 = angiotensin-II receptor type 1; ATR-2 = angiotensin-II receptor type II. Note the two loops of vicious cycle, proteinuria and the activation of profibrotic signaling molecules. Note also the protective action of the ATR-2; this activation by high circulating and local angiotensin II levels may explain the suggested additive benefit of ATR-1-antagonists; RAS = renin-angiotensin system.

apart from its vasoconstrictory effects, induces local proinflammatory signaling molecules such as transforming growth factor-β (TGF-β), transforming necrosis factor-α (TNF-α), RANTES, or membrane cofactor protein-1 (MCP-1) at the tubulointerstitial level, ultimately leading to increased matrix deposition, interstitial scarring, and glomerular sclerosis.[1,5]

Genetics, RAS, and the Progression of Chronic Renal Failure in Children

Since information on candidate genes became available, several researchers have investigated the role of genetics and its correlation to BP in chronic renal disease. The angiotensin converting enzyme (ACE) gene polymorphism has received most attention so far, the DD genotype being associated with increased transcription of the gene, higher circulating levels of ACE, and more rapid progression in a variety of renal diseases,[6] without clear-cut correlation to systemic BP levels. In children, the ACE genotype has been found to be unrelated to the occurrence, but strongly related to the prognosis, of malformations of the urinary tract; renoparenchymal scarring in children with vesicorenal reflux almost exclusively occurred in children with the DD genotype,[7] and this genotype was also a strong independent risk factor for the progressive loss of renal function in children with hypoplastic or dysplastic kidneys.[8] In the absence of systemic BP changes, the local intrarenal activity of the RAS and its noncirculatory profibrotic effects are supposed to explain these observations.

Lessons From Nephrology in Adults: Diabetic and Nondiabetic Nephropathies

The association of hypertension with rapid progression of renal damage has been recognized for decades. However, it was unclear whether hypertension was the cause or merely a marker of progression—and thereby, whether lowering of BP would be beneficial.

Diabetic nephropathy has served as an excellent model to investigate progressive renal disease, as many young patients with this rather uniform disease have been followed by teams of clinicians devoted to clinical research, initially in Scandinavian countries. Years before the availability of ACE inhibitors, clinical studies demonstrated that lowering BP to what was then considered upper normal range[9] or lower[10] slowed down the loss of renal function and yielded a simultaneous decrease in proteinuria. Larger studies fully confirmed these results.[11]

Several studies performed in adults with nondiabetic renal disease have also found a high risk of progression of chronic renal insufficiency associated with high BP,[12] and a beneficial effect of lowering BP for the preservation of renal function.[13,14]

A particular risk of rapid progression seems to be associated with nocturnal hypertension.[15] We do not yet know whether restoring the nocturnal BP dipping might optimize the renoprotective effect of antihypertensive treatment in chronic renal disease.

The ACE inhibitors seemed to offer better preservation of renal function than other antihypertensive agents,[16] most importantly in proteinuric patients.[17] In most studies, BP was slightly better controlled in the group who received ACE inhibitors. In the absence of ambulatory blood

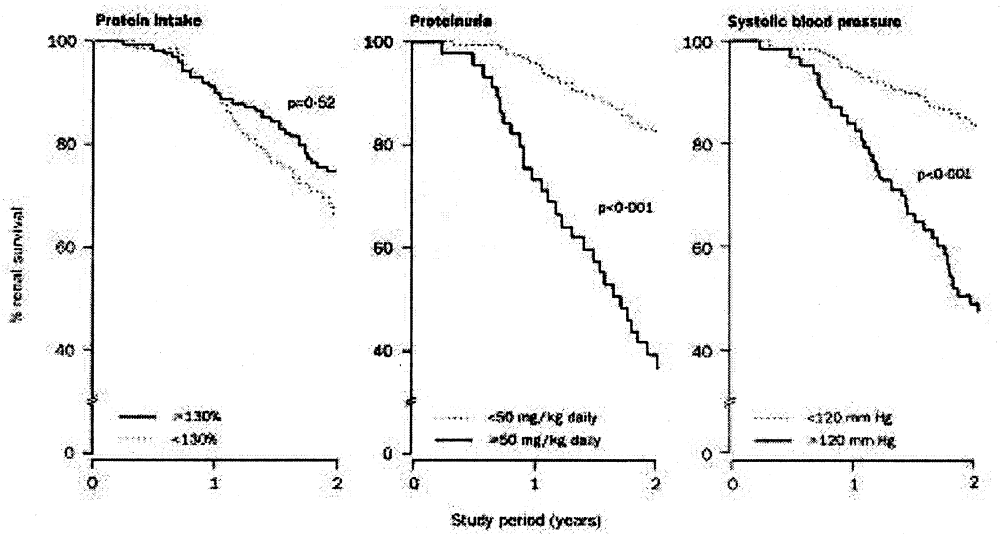

FIG. 2. Renal survival during follow-up with regular pediatric nephrologic appointments and dietetic counseling. Percentage of renal survival was unrelated to the protein content of the diet and strongly correlated with proteinuria or hypertension.

pressure monitoring recordings, the difference may even have been underestimated; ACE inhibitors seem to have particular advantages for nocturnal BP control, which escapes observation by casual BP. Additional benefit has been attributed to the inhibition of "local" actions of angiotensin II, that is, glomerular hypertension and hyperfiltration, proteinuria, and trophic proinflammatory effects.[18] Recent studies suggest that angiotensin II receptor antagonists offer at least similar renoprotection.

Pediatric Renal Disease

Children with chronic renal failure represent a unique population. In contrast to adults with chronic renal insufficiency, glomerulopathies (including diabetic nephropathy) are rare disorders in this age group, and the largest population is children with reduced renal mass. Most of these patients have normal or only slightly elevated BP, modest proteinuria, and a natural course of slow progression. Would BP still be correlated to the progression of CRF under these circumstances?

In a pediatric prospective multicenter study,[19] a casual systolic BP of more than 120 mm Hg, as well as a moderate proteinuria (>50 mg/kg body weight per day) proved to be significant risk factors for progression of renal failure, whereas the protein content of the diet had no influence (Fig. 2). Thus, the progression of renal failure in children with reduced renal mass appears to be correlated to the same risk factors as in adults, and it could be speculated that the optimal prevention for progression of CRF in adults—aggressive BP lowering and inhibition of the RAS—should offer renoprotection in children as well.

The evidence of renoprotection by ACE inhibitors, as well as their antihypertensive efficacy with little side effects, have lead to a widespread use of these agents in pediatric renal patients despite few published pediatric data. Therefore, a controlled study to evaluate ACE inhibitors in children with chronic renal insufficiency actually seems unacceptable for ethical as well as for practical reasons.

The benefit of aggressive BP control for the progression of chronic renal failure in children is addressed by an ongoing European multicenter study. Patients aged 3 to 18 years with a GFR between 15 and 75 mL/min/1.73 m^2 and a spontaneous BP above the 50th percentile are observed for 3 years with regular evaluation of ABPM and GFR. For the ethical reasons described previously, all patients receive ramipril. They are randomized to a target BP below the height-related 50th percentile, or between the 50th and the 95th percentile, based on the ABPM 24-h means. The feasibility and patient tolerance of such intensified BP control in children with CRF seems to be good. The final results of the study are expected in 2004.

In conclusion, large studies in adults with diabetic or nondiabetic renal disease have shown the association of high BP with rapid progression of CRF, the benefit of decreasing BP, and the specific advantages of ACE inhibitors. For children, the correlation of BP to the rate of CRF progression was shown. Although the efficacy of renoprotection by ACE inhibitors has not been (and probably will never be) demonstrated in controlled pediatric trials, it appears highly likely based on the results in adults and the proven renal risk inferred by high BP and proteinuria in children with chronic renal disease. The optimal target BP for children with CRF is currently being determined.

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