# A Clinical Approach in Regression of glomerulosclerosis

*Stoian M*[1], *Radulian G*[2], *Dumitrescu A*[3], *Simion E*[3]

*1. Universitary assistent of Internal Medicine and Nephrology, Carol Davila University of Medicine, Bucharest Department of Internal Medicine "Dr.I.Cantacuzino" Hospital, Bucharest*
*2. Associate Professor of Nutrition and Diabetes Carol Davila University of Medicine, Bucharest*
*3. Department of Internal Medicine "Dr.I.Cantacuzino" Hospital, Bucharest*

## Abstract

The role of the renin angiotensin System (RAS) in hypertension and end organ damage has long been recognized. Recent advances in genetic models and newly available pharmacological tools have allowed dissection of the mechanisms of actions of the components of the RAS in fibrotic kidney disease. Numerous studies have shown that angiotensin 1 converting enzyme inhibitors (ACEI) are superior to other antihypertensive agents in protecting the kidney against progressive deterioration, even in normotensive persons[2,3]. Like ACEI, angiotensin II type 1 receptor antagonists (AT1RA) ameliorate or even reverse glomerulosclerosis in rat animal models. These findings suggest that angiotensin II. The beneficial effect on renal fibrosis of inhibiting the RAS likely reflects the central role that angiotensin has in regulating renal function and structure by its various actions. This article explores the interaction of the renin angiotensin aldosterone System with PAI-1, and the potential significance of these interactions in the pathogenesis of progressive renal disease and remodeling of renal sclerosis.

**Key words**: renin angiotensin System (RAS), plasminogen activator-inhibitor 1(PAI-1), renal fibrosis, glomerulosclerosis, aldosterone.

The RAS is now recognized to be linked to induction of plasminogen activator-inhibitor-1 (PAI-1), possibly via the AT4 receptor, thus promoting both thrombosis and fibrosis.

(Ang II) has nonhemodynamic effects in progressive renal disease. The RAS is now Interactions of the RAS with aldosterone and bradykinin may have an impact on both blood pressure and tissue injury.

## Angiotensin and PAI-1- A Link between Vasoactive and Thrombotic Systems

PAI-1 is the major physiological Inhibitor of tissue plasminogen activator, t-PA, and urokinase-like plasminogen activator (u-PA), both of which activate plasminogen to plasmin, thus promoting fibrinolysis and proteolysis, and also activate other matrix metalloproteinases. Angiotensin induces PAI-1 via its metabolite Ang IV which binds to the AT4 receptor in vascular smooth muscle cells and bovine aortic endothelial cells in vitro.

Angiotensin induction of PAI-1 in vitro was found to be direct in the early phase with a later component dependent on co induction of TGF-b by angiotensin[2].

Further, increased RAS activity, whether by exogenous infusion of phsiologyc amounts of Angll, or by endogenous increase linked to the ACE DD polymorphism increases PAI-1 levels in humans with no effect on t-PA[3]. PAI-1 activity is also genetically modulated by the common 4G/5G polymorphism located -675 base pairs from the transcription start of PAI-1. Patients homozygous for the 4G allele have increased PAI-1 levels, and also increased risk for cardiovascular disease. Compound homozygosity (i.e. ACE D/D + PAI-1 4G/4G) for ACE and PAI-1 polymorphisms that have been linked to increased cardiovascular disease and renal disease was associated with increased incidence of macroangiopathic disease in diabetic patients. This may relate to the linked effects of PAI-1 and RAS to promote thrombosis and fibrosis. Indeed, Inhibitors of RAS significantly reduced thrombus formation in an animal model. Increased PAI-1 has also been associated with fibrosis. PAI-1 expression was tightly correlated with sites of glomerular injury in a radiation model where thrombosis progresses to glomerulosclerosis. Decreased injury in animal models was associated with maneuvers that decreased PAI-1 by treatment with an ACEI or AT1 RA. Modulation of PAI-1 by ACEI also occurs in humans. Inhibition of angiotensin with ACEI significantly decreased PAI-1 antigen and activity in patients following acute myocardial infarction, with no effect on t-PA antigen levels. Thus, the choice of RAS Inhibitor, whether the Intervention affects AT4, which at least in vitro induces PAI-1, or augments bradykinin, which stimulates t-PA, could potentially have profound impact on the balance of thrombosis/fibrosis versus fibrinolysis/ECM degradation (see below).

## Interactions of RAS and Aldosterone

Angll may also affect sclerosis via aldosterone. Addition of aldosterone antagonism over angiotensin inhibition alone provided additional benefit on glomerulosclerosis in animal studies. Aldosterone antagonism alone also decreased vascular injury in the stroke-prone hypertensive rat model. Importantly, aldosterone enhanced angiotensin induction of PAI-1 in vitro. In animal studies in the nonhypertensive radiation nephropathy model, spironolactone, an aldosterone receptor antagonist, ameliorates sclerosis. This finding was not linked to effects on blood pressure or proteinuria, but was tightly associated with decreased PAI-1 expression.

These data demonstrate that Inhibition of aldosterone can decrease PAI-1 in vivo, and suggest that targeting of both angiotensin and aldosterone may be necessary for optimal effect on PAI-1 and progression of glomerulosclerosis.

## Can Regression of Disease-Related Sclerosis Be Achieved?

In addition to increased matrix synthesis, decreased ECM proteolysis contributes to progressive renal fibrosis. PAI-1 inhibits not only fibrinolysis, but also proteolysis, by inhibiting activation of plasminogen activators.

Plasmin can cleave most ECM proteins, and both t-PA and u-PA play important roles in vascular remodeling, angiogenesis and tumor metastasis. t-PA primarily effects fibrinolysis, whereas u-PA has less affinity for fibrin but avidly degrades matrix. PAI-1 expression is normally present in very low levels in the kidney, and is expressed in vitro in many cells, including endothelial and visceral epithelial cells[9]. PAI-1 is increased in settings of vascular injury, whether thrombotic or fibrotic. Increased PAI-1 levels, whether due to the functional 4G/4G polymorphism of the PAI-1 gene promoter, or due to other causes, are associated with cardiovascular disease. TGF-b 1 effects to induce fibrosis may also in part relate to PAI-1 actions: TGF-b 1 induces PAI-1 to greater extent than u-PA in cultured endothelial cells, thus promoting fibrosis. Renal biopsy studies in humans show that ACEI not only slows progressive loss of GFR, but also prevents ongoing structural injury. In a small study of diabetic patients treated with either ACEI or beta blocker, repeat renal biopsies were performed. Over three years, there was a slight increase in afferent arteriolar medial matrix with beta blocker, while no increase was seen with ACEI. In another study, ACEI prevented interstitial expansion in hypertensive patients with diabetic nephropathy[1,4]. Even more dramatic results, with regression of glomerulosclerosis and interstitial fibrosis, were achieved in diabetic patients with nephropathy whose diabetes was cured by pancreas transplantation. Repeat biopsies over a 10-year interval showed regression of mesangial expansion, more patent glomerular loops and proportional decrease in tubulointerstitial fibrosis[5].

Experimental models have shed light on some of the mechanisms involved in achieving regression of glomerulosclerosis. Spontaneous resolution of mesangial matrix accumulation occurs in the anti-Thy-1 model with attendant changes in cell proliferation and increasing metalloproteinase activity. Regression of matrix expansion resulted from pancreatic transplant in a rat model of diabetes [6,7,10]. Delayed onset treatment in the puromycin aminonucleoside model of glomerulosclerosis with either ACEI or low protein diet also was also inferred to regress glomerulosclerosis by comparison of cohorts of animals sacrificed at different time interval [8, 15].

Increased PAI-1 expression localized to sites of sclerosis, and decreased PAI-1 was linked to resolution of sclerosis. Rats with regression also had an improved renal function. These findings implicate inhibition of PAI-1 by high dose AT1 RA or ACEI and resulting increased matrix degradation in regression of glomerulosclerosis. The link between PAI-1 expression and sclerosis was also demonstrated in the radiation nephropathy model, a nonhypertensive model of early endothelial injury followed by late sclerosis. PAI-1 mRNA expression by in situ hybridization was closely associated with sites of glomerular injury, assessed by serial section morphologic analysis. PAI-1 mRNA in glomeruli was localized to injured mesangial and endothelial areas, with focal expression in glomerular visceral and parietal epithelial cells[11]. Thus, autocrine effects are involved, since these cells also express receptors for angiotensin (AT1 and possibly AT4 receptors). Treatment with AT1 RA or ACEI significantly inhibited the up regulation of PAI-1 mRNA without affecting t-PA or u-PA expression.

Importantly, kidney sclerosis was prevented by treatment with either ACEI or AT1 RA.

## Can Regression of Age-related Sclerosis be Achieved?

Recently, was found that existing age-related glomerular and vascular sclerosis in the rat could be remodeled, with regression and decreased collagen content induced by starting AT1 RA treatment in aging rats. Aging sclerosis was accompanied by increased apoptosis in tubular and interstitial cells in kidney, which was abolished by AT1RA treatment. [12, 13, 14]. PAI-1 and TGF-beta were increased in aging, while remodeling and regression were associated with decreased PAI-1 and TGF-beta. Thus, these data support that both decreased ECM synthesis, in part due to decreased TGF-beta, and increased ECM degradation, determinated by Inhibition of PAI-1, contribute to the regression of sclerosis.

## Summary

These data demonstrate that regression of biopsy proven glomerulosclerosis can be achieved in various experimental settings. The potential importance of the RAS in renal fibrosis is underscored by the effectiveness of therapies that aim to inhibit its various actions, including induction of PAI-1. Ongoing studies will establish which of these recent provocative findings from animal models are relevant to human diseases, and may lead to optimal therapies to forestall progression and perhaps even induce regression of sclerosis.

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