BANTAO Journal 3 (2): p 36; 2005

Regression of Glomerulosclerosis: Fact or Myth?

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A number of studies has documented in the past, that most progressive renal diseases exhibit an apparently relentless, linear loss of glomerular filtration rate. New therapeutic options of supportive therapy (i.e. ACE-inhibitors, AT1-receptor blockers etc.) allow to reduce or even arrest this linear function loss. Morever, these options even raise hopes that we may not only be able to reduce or arrest but rather to reverse established sclerotic lesions.

Very few clinical studies so far have addressed the question of regressing glomerular sclerotic changes. However, in single cases it has been documented that diabetic mesangial or non-diabetic, mesangioproliferative changes can be reversed if such organs are inadvertently transplanted. Probably the most convincing evidence for the possibility of regression of an established glomerulosclerosis is derived from the observation that type 1 diabetics with established nephropathy can experience a complete reversal of their glomerular lesions following a successful pancreas transplantation [1]. Of note, in this study, 10 years were necessary for complete reversal and relatively little change was apparent at 5 years after pancreas transplantation. This implies, that clinical studies addressing this topic will be very difficult to perform.

Much more information is available on the issue of regression from various experimental studies:

a) Ma and colleagues [2] described that in 18 months old Sprague Dawley rats a subsequent 6 months long Losartan therapy lead to regression of spontaneous, age-dependent glomerulosclerosis. However, it is important to note that the sclerotic changes even in untreated animals were very mild at 24 months of age.

b) Boffa and colleagues described that glomerular extracellular matrix expansion in a hypertensive rat model were reversible during Losartan therapy [3].

c) Remuzzi and colleagues documented a regression of spontaneous, age-dependent „sclerotic changes“ (no specific definition is given in the paper) in the kidney of MWF-rats following institution of a Lisinopril plus Valsartan therapy [4].

d) Adamczak et al. [5] reported that an extremely high-dose Enalapril therapy (48 mg/kg/day) lead to regression of, mostly mild, glomerular fibrotic changes. In parallel a reduction of mesangial and endothelial cell expansion in the glomeruli was noted, whereas podocyte number and podocytic hypertrophy remained unchanged.

Are we therefore within reach of being able to healing sclerotic changes in the kidney? The answer to this question unfortunately has to remain vague at present, since the interpretation of all of the above experimental data is exquisitely dependent on how “glomerulosclerosis” is defined. If “glomerulosclerosis” refers to expansion of the mesangial extracellular matrix and/or of the mesangial cell population, both experimental [5, 6] and human [1] data clearly document that such changes can indeed be fully resolved. Endothelial changes, including considerable loss of glomerular capillaries, also can be restored to normal *in vivo* via processes that exhibit many similarities with angiogenesis [7, 8]. Thus, glomerulosclerosis, if defined as loss of glomerular capillary loops, is also potentially reversible. However, the typical focal segmental or even global glomerulosclerosis (both the clinical disease entity as well as the descriptive pathological term) usually also includes damage to the third glomerular cell population, i.e. the podocytes, as well. This results in loss of podocytes, early synechia formation between the capillary loops and Bowman’s capsule, followed by progression of these lesions, e.g. via so-called “misdirected filtration” into the periglomerular interstitium [6, 9, 10].

In contrast to glomerular endothelial and mesangial cells, podocytes only exhibit a very low potential for regeneration. Whereas it was assumed in the past, that podocytes are terminally differentiated cells and thus unable to undergo cell division, it is now well established that these cells possess the principal ability to enter the cell cycle [11]. A central problem of podocytes, which so far is not well understood, is the fact that they apparently can enter mitosis and undergo nuclear but not complete cell division. Consistent with this, both experimental data and clinical observations have documented the existence of bi- or even multinucleated podocytes [9]. The cellular hypertrophy, which occurs in such instances, certainly is a useful attempt of the podocytes to compensate the loss of neighboring cells and to respond to glomerular hypertrophy and hypertension. However, very recently it was demonstrated that entrance of podocytes into the cell cycle obviously can also lead to a very vulnerable situation, since these very cells may be detected in the urine [12]. It is hypothesized that entrance of podocytes into the cell cycle induces altered expression of adhesion molecules and may therefore potentially weaken the attachment of these cells to the glomerular basement membrane, such that some of them lift off and are lost into the urine. In first clinical studies we have been able to also demonstrate viable podocytes in the urine of patients with glomerulonephritides. This finding raises the hope that the detection of viable podocytes in the urine of patients with glomerulonephritides could become a very specific marker for ongoing disease activity in the glomerulus and that this might serve as an important guide to prognosis and therapy. We suspect that in cases of high podocyturia or other types of podocyte loss, e.g. via apoptosis, the possibility for regression of glomerulosclerosis is markedly impaired if not impossible. Consistent with this hypothesis, glomerular lesions that regressed in the above studies usually were in

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relatively early stages of glomerulosclerosis, whereas advanced lesions, in particular synechiae, progressed despite intensive therapy [4]. In cases of a completely scarred glomerulus or an atubular glomerulus, current knowledge suggests that reversal is no longer possible.
The answer to the title therefore is "*..yes, but...*": *Yes*, regression of glomerular fibrotic or sclerotic lesions is reality, *but* only if the diagnosis is made in time and therapy starts at an early stage.

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