The kidney as a cause and target of hypertension

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SUMMARY There is a unique relation between the kidney and blood pressure. On the one hand, renal dysfunction and particularly renal disease can cause an increase in blood pressure, while on the other hand, high blood pressure accelerates loss of function of the diseased kidney.

Transplantation studies, both in experimental animals and humans, documented that „blood pressure goes with the kidney": a normotensive recipient of a kidney genetically programmed for hypertension will become hypertensive, while conversely hypertensive patients with renal failure receiving the kidney of a normotensive donor may become normotensive. Family studies showed higher blood pressure values and more frequent hypertension in first degree relatives of patients with primary glomerulonephritis or diabetic nephropathy, suggesting that genes coding for hypertension increase also the risk of renal disease.

The mechanisms through which blood pressure increases in renal disease comprise: salt and water retention, inappropriate activity of the renin angiotensin system (RAS) and of the sympathetic nerve system as well as impaired endothelial cell-mediated vasodilatation.

There is ample evidence, both in primary renal disease and in nephropathy of type 1 or type 2 diabetes, that pharmacological blockade of the RAS by angiotensin converting enzyme inhibitors (ACEI) or angiotensin II type 1 receptor blockers (ATRB) has blood pressure-independent renoprotective effects, and may reduce proteinuria. Since, according to recent concepts, proteinuria is a „nephrotoxin", apart from blood pressure, proteinuria is a further (and partially blood pressure independent) indication for antihypertensive treatment using ACEI or ATRB for patients with diabetic nephropathy or primary renal diseases.

Key-words: **hypertension, kidney, renal disease, renin angiotensin system, proteinuria**

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1. THE ROLE OF THE KIDNEY IN THE GENESIS OF HYPERTENSION About 20% of the adult population suffer from hypertension. In about 90% no evident organic cause can be detected (essential hypertension). *Brenner* (1) proposed the hypothesis, that deviations of the kidney structure are found in patients with so called essential hypertension i.e. a reduced number of glomeruli and nephrons, so called „nephron underdosing". This hypothesis is supported by a number of experimental and clinical observations. A recent experimental study on mice with a mutation resulting in reduced nephron

number demonstrated, that these mice have elevated blood-pressure, but normal GFR. Stereologic investigation of the kidney revealed significant glomerular enlargement (2). Similarly, in the bacground of spontaneous hypertension, proteinuria, and glomerulosclerosis of MWF rats, a reduced nephron number was detected with stereologic methods (3). *Recently, Keller et al* (4) counted the number of glomeruli in 10 middle aged victims of fatal accidents in whom hypertension and/or left ventricular hypertrophy was present and in 10 normotensive control victims matched for age, sex and body mass index. The number of glomeruli and glomerular volume were investigated stereologically with a modified Gundersen fractionator method. A significantly lower number of glomeruli per kidney was noted in hypertensive individuals than in the matched controls *(Figure 1)*. At the same time, the glomerular volume was significantly greater in hypertensive individuals than in matched controls *(Figure 1)*. Such increase in glomerular volume may constitute a compensatory mechanism. Of course it was important to exclude one artefact, i.e. that in hypertensive patients the glomeruli were simply obliterated or had completely disappeared as a result of hypertensive damage. In this study there was no histological evidence of glomerular loss (hypertensive nephropathy).

The findings of this postmortal human study fits nicely with a series of animal experiments which have shown that hypertension and normotension can be transferred from a donor to a recipient by transplanting a kidney, i.e „blood pressure goes with the kidney" (5-7). The most elegant studies on this topics were reported by *Rettig et al* (6). He showed that, transplantation of a kidney from a genetically hypertension-prone donor rat, even when it had been kept normotensive from weaning by antihypertensive medication, caused a progressive increase of blood pressure in a recipient animal which was immunologically manipulated to prevent rejection. This finding is extremely interesting: a kidney genetically programmed to develop high blood pressure forces an organism programmed for normotension to develop hypertension, although the recipient's central nervous system, volume control systems, sympathetic nervous system, heart function etc are all geared for normotension. In contrast, and quantitatively less impressive, transplantation of a kidney from a donor genetically programmed for normotension lowered blood pressure in the recipient (7). Although animal experiments are very nice, most reader of this paper deal with hypertensive patients and not hypertensive rats. Is the above experimental observation also true for humans? Of course, no controlled studies are available where kidneys from patients with essential hypertension were transplanted to normotensive recipients or conversely. However uncontrolled data strongly suggest that recipients of kidneys from donors with essential hypertension develop hypertension more frequently than recipients of kidneys from normotensive donors (8, 9). It has also been shown that kidney graft recipients required more antihypertensive medication if the grafts had been obtained from genetically hypertension-prone donors (8). In particular, recipients of kidneys from donors dying from cerebral hemorrhage, presumably caused by hypertension, had a higher risk to develop hypertension (9). Because of numerous

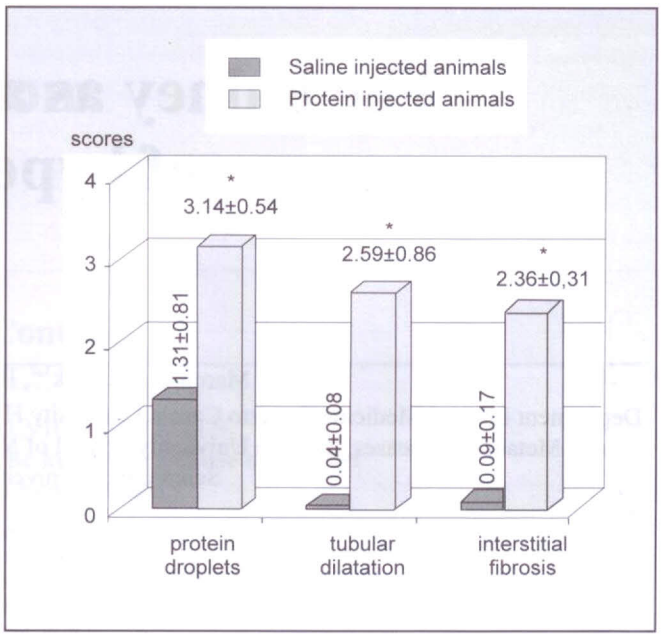

Figure 1 **Number of glomeruli and glomerular volume in 10 middle aged victims of fatal accidents in whom hypertension and/or left ventricular hypertrophy was present compared to 10 normotensive controls of the same age, sex and body mass index**
Modified after Keller et al (2)

confounding factors such as: the effects of brain death on graft function (10), bloodpressure eleveating effect of calcineurin inhibitors etc. the findings of such studies must be taken with a grain of salt. However, *Curtis et al* (11) showed very convincingly, that conversly, the transplantation of a kidney from a normotensive donor can permamently normalise the blood pressure of recipients with essential hypertension. He studied 6 black patients with essential hypertension of unknown origin who became dialysis dependent as a result of hypertensive nephrosclerosis without any histologic signs of primary kidney disease. After these patients had received a kidney from a normotensive donor, all of them became normotensive and this persisted during a 4.5 years follow up. There was evidence of reversal of hypertensive damage to the heart and retinal vessels, and of completely normal blood pressure responses to salt deprivation and salt loading.

Which factors, genetic or environmental, could be potentially responsible for the hypertensinogenic effects of the kidney and, according to Brenner's hypothesis for so called „nephron underdosing"? Since the pioneering experiment of *Weitz* in the 20-ies of the last century we know that genetic factors play a key role in essential hypertension (12). We must, therefore, suppose that the number of functional nephrons is genetically determined. This hypothesis is also supported by the race dependent differences in glomerular count in humans (13). However, there are also many animal experiments and human studies which suggest that during the fetal period environmental factors may also influence renal

development. *Langley et al* (14) have shown that dietary protein restriction of pregnant rats caused high blood pressure in the offspring. In humans *Merlet-Benichou et al* (15) showed that newborns with lower birth weight (as an indirect sign of fetal malnutrition) had a lower nephron number than newborns with normal birth weight.

The role of the kidney in the pathogenesis of essential hypertension is probably not only due to potential structural alterations, such as lower nephron number, but also due to changes in kidney function. Based on experimental evidence 3 decades ago *Guyton* (16) proposed the hypothesis that a disturbance of the blood pressure/natriuresis relationship („renal function curve") is responsible for blood pressure elevation in any form of hypertension. According to this concept, because the gain of the blood-pressure-natriuresis relationship overrides all other regulatory systems, the ultimate determinant of blood pressure must always be the renal handling of sodium. It is interesting that renal function, as reflected by the blood pressure-natriuresis – relationship, can be disturbed as a consequence of extrarenal causes. *Lombardi et al* (17) performed a very interesting experiment. In normotensive rats an increase in dietary sodium intake did not increase blood pressure because the blood pressure/natriuresis relationship was normal. However when normotensive rats had temporarily been rendered hypertensive by infusing angiotensin II and after they had subsequently become normotensive when angiotensin II infusion had been stopped, they had permanently become „sodium sensitive". The kidney „remembered" so to speak the injury induced by angiotensin II. If these animals were later exposed to a high sodium intake their blood pressure increased and they again developed hypertension. The shift of the blood pressure-natriuresis-relationship under hormonal influences such as mineralo and glucocorticoid excess (18), testosteron (19) and estrogen (20) etc is well known. However it is also interesting that for example dietary factors such as high intake of unsaturated fatty acid (21), or high potassium intake (22, 23) can shift this relationship. These experimental findings prompted the DASH study, designed to investigate the influence of such dietary factors on blood pressure in humans (24).

2. RELATION BETWEEN RENAL DISEASE AND BLOOD PRESSURE It is well known that primary kidney diseases causes hypertension. Which mechanisms cause the increase of blood pressure in kidney disease?

Patients with kidney diseases are characterized by a disturbance of the blood pressure/natriuresis relationship. Elegant evidence for disturbed renal sodium excretion leading to hypervolemia was provided by *Schmid et al* (25). In his study blood pressure of patients with polycystic kidney disease (PKD) was increased after a high sodium load, even when glomerular filtration was still normal. In PKD patients, concentrations of atrial natriuretic peptide (ANP) were higher indicating hypervolemia, both at low and high sodium intake.

It is well known that in patients with primary renal disease the activity of the renin-angiotensin system is inadequately high. *Kuczera et al* (26) showed in the isolated perfused hindlimb preparation of subtotally nephrectomized rats that this is true not only for the renal, but also for the local renin-angiotensin system of the vessel wall. In the kidney an important (but not the sole) mechanism, responsible for increased and unregulated renin secretion is luminal narrowing of preglomerular vessels because of vascular sclerosis. Consequently the baroreceptor will measure a falsely low perfusion pressure analogous to the kidney with a Goldblatt clip on the renal artery. More renin will therefore be secreted. In subjects with healthy kidneys plasma renin activity falls asymptotically with increasing blood pressure. In contrast in patients with kidney disease renin secretion is inadequately suppressed and plasma renin activity remains inappropriately high. In the past it was thought that the above two mechanisms i.e (a) alterations of the pressure/natriuresis relationship and (b) high activity of renin systems were the sole cause of hypertension in kidney disease. Today we know that this concept is an oversimplification.

DiBona et al (27) showed that the kidney contains chemoreceptors and baroreceptors. These receptors are stimulated in a diseased kidney (28). Afferent signals then travel to the hypothalamus where the activity of the centers controlling sympathetic tone is increased (29). This causes elevation of the efferent sympathetic nerve activity. This phenomenon is not only important for the development of high blood pressure, but also for progression of kidney disease. Non-hypotensive doses of the central sympathicoplegic agent moxonidine reduced the development of glomerulosclosis and of albuminuria in subtotally nephrectomized rats (30). That this effect is not unique to the centrally acting drug moxonidine is shown by further experiments: metoprolol at doses which failed to affect systemic blood pressure (31), or surgical denervation of the kidney had a similar renoprotective effects (28, 29). This opens of course perspectives for the therapy of kidney diseases.

Is the sympathetic activity elevated in humans with kidney diseases as well? Converse et al (32) was the first to use microneurographic techniques and to document that sympathetic activity of the sural nerve was increased in dialysis patients. The number of discharges was doubled in hemodialyzed patients with chronic renal failure as compared to controls. On the other hand if the non-functional kidneys of dialysed patients had been removed by binephrectomy the frequency of discharges was completely normalized (32). Recently, Hausberg et al (34) showed that correction of uremia by kidney transplantation did not normalise elevated sympathetic nervous activity. It was normalized, however, by nephrectomy of the recipients own kidneys. These observations provide evidence that afferent signals emanating from the kidney cause sympathetic overactivity in humans as well.

Interestingly there are interactions between the renin angiotensin system and sympathetic nerve system. *Ligtenberg et al* (35) found that the elevated sympathetic activity of patients with chronic renal failure decreased after administration of an angiotensin converting enzyme inhibitor. The same was recently showed by *Klein et al* (36) with respect to angiotensin II receptor type 1 blocker. This could be one of the reasons why angiotensin converting enzyme inhibitors and angiotensin II receptor type 1 blockers prevent progression of kidney diseases.

Table 1. **Blood pressure status, venticular septum thickness (VS) and mitral inflow velocity (E/A= velocity, early diastole/atrial contraction) in patients with IgA glomerulonephritis and normal inulin clearence** [after ref (37)]

	Casual BP (mmHg)		24-h BP (mmHg)		Day-time BP (mmHg)		Night-time BP (mmHg)		VS (mm)	E/A ratio (m/s)
	Syst	Diast	Syst	Diast	Syst	Diast	Syst	Diast	Syst	Syst
Glomerulo-nephritis (n=20)	125 (110-140)	80 (70-90)	124.5 (107-135)	76.5 (69-84)	129 (107-141)	82 (73-88)	111 (97-129)	64.8 (56.5-72)	9.0 (7-12)	1.77 (1.03-2.42)
Matched controls (n=20)	120 (105-130)	72,5 (60-85)	114.5 (106-135)	70.5 (62-79)	119 (108-144)	75 (66-87)	103 (91-117)	58 (48-70)	8.0 (7-9.5)	2.29 (1.61-3.19)
p	0.04	0.04	0.007	0.0006	0.012	0.003	0.003	0.001	0.001	0.0003

Clinical and experimental evidence shows that patients with chronic renal failure have a significantly greater incidence of cardiovascular complications (37). In this context there is of interest, that endothelial dysfunction has been demonstrated, which is in part due to reduced nitric oxide (NO) production (38). This leads to reduced endothelial cell dependent vasodilation (39). One of the possible causes of reduced NO production is the inhibition of NO synthase (NOS) by the competitive antagonist asymmetric dimethyl arginine (ADMA). An elevated plasma concentration of ADMA was found even in renal patients with normal inulin clearance (40). According to our observations in vitro, a complementary abnormality reducing NO dependent vasodilation, is reduced NO bioavailability in uremic rats (41) and patients (42) presumably secondary to scavanging by reactive oxigen species. In any case, endothelial NO dependent vasodilation is impaired in uremia, contributing to increased total peripheral resistance.

In summary, a number of factors participate in the pathogenesis of hypertension of patients with kidney disease:

- disturbed pressure-natriuresis relationship causing sodium retention,
- inappropriately high activity of renin-angiotensin system
- increased activity of the sympathetic nervous system and
- endothelial cell dysfunction leading to reduced vasodilation.

3. AT WHAT STAGE OF KIDNEY DISEASE DOES BLOOD PRESSURE INCREASE? In the past, the misconception prevailed that blood pressure increased only once glomerular filtration rate was markedly reduced. This view is definitely not correct. In children with a nephrotic syndrome, *Küster et al* (43) found that blood pressure values were systematically higher during the nephrotic episode than after remission of the disease. That a reduction of whole kidney glomerular filtration rate (GFR) is not a prerequisite for the increase in blood pressure was also shown by *Stefanski et al (Table 1)* (44). In patients with biopsy-confirmed IgA glomerulonephritis and normal inulin clearance, he observed higher 24 h blood pressure values and this was accompanied by greater septal thickness and evidence of impaired compliance of the left ventricle. Thus blood pressure (especially nighttime blood pressure) increases and leads to target organ injury even when overall GFR is still normal. (A normal overall GFR does of course not preclude loss of nephrons since single nephron GFR is compensatorily increased in the remnant nephrons.) Consequently we propose that such patients should be treated with antihypertensive drugs even when blood pressure values are still in the range of normotension.

4. GENETIC PREDISPOSITION TO HYPERTENSION INCREASES THE RISK TO DEVELOP RENAL DISEASE It has recently emerged that the relationship between kidney disease and hypertension is quite complex. Whilst undoubtedly renal disease causes hypertension, there is increasing evidence that a genetic predisposition to hypertension increases the risk to develop renal disease. This has been shown in patients with glomerulonephritis *(Table 2)* (45). Blood pressure values were higher in the parents of

Table 2. **Blood pressure status of parents with biopsy-confirmed glomerulonephritis and controls** [after ref (38)]

	Glomerulonephritis (n=39)	Control (n=87)
Hypertensive	43 (68%)	56 (41%)*
Normotensive	20 (32%)	82 (59%)

Significant difference (by χ^2 test) between hypertensives versus others with glomerulonephritis and controls. Hypertensive – blood pressure ≥140/90 mmHg or on antihypertensive medication

patients with glomerulonephritis than in the parents of matched controls. The same is true for diabetic nephropathy. Higher blood pressure values were found in parents of type 1 diabetic patients with as compared to parents of patients without nephropathy (46). *Strojek et al* (47) found higher blood pressure values by ambulatory blood pressure measurement in offsprings of type 2 diabetic patients with, as compared to offsprings of type 2 diabetic parents without diabetic nephropathy *(Table 3)*. In the offsprings of diabetic parents with nephropathy, blood pressure was also sodium-dependent compared to offsprings of diabetic parents without hypertension. The increased salt sensitivity is therefore possibly an interesting intermediate phenotype predisposing to the development of kidney disease.

Table 3. **Blood pressure and urinary albumin excretion in offspring of parents with type 2 diabetes according to absence or presence of diabetic nephropathy in the parents** [after ref (40)]

	Parents type 2 diabetes	
	Without nephropathy offspring (n=30)	With nephropathy offspring (n=26)
Ambulatory blood pressure (mmHg systolic)	117 ±12.9	125 ±16.9
Albumin excretion rate (g mL^{-1})	4.8 (0.36–17.5)	7.8 (1.04–19.0)
Increase in urinary albumin after ergometry	6.3 fold (1.5–231)	16-fold (1.2–236)

5. WHAT IS THE APPROPRIATE TARGET BLOOD PRESSURE IN PATIENTS WITH KIDNEY DISEASE?

There has been increasing recognition in recent years that elevation of blood pressure or frank hypertension are factors of overriding importance in the progression of renal failure. The deleterious effect of high blood pressure values on progression has first been proven by observational studies in diabetic (48, 49) and later non-diabetic renal disease (50). However, observational studies do not prove causality. To this end, interventional studies are necessary. Meanwhile, it has been shown that lowering of blood pressure by antihypertensive medication attenuates progression of renal insufficiency both in patients with diabetic and nondiabetic renal disease *(Table 4)*. Once the detrimental effect of high blood pressure on progression of renal disease had been established,

Table 4. **Selected studies showing renoprotective properties of angiotensin converting enzyme inhibitors (ACEI) or angiotensin II receptor type 1 antagonists (ATRB)**

Study (Reference)	AIPRI (53)	REIN (54)	Lewis et al. (55)	IDNT (56)	RENAAL (57)
Study group	Various nephropathies*	Non diabetic nephropathy	Nephropathy in type 1 diabetes	Nephropathy in type 2 diabetes	Nephropathy in type 2 diabetes
Sample size	583	323	409	1715	1513
Planned duration of follow-up (years)	3.0	2.2	3.0	2.6	4.5
Study medication (ACEI or ATRB)	Benazepril	Ramipril	Captopril	Irbesartan	Losartan
Dosage of study medication (mg/d)	10	1.25–5.0	75	75–300	50–100
Baseline serum creatinine concentration (μmol/l)	186	194	115	148	168
Relative risk (95% CI) of ESRD in the treated group	0.89 (0.06-14.2)	0.51 (0.30-0.87)	0.50 (0.18-0.70)#	0.83 (0.62-1.11)	0.75
Relative risk (95% CI) of doubling serum creatinine in the treated group	0.44 (0.27-0.70)	0.47 (0.29-0.77)	0.48 (0.16-0.69)	0.71 (0.54-0.92)	0.72

* mainly non diabetic nephropathy - diabetic nephropathy was the cause of renal insufficiency only in 21 of 583 patients,
# combined end points (death, dialysis or kidney transplantation) relative risk

an important issue arose i.e. which blood pressure value is optimal for the patient with progressive renal disease?

There is a continuous increase of renal risk with increasing blood pressure without a definite threshold. One piece of observation comes from the study of *Opelz et al* (51) that in renal graft recipients (as one model of renal damage) 6 year graft survival is progressively worse for increasing levels of systolic blood pressure measured 1 year after kidney transplantation (at the time when postoperative technical and immunological problems have mostly been eliminated). The relative risk of graft loss for a systolic blood pressure between 140-149 mmHg was higher by 19%, and for values above 179 mmHg the relative risk was even increased by 117%. The relationship between systolic blood pressure and graft function was especially impressive in young graft recipients. In young recipients even more so than in adults systolic blood pressure values still in the normal range significantly increased the risk of transplant failure.

Interestingly systolic blood pressure was much more predictive than mean or diastolic blood pressure. This observation is surprising because normally the glomerulus is protected against the pulsatile variation of blood pressure in the aorta by the high resistance of preglomerular arteries. This paradoxical observation can be rationalized with the concept that in the acutely injured kidney afferent preglomerular vessels vasodilate as a response to the acute injury. Such dilated vessels are not able to autoregulate to the pressure load, so that aortic blood pressure, and its pulsatile variation, can be more easily transmitted into the glomerular vascular bed, causing glomerular hypertension (52, 53). In the long run, the afferent vessels will develop sclerotic lesions as well, further contributing to conduction of systemic pressure into the glomeruli.

The transplanted kidney graft is a good model of kidney injury and „mutatis mutandis" the same should be true for diabetic or nondiabetic kidney disease. One could argue that in hypertensive graft recipients an elevated systolic blood pressure only indicates that latent kidney injury is present which could not yet be detected by measuring serum creatinine concentrations. For several reasons this is extremely unlikely. The most convincing argument comes from the observation that the same relationship between systolic blood pressure 1 year after transplantation and 7 year graft survival is found in transplant recipients without any rejection episodes within the first year after transplantation. In other words, high blood pressure is associated with long term outcome even in the absence of rejection. This observation is consistent with the hypothesis that blood pressure is, at least in part, the cause, and not the consequence, of kidney malfunction.

The concept that there is a continuous increase of renal risk with increasing blood pressure without a definite threshold has recently been confirmed by a meta-analysis of all controlled intervention trials in patients with non-diabetic renal disease. The best renal prognosis was found in individuals with systolic blood pressure values lower than 110 mmHg (54). *Peterson et al* (55) analysed the data of The Modification of Diet in Renal Disease Study (MDRD) and showed that in patients with proteinuric renal disease a direct relationship existed between achieved blood pressure and loss of renal function. The lower the achieved mean arterial pressure values, the lower the rate of loss of glomerular filtration rate (GFR). A minimum rate of loss of GFR was seen when a mean arterial blood pressure of 85–90 mmHg was reached. More recently, *Schrier et al* (56) showed that in normotensive patients with diabetes mellitus type 2, intensive (≈128/75 mmHg) as compared to moderate (≈137/81 mmHg) blood pressure control, resulted in decreased progression from normalbuminuria to microalbuminuria and from microalbuminuria to overt proteinuria.

As a result, today there is widespread consensus that in patients with proteinuric renal disease, blood pressure should be lowered to values below the currently accepted upper value of normotension, i.e. 130/85 mmHg (57, 58). Most authorities propose a target blood pressure of 120/75 mmHg (59, 60). Such low blood pressure values are beneficial also for prevention of target organ damage in other organ systems such as the heart or brain. Nevertheless, therapeutic lowering of bloodpressure must be done slowly, because of endothelial dysfunction and impaired vasodilation in hypertensive patients, and stenotic lesions of the extracranial vessels have to be excluded (61).

6. SHOULD ANTIHYPERTENSIVE AGENTS BE ADMINISTERED ACCORDING TO BLOOD PRESSURE ONLY? First animal experimental evidence suggested, the superior effect of antihypertensive drugs targeted at the renin-angiotensin system, compared to antihypertensives not influencing the renin-angiotensin system (62). A number of prospective clinical studies showed that the intensity of proteinuria is closely related to the rate of renal failure progression, both in diabetic and nondiabetic nephropathies. Drugs blocking renin angiotensin system have shown striking antiproteinuric properties. Therefore there is no more doubt that pharmacological blockade of this system by administration of angiotensin converting enzyme inhibitors (ACEI) or angiotensin II receptor type 1 blockers (ATRB) provides blood pressure-independent renoprotection. The results of the major studies, i.e. the AIPRI (63) and REIN (64) trials in non-diabetic renal disease and the Lewis trial in type 1 (65) as well as the IDNT (66) and RENAAL (67) trials in type 2 diabetes are summarised in table 4. In one of the above mentioned studies performed by the Gruppo Italiano di Studi Epidemiologici in Nefrologia (63) patients with proteinuria <1 g; 1–3 g and >3 g per day were treated either with an ACEI (Ramipril) or placebo. Under placebo the loss of GFR increased with increasing proteinuria. On the other hand it was the high risk patients with high proteinuria who had the most pronounced advantage from treatment with Ramipril. This benefit was independent of blood pressure, because patients in both groups were treated to reach identical casual blood pressure values.

Why is proteinuria so destructive to the kidney? According to recent concepts, proteinuria is a „nephrotoxin" (68) and exposure of tubular epithelial cells to protein induces cell activation and causes an inflammatory phenotype (69). Recently *Gross et al* (70) elegantly proved this point in amphibians. The kidneys of Axolotl contains not only closed

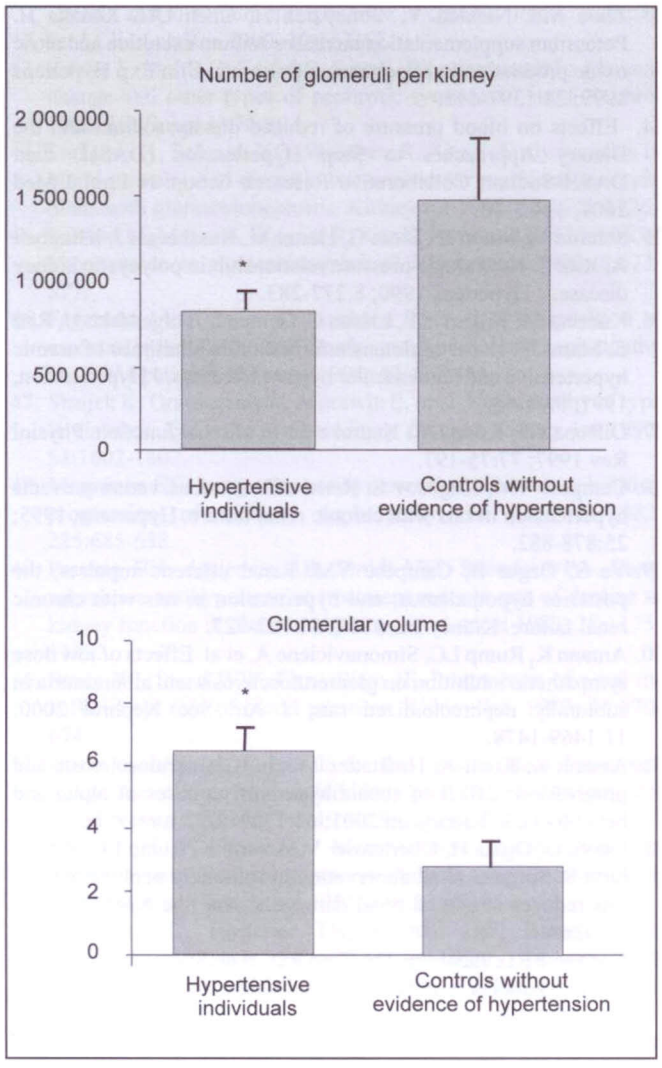

Figure 2 **Morphological features of renal damage in the amphibian kidney (Axolotl) after injection of protein into the peritoneal cavity. Protein droplets, tubular dilatation and interstitial fibrosis were evaluated using a scoring system (scores from 1 to 4). Data taken from Gross et al (60).**

nephrons receiving filtrate from glomeruli, but also nephrons with ciliated peritoneal funnels that have access to the peritoneal fluid. Injection of protein into the peritoneal cavity fails to expose closed nephrons to a protein load, but causes selective uptake and storage of proteins in tubular epithelial cells of nephrons which have access to peritoneal cavity. Protein-loaded tubuli showed luminal dilatation and accumulation of protein and lipid containing droplets. This was accompanied by fibrosis in the interstitium surrounding protein-loaded nephrons but not the other nephrons *(Figure 2)*. The protein loaded tubular cells exhibited pronounced immunohistochemical staining for TGF-beta, fibronectin and collagen I. This experiment proves that proteinuria is not merely a marker of the severity of glomerular injury, but also a direct tubulotoxic agent. Therefore interventions that reduce proteinuria should be beneficial for the maintenance of kidney function.

Praga and Morales (71) recently documented that even in normotensive patients (mean arterial blood pressure 82 mmHg) long-term ACEI treatment caused a sustained decrease of proteinuria while renal function remain stable. In patients with IgA nephropathy Palla et al (72) showed that increasing the dose of ACEI resulted in progressive reduction of proteinuria, although blood pressure values were not reduced any further. In animal experiments increasing the dose of ACEI led to blood pressure independent clear-cut further reduction of progression (73). Without going into details the cause why doses which failed to further lower blood pressure are beneficial is probably that in the renal interstium and in the tubular fluid the concentration of angiotensin II is about 100 times higher than in the plasma (74). The angiotensin II concentration in these fluids is only minimally influenced by systemic application of Enalapril suggesting that penetration into deep compartments is problematic. In this study interestingly differences were found between different ACEI and ATRB. The opinion is widely held that when proteinuria in a renal patient exceeds 1 g per day, the dose of ACEI or ATRB should be further increased until proteinuria is reduced to the target value.

Based on the data of the MDRD study (55) Peterson et al postulated that in patients whose urinary protein excretion exceeded 1 g per day one should aim for blood pressure values of at least 125/75 mmHg in order to maximally reduce the rate of progression of renal insufficiency. In the patient with a lower rate of protein excretion higher blood pressure value can be accepted. It is reasonable to think, however, that in the long run, lower blood pressure values are better even in these patients.

In conclusion it should be stated that in patients with diabetic and nondiabetic renal disease proteinuria is a further, and partially blood pressure independent, indication for antihypertensive treatment with ACEI and ATRB.

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