The ACE (I/D) polymorphism and the RAAS in type 1 diabetes mellitus

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Section III

Diabetic Nephropathy

Chapter 7

A comparison of progression in diabetic and non-diabetic renal disease: similarity of progression promotors.

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The Kidney and Hypertension in Diabetes Mellitus, 6th Edition
C.E.Mogensen, EditorMartin Dunitz, Ltd.

The prevention of progressive renal function loss remains the major challenge for nephrologists today. Traditionally the progressive nature of renal function loss was attributed to the underlying disease, with a major role for hypertension (1). The hypothesis, however, that common mechanisms account for progressive renal function loss in many different renal conditions regardless the nature of initial renal damage (2) was fueled by several observations. These include the linear renal function deterioration that occurs in many patients regardless their initial renal disease (3), as well as the similarity in histopathological abnormalities in end-stage kidneys with different underlying diseases. Systemic (4) and glomerular hypertension, proteinuria (5) and lipid abnormalities (6) are assumed to be common mediators in the pathogenesis of focal segmental glomerulosclerosis, the alleged final common pathway of progressive renal disease (7). Here we will briefly review current knowledge on progressive renal function loss in human diabetic and non-diabetic renal disease and on the response to intervention treatment. We will focus on clinical evidence regarding the hypothesis that common mechanisms underlie progressive renal function loss in diabetic and non-diabetic renal disease; this will help to devise future prevention strategies.

Natural history

The initiation and progression of renal damage

In type 1 DM the natural history of nephropathy is well-characterized, as, contrary to non-diabetic renal disease and partly type 2 DM, most patients come to medical attention years before renal abnormalities develop. It is still not understood why some 30 to 40 per cent of diabetic patients develop nephropathy whereas others don't; familial clustering, however, since long suggests genetically determined susceptibility (8;9) and indeed, for type 2 DM genetic factors predisposing to nephropathy were recently identified (10). In diabetic patients that develop nephropathy, a typical, biphasic clinical course of renal function occurs, with elevated GFR in the early stages, followed by micro-albuminuria (11;12). The elevated GFR presumably reflects glomerular hypertension, due to afferent arteriolar dysfunction with increased transmission of systemic pressure to glomerular capillaries. The ensuing glomerular capillary damage and protein leakage are important mechanisms in initiation and perpetuation of renal damage in these patients (13). These functional abnormalities are accompanied by renal and glomerular enlargement (14).

The transition from normoalbuminuria to microalbuminuria is associated with a slight increase in systemic blood pressure (15). When micro-albuminuria progresses to overt proteinuria, usually in association with a further rise in arterial blood pressure, glomerular filtration rate decreases, and gradual progression to end-stage renal failure occurs, albeit with large interindividual differences in progression rate (11). In type 2 DM the sequence of events in development of nephropathy is somewhat more complicated to unravel, as patients present at a later stage, often have pre-existent hypertension, and moreover renal abnormalities are already present in a considerable proportion of the patients by the time diabetes is diagnosed. Yet, recent data support a bifasic course of GFR in type 2 DM as well (12). Moreover, data in a cohort of type 2 DM patients normotensive at diagnosis support the concordance of albuminuria and a rise in blood pressure during follow-up in this population as well (16).

In non-diabetic renal disease the factors that initiate renal damage are heterogeneous, and can include primarily glomerular or vascular, or tubulo-interstitial damage. Little is known about possible factors preceding the development of non-diabetic renal disease, as by the time patients come to medical attention overt renal damage is usually present. Patients with hypertension may be an exception. Remarkably, microalbuminuria (17) as well as glomerular hyperfiltration (18), two hallmarks of incipient diabetic nephropathy, occur in subsets of patients with essential hypertension. In the general population an association between high-normal blood pressure and albuminuria was observed as well (19). Interestingly, in the general population we observed a biphasic relationship between albuminuria and creatinine clearance with a striking similarity to the pattern in diabetes, with an association between hyperfiltration and micro-albuminuria or high high-normal albumin excretion and hypofiltration becoming more prevalent among those with macroalbuminuria (20). Whereas in non-diabetic populations the prognostic value of microalbuminuria and glomerular hyperfiltration for long term renal function are not yet established, nevertheless, these data suggest that the sequence of events in diabetic and nephropathy also occurs in at least some forms of non-diabetic renal damage.

The contribution of factors specific for the underlying disease as determinants of progression rate relative to common factors is not equivocal - and probably not uniform -across different renal conditions. In diabetes, the impact of glycemic control on renal prognosis in type 1 DM and type 2 DM represents a clear-cut diagnosis-specific renal risk factor (21;22). In non-diabetic patients, studies on the role of the underlying disorder provide conflicting data, with no effect of underlying disease on progression rate in some studies (3;23), whereas other studies found a faster progression rate in glomerulonephritis

and diabetic nephropathy than in chronic pyelonephritis, analgesic nephropathy or hypertensive nephrosclerosis (5;24-29). In most studies, polycystic kidney disease is associated with a faster progression rate as well (26;29-32) although not uniformly so (5;18). Taken together, the nature of the underlying disease appears not to be indifferent to the rate of long-term renal function loss. Of note, in conditions where the primary cause of damage can be reliably eliminated (such as obstructive uropathy, analgesic abuse, or primary hypertension) the course of renal function is more favorable than in conditions where the initiating factors cannot (or not reliably) be annihilated (e.g diabetic nephropathy, glomerulonephritis, or polycystic kidney disease). This suggests that either primary causes still exert effect, or that they trigger the alleged common perpetuating factors to a greater extent than other conditions.

Whereas in nephropathy due to type 1 DM, linear progression appears to be the rule (33), in non-diabetic renal disease (5;30) or type 2 DM (34), considerable subpopulations (up to 20-25% of the patients) may have stable renal function or non-linear progression. Such a heterogeneity in patient populations might partly explain the difficulties in reproducing clear-cut renoprotective effects obtained by specific treatment modalities in experimental animals, in particular for nondiabetic renal disease (5;35).

Common progression promoters

In diabetic as well as non-diabetic populations (3) considerable interindividual variability is apparent in the rate of renal function loss for any given disease. Many studies investigated the determinants of this variability (see also Table 1), evaluating the clinical relevance of common progression promoters identified in experimental renal disease, such as systemic and glomerular hypertension, proteinuria, lipid abnormalities, obesity, low grade inflammation and smoking. In the interpretation of these studies, however, the close interaction of these factors as to their effects on long-term renal function (2) should be kept in mind. As a consequence, their respective contributions are often hard to dissect.

In both diabetic (36;37) and non-diabetic renal disease (5;31;32;38) the severity of proteinuria is a predictive factor for progression rate. Interestingly, Wight (31) showed that differences in progression rate between most renal conditions were no longer apparent after correction for proteinuria (with the sole exception of polycystic kidney disease). Moreover, the association between proteinuria and progression not only occurs in conditions where proteinuria might reflect activity of the primary glomerular disorder, such as diabetic nephropathy and glomerulonephritis, but also in chronic pyelonephritis (5).

Table 1. Clinical characteristics of progressive renal function loss in diabetic and non-diabetic renal disease

	Diabetic nephropathy	**Non-diabetic nephropathy**
natural history		
Course of renal hemodynamics	Typically biphasic	Possibly biphasic in some conditions
renal function loss	Invariably progressive	Progressive in many patients
predictors of progression	Diabetes control Proteinuria Blood pressure Cholesterol DD genotype ACE gene Obesity (type 2 DM)? Smoking Low-grade inflammation?	Underlying disease Proteinuria Blood pressure Cholesterol DD genotype ACE gene Obesity Smoking Low-grade inflammation?
Prevention of progressive renal function loss		
Protein restriction	Probably effective	Effective
Antihypertensive therapy	Effective	Effective; benefit proportional to severity of proteinuria.
Predictors renoprotection	Initial antiproteinuric effect Initial renal hemodynamic effect	Initial antiproteinuric effect Initial renal hemodynamic effect
Response to specific renoprotective drugs		
ACE inhibitors/ AT1 blockers	Reduce proteinuria Reduce progression rate Independent from blood pressure effect	Reduce proteinuria Reduce progression rate Independent from blood pressure effect
Non-ACE inhibitor antihypertensives	Reduce proteinuria in a strongly pressure-dependent fashion	Slight, pressure-dependent effect on proteinuria

Taken together, this evidence strongly suggests that, once a certain renal disorder is present, the severity of proteinuria rather than the underlying disorder per se predicts renal outcome. The case of polycystic kidney disease however, illustrates that disease-specific mechanisms may predominate over common mechanisms in some conditions (39;40).

Importantly, the reduction of proteinuria at onset of antihypertensive therapy predicts

the subsequent course of renal function, in both non-diabetic (41) and diabetic (42) proteinuric renal patients. Remarkably, this is independent of the way the reduction of proteinuria was achieved (i.e. drug therapy or low protein diet (32;43) or class of drug (41)). For therapeutic purposes, importantly, this allows early identification of patients who need more aggressive renoprotective intervention. The pathophysiological basis of the prognostic impact of antiproteinuric response is likely to be twofold. First, the reduction in proteinuria identifies subjects with less severe renal structural damage – as suggested by retrospective data in man (44), and by prospective data in experimental proteinuria (45). Although difficult to substantiate prospectively in man, these data would implicate that renoprotective efficacy could be optimized by starting as early as possible in the course of the disease, which can be considered in line with the data in diabetic subjects – where ACE inhibition has been shown to be effective not only in the treatment, but also in the prevention of progression towards nephropathy (16). Second, a poor antiproteinuric response leads to a higher residual proteinuria, which in turn further aggravates renal damage. In addition to the early antiproteinuric response, also the early response of glomerular filtration to antihypertensive therapy predicts the subsequent course of renal function in diabetic as well as non-diabetic patients with a more favorable course in subjects with a slight initial drop in filtration - presumably reflecting a drop in filtration pressure . Again, this predictive effect does not depend on the mode of intervention, as it occurs irrespective of the class of drug (i.e ACEi or beta-blocker) and also applies to the early response to low protein diet (43).

As to hypertension, in type 1 DM the development of hypertension is closely associated with transition from normoalbuminuria to microalbuminuria (15) and subsequently with further progression to overt proteinuria and progressive renal function loss (46-48). In type 2 DM, the timecourse is less extensively documented, and presumably more diverse, as almost half of the patients is hypertensive at the time of diagnosis (49), yet blood pressure was found as a major risk factor for the progression to diabetic nephropathy (16;50). In non-diabetic renal disease also, high blood pressure is usually associated with a poor renal outcome (23;26;31;32), and moreover, the antihypertensive response to treatment is associated with reduction of the rate of renal function loss (4). Blood pressure was a strong predictor for end stage renal failure in the large MRFIT cohort (51). Yet, somewhat surprisingly, several studies in renal patients failed to demonstrate that blood pressure was an independent determinant of progression rate (5;25;26). In these studies, however, proteinuria and blood pressure were closely related and a predominant effect of proteinuria might obscure the role of a co-linear factor such as blood pressure.

Lipid profile is increasingly recognized as relevant to progression rate. An elevated

serum cholesterol is associated with a faster progression rate in type 1 DM (52;53), type 2 DM (16) and non-diabetic renal diseases (41;54). There is no definitive proof however, that this reflects an independent effect of lipids - as patients with more severe hyperlipidemia also tend to be the ones with the more severe proteinuria (55).

Morbid obesity - usually associated with impaired glucose tolerance, insulin resistance or overt diabetes - is a well-known cause for so-called obesity-related glomerulopathy, a proteinuric condition with glomerular enlargement and eventually glomerulosclerosis (56). Recent data support a role for less extreme obesity as a risk enhancer in primary renal conditions as well, i.e, IgA nephropathy (57), after unilateral nephrectomy (58) and in renal transplant patients (59), albeit not uniformely so (60). Elevated filtration pressure is likely to be involved as a mechanism, as suggested by the elevated GFR and filtration fraction in morbidly obese subjects and in obese hypertensives (61;62). This may promote proteinuria - as suggested by the beneficial effects of weight reduction on proteinuria in both non-diabetic and diabetic subjects (63). Remarkably the association between higher BMI and elevated filtration fraction is already present in moderately overweight subjects (64), suggesting that on a population basis the impact of excess body weight on renal risk may be larger than recognized. Considering the diabetes-like renal abnormalities in obesity and the alleged role of insulin resistance, one might expect BMI to be a prominent renal risk factor in diabetes as well - at least in type 2 DM. However, data are not uniform. Whereas Ravid et al found that higher BMI predicted faster progression towards albuminuria (16) - Lee et al reported a negative association between overweight and renal failure in type 2 DM (50) - a discrepancy that may partly be explained by competing cardiovascular and renal risks. In type 1 DM - where overweight is less prevalent - the role of BMI as a renal risk factor has not been well-defined - and is likely to be more complex considering the interactions between glycemic control and body weight (65).

Association studies suggested that low-grade inflammation might be associated with progressive renal function loss in diabetic (66;67) as well as non-diabetic renal disease (68) and in the general population. A post-hoc analysis of the MDRD-study, however, reported that higher CRP (and leptin) was not an independent risk factor for the progression of non-diabetic kidney disease (69). Further prospective studies are needed in this respect.

Smoking is increasingly recognized as a renal risk factor, as reviewed recently (70). In type 1 (71) and type 2 diabetes mellitus (72) smoking accelerates the rate of progression from microalbuminuria to macroalbuminuria and rate of progressive renal function loss. Prospective data in type 1 DM, however, could not confirm this (73). In non-diabetic subjects, smoking was associated with renal risk as well (74), in hypertensive renal damage

(75-77), as well as renal transplant recipients (78). Moreover, smoking is associated with albuminuria and a biphasic renal function pattern in the general population (79).

The recent developments in genetics provide a basis to unravel the genetic factors underlying in the interindividual difference in the progression of renal diseases. So far, most data are available on the insertion/deletion polymorphism of the ACE-gene, which was found to be a determinant of the rate of renal function loss in patients with non-diabetic (80) as well as diabetic nephropathy (81-83) with an increased rate of renal function loss in patients homozygous for the D-allele. However, the results from different studies are far from uniform, which should not come as a surprise for the role of a common genetic variant in a multifactorial condition like progressive renal function loss. Rather, this prompts to identify the conditions that allow this genetic variant to exert a pathophysiologically relevant effect. In this respect, it may be significant that a large prospective study in type 1 diabetes mellitus, found the D-allele to be a risk factor for progression of diabetic nephropathy especially when glycemic control was poor (84) suggesting gene-environment interaction with glycemic status. These data are in line with our observations on angI responses in uncomplicated type 1 DM, that also showed interaction between ACE-genotype and glycemic control (85). Moreover, interaction with sodium status was observed, which is in line with prior observations in non-diabetic subjects, where high sodium intake elicited differences in the responses of blood pressure and proteinuria to ACEi between the different genotypes (86). The interaction between ACE genotype and sodium intake was confirmed in a prospective study on angI responses in healthy volunteers (87). Data on the clinical impact of ACE genotype on the antiproteinuric response to ACE inhibition are so far conflicting in non-diabetic as well as diabetic patients and suggest impact of interaction with other factors, such as sodium status, and gender (86;88-91). Further studies will have to elucidate the nature of these interactions.

Response to renoprotective treatment

As a matter of clinical common sense, renoprotective treatment should, first, aim at eliminating primary damaging factors. This may halt progression in some patients with specific disorders, such as obstructive uropathy (5) and analgesic nephropathy (92). In diabetes, strict metabolic control can reverse early hyperfiltration, and retard the progression of renal function loss (21). Progressive renal function loss in the large proportion of patients

in whom the initial cause of renal damage is no longer present (3), however, prompted the development of additional treatment strategies aimed at intervention with factors thought to be involved in the alleged final common pathway for progressive renal function loss; i.e, systemic and glomerular pressure, proteinuria and lipid abnormalities.

Intervention studies have focused on reduction of blood pressure and reduction of protein intake. Reduction of blood pressure has proven a cornerstone of renoprotective intervention in non-diabetic and diabetic renal disease (4;23;55). Restriction of dietary protein intake has elicited extensive discussions as to its efficacy and feasibility - but all in all it appears that a well-kept low protein diet indeed retards the rate of renal function loss on non-diabetic and diabetic renal patients (93;94). Increasing evidence supports the role of reduction of proteinuria as a mechanism of renoprotection, in diabetic and non-diabetic renal disease. As already mentioned above, the reduction in proteinuria at onset of treatment predicts subsequent renoprotective efficacy in non-diabetic as well as diabetic subjects. Moreover, drug regimens that reduce proteinuria more effectively invariably provide more effective long term renoprotection.

The question whether RAS-blockade, by virtue of its specific renal effects, offers better renoprotection than other antihypertensives has long been subject of debate. Experimental data long since supported the assumption of specific renoprotective effects of RAS-blockade (95), and in man renoprotective effects beyond reduction of blood pressure were supported by studies in normotensive diabetic patients where ACE inhibition was able to reverse microalbuminuria (96) and to prevent progression to overt proteinuria (97;98). Moreover, in both diabetic and non-diabetic patients ACE inhibitors can reduce proteinuria (99;99;100), progression rate (101) and the risk to reach end stage renal failure or death (55) Nevertheless, the interpretation as to specific renal effects was hampered by the slightly more effective blood pressure reduction by the ACE-inhibitor regimens (55;102).

The results of several recent large clinical trials now allow the conclusion that indeed RAS-blockade has specific renoprotective effects in addition to its effects on blood pressure. This applies to both ACE-inhibition and AT1-blockade, and has been demonstrated in diabetic as well as non-diabetic renal damage (103-106). Across these different studies, the better renoprotective effect is consistently explained by the better antiproteinuric efficacy of the RAS-blockers.

Several important insights have been gained from the large intervention trials of the last decade. First, importantly, in non-diabetic patients the long-term benefit of lower blood pressure (whether or not achieved with ACE inhibitors) on renal function was more pronounced in proteinuric patients (107-110). Thus, like diabetic patients (in whom

proteinuria is the hallmark of renal involvement), proteinuric patients with non-diabetic renal disease display greater renal sensitivity to the effect of elevated systemic blood pressure than their non-proteinuric counterparts. Whether this similarity simply reflects the long-term benefits of reduction of proteinuria secondary to the lower blood pressure, or whether proteinuria is a marker (or even a mediator) of the susceptibility of the glomerular vascular bed to hypertensive damage is as yet unknown. Second, the specific benefit of RAS-blockade over other modes of antihypertensive therapy appears to be proportional to the severity of proteinuria across non-diabetic and diabetic populations (103;111-113). Finally, recent studies have shown that dual blockade of the RAS reduces proteinuria and progression rate more effectively than monotherapy with ACE inhibitor or AT1 blockade (114-116).

Individual differences in the response to renoprotective intervention

In spite of the major improvements in renoprotective treatment, nevertheless in many patients the response to antihypertensive and antiproteinuric intervention is sub optimal, with residual proteinuria, and consequently ongoing renal function loss. In fact, the interindividual differences in responsiveness to antiproteinuric intervention by far exceed the differences in efficacy between different regimens – which is in line with a well-designed analysis in essential hypertension (117). This notion – which is often overlooked – underlines the importance of unravelling the mechanisms underlying individual differences in responsiveness to therapy. By applying different treatment schedules in the same patients, we could demonstrate that responsiveness to antiproteinuric intervention is indeed an individual characteristic – both in non-diabetic and diabetic nephropathy. The individual differences were not altered by increasing the dose of the ACE inhibitor, by increasing the dose of the AT1 blocker, or by switching from one class to the other – or even by switching to NSAID (118). The difference between good and poor responders persisted when the mean response for the group was unaltered, but, remarkably, also when the mean response for the group was enhanced by dose increase or dietary sodium restriction. In other words, maneuvers that enhance therapy response at group level do not make the poor responders catch up with the good responders – neither in diabetic, nor in non-diabetic proteinuric patients (119). Thus, in order to improve renoprotective efficacy in poor responders, other modes of intervention, and combined intervention in different pathophysiological pathways will be have to be explored (120).

Conclusions and implications for renoprotective treatment

Promoters for progression in patients with diabetic and non-diabetic nephropathy display striking similarities. Moreover, predictors for efficacy of long-term renoprotective therapy are similar as well. This supports the hypothesis that common mechanisms underlie progressive renal function loss in diabetic and many non-diabetic renal patients, with the possible exception of specific diagnostic categories, such as polycystic kidneys (40), where disease-specific mechanisms may be the main determinants of progression. The similarities are most readily apparent for patients with proteinuria, supporting the assumption that proteinuria is pivotal in the alleged common mechanisms (7).

Several implications for renoprotective treatment can be derived from the current evidence. First, to provide renoprotection in proteinuric patients (with or without diabetes) target blood pressure should be lower than in non-proteinuric patients. For diabetic patients the need for a low target blood pressure has already gained general acceptance (121). For non-diabetic proteinuric patients, data from the MDRD study demonstrated that the lowest mean arterial pressure attained (≤92 mmHg, corresponding to 125/75 mmHg) provided improved renoprotection, without signs of a J-shape pattern (122). From a renal perspective, therefore, target mean arterial blood pressure in proteinuric patients may have to be even lower than 90 mmHg. For such an aggressive approach to be feasible, short-term titration criteria predictive for long-term renoprotection are indispensable - but fortunately, reduction of proteinuria is a consistent predictor for long term outcome, in diabetic as well as non-diabetic patients. The latter suggests that specific titration for reduction of proteinuria may allow to further improve renoprotective efficacy in diabetic as well as non-diabetic patients, and it is recommended that future studies explore the renoprotective potential of specific titration for proteinuria reduction.

Studies including hard end-points have demonstrated that regimens based on RAS-blockade provide better reduction of proteinuria and consequently renoprotection – and recent data indicate that dual blockade of the RAS may even be more effective. Nevertheless, therapeutic benefit is still suboptimal in a substantial proportion of the patients – and exploration of regimens combining blockade in different pathophysiological pathways may provide a strategy to further improve the efficacy of long term renoprotection.

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