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REVIEW

Current concepts in the management of diabetic nephropathy

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ABSTRACT

Although much progress has been made in slowing the progression of diabetic nephropathy, renal dysfunction and development of end-stage renal disease (ESRD) remain major concerns in diabetes. In addition, diabetic patients with microalbuminuria have an increased cardiovascular mortality. Therefore, new treatment modalities or strategies are needed to prevent or slow the progression of diabetic nephropathy and prevent cardiovascular disease in diabetes. In this review we describe current concepts in pathophysiology, treatment goals and we discuss future developments in the treatment of diabetic nephropathy.

Common risk factors for diabetic nephropathy and its progression are longer duration, poor glycaemic control, hypertension and the presence of albuminuria. Available treatment options, especially renin-angiotensin aldosterone system (RAAS) blockade, but also better blood pressure and blood glucose control, decrease the incidence of cardiovascular disease and renal disease in diabetes. It is important that treatment goals are tailored to the individual patient with individual treatment goals of glycaemic control and blood pressure, depending on age, type of diabetes and diabetes duration. Aggressive treatment of glucose control and blood pressure might not always be best practice for every patient. Since the proportion of ESRD due to diabetic nephropathy remains high, optimisation of RAAS blockade is advocated and can be achieved by adequate sodium restriction and/or diuretic treatment. Moreover, aldosterone blockade might be a valuable strategy, which has potency to slow the progression of diabetic renal disease. Other possible future interventions are under investigation, but large clinical trials have to be awaited to confirm the safety and efficacy of these drugs.

KEYWORDS

Diabetic nephropathy, albuminuria, renin-angiotensin aldosterone system, sodium restriction, tailored treatment

INTRODUCTION

Diabetic nephropathy is one of the leading causes of end-stage renal disease (ESRD) in the Netherlands. In 2011, 15.6% of the 1950 patients developed ESRD due to diabetic nephropathy (www.renine.nl). When taking the group with missing primary diagnoses into account, this number might even increase to 19.5%. Between 2011 and 2030 the expected number of patients with type 2 diabetes in the Netherlands will increase by 35% (RIVM. Nationaal Kompas Volksgezondheid, sectie: Hoe vaak komt diabetes mellitus voor en hoeveel mensen sterven eraan? Webpage www.nationaalkompas.nl. June 2013), leading to an increase in patients reaching ESRD due to diabetic nephropathy. Moreover, diabetic subjects with microalbuminuria have an increased mortality risk, especially due to cardiovascular disease.[1] Both renal function decline and albuminuria are, with a strong synergistic interaction, of prognostic value for both progression to ESRD and death.[2,3]

The natural history of diabetic nephropathy has mainly been studied in type I diabetes, since in type I diabetic patients, the time of onset of diabetic disease is usually evident. For patients with type I diabetes with a duration of more than five years, the presence of sustained microalbuminuria (30-300 mg urinary albumin excretion per day for at least three months) is associated with the development of diabetic nephropathy.[4] In 20-30% of type I diabetic patients persistent microalbuminuria appears within the first 15 years of diabetes.[5] Microalbuminuria precedes macroalbuminuria (>300 mg of urinary albumin excretion per day) in both type 1 and type 2 diabetes. Renal endpoints (ESRD or doubling of serum creatinine) generally occur within ten years in approximately 20% of microalbuminuric patients, but in 60% of macroalbuminuric patients.[6]

In contrast to type I diabetics, the exact duration of diabetes is unclear in type 2 diabetic patients as time to diagnosis usually takes 5-7 years. Thus, sustained microalbuminuria in type 2 diabetes may even be present at diagnosis. However, only 20% of type 2 diabetic patients with microalbuminuria

progress to overt nephropathy after ten years of follow-up in contrast to over 80% of type 1 diabetic patients.[1] The rate of development of renal complications, however, is thought to be more or less similar in type 1 and 2 diabetes. Glomerular hyperfiltration is present in patients with non-insulin dependent diabetes from the onset of the disease until the time macroalbuminuria appears.[7] After the development of macroalbuminuria, the glomerular filtration rate in these patients declines at least as rapidly as has been reported in patients with insulin-dependent diabetes.[7] This pattern is consistent with the hypothesis that glomerular hyperfiltration causes progressive glomerular damage. Compared with type 1 diabetic patients, type 2 diabetic patients with microalbuminuria have different patterns of renal damage.[8] In type 1 diabetes 'typical' pathological changes include expansion of mesangium, due to accumulation of extracellular matrix protein. These lesions are most closely related to the decline in renal function in type 1 diabetes as was shown by quantitative morphometric studies.[9] Moreover, arteriolar hyalinosis affecting both afferent and efferent glomerular arterioles, ensuing thickening of glomerular and tubular basement membranes, tubulointerstitial fibrosis and glomerulosclerosis occurs in diabetic nephropathy. 'Typical' diabetic nephropathy patterns are seen in a minority of microalbuminuric type 2 diabetic patients and only in those patients with (proliferative) retinopathy and a normal body mass index (BMI), while 'atypical' patterns of renal injury (severe tubulointerstitial and/or vascular lesions disproportionate to the mild glomerular involvement) are more common among those with increased BMI and background or no retinopathy.[8] Finally, microalbuminuria is a reflection of generalised endothelial dysfunction in a subset of microalbuminuric type 2 diabetic patients who have near-normal renal structure.[8]

Although much progress has been made in slowing the progression of diabetic nephropathy, renal dysfunction and development of ESRD remain major concerns in diabetes. In addition, diabetic patients with microalbuminuria have an increased cardiovascular mortality compared with normoalbuminuric patients.[1] Therefore, new treatment modalities or strategies are needed to prevent or slow the progression of diabetic nephropathy, decrease albuminuria and prevent cardiovascular disease in diabetes. In this review we describe current concepts in pathophysiology, treatment goals and we discuss future developments in the treatment of diabetic nephropathy.

PATHWAYS AND MECHANISMS OF RENAL INJURY

The exact pathogenesis of diabetic nephropathy is complex and not completely understood. Pathogenetic factors include hyperglycaemia, increased activity of the renin-angiotensin aldosterone system (RAAS) and increased intraglomerular and systemic blood pressure. Moreover, several cytokines and growth factors, metabolic and haemodynamic factors, which have complex mutual interactions, have been identified and may cause damaging effects on the kidney. Renal response on these noxious effects further enhances renal damage.

Longstanding exposure to hyperglycaemia results in renal damage due to metabolic effects as well as direct haemodynamic effects. In experimental human studies in patients with type 1 diabetes mildly elevated serum glucose values resulted in increased blood pressure and volume expansion.[10] It is thought that these effects lead to renal hyperperfusion, glomerular hypertension and subsequent hyperfiltration. Necessary triggers for hyperfiltration and subsequent kidney growth in experimental diabetes are hyperglycaemia and a (transient) increase in growth factors as insulin-like growth factor-1 (IGF-1), TGF-beta and VEGF.[11,12] Indeed, large kidneys and a supranormal glomerular filtration rate (GFR), i.e. hyperfiltration, confer an increased risk for the development of diabetic nephropathy. Patients with type 1 diabetes and an increased kidney volume have an increased risk of developing microalbuminuria, as was shown in a cohort study.[13] Furthermore, kidney volume and hyperfiltration have an association with the rate of decline in renal function.[14] The exact molecular and cellular mechanisms linking hyperglycaemia and hyperfiltration to renal damage are only partially understood. However, glomerulosclerosis seems to develop from a cascade with mesangial matrix hypertrophy, proliferation, contraction and extracellular matrix accumulation. Of note, expansion of the mesangium, due to accumulation of extracellular matrix protein, is most closely related to the decline in renal function in type 1 diabetes, as was shown by quantitative morphometric studies.[15] Upregulation of the RAAS and endothelin-1, upregulated growth factors, oxidative stress and AGE formation all seem to be involved. The RAAS is the main homeostatic system for regulation of extracellular fluid volume, systemic and renal haemodynamics. Diabetic nephropathy is characterised by an upregulation of the RAAS, with glomerular hypertension as a key feature. However, the RAAS also seems to have non-haemodynamic effects in the development of diabetic nephropathy. In experimental studies, long-term hyperglycaemia increases the formation of mesangial angiotensin II.[16] Mesangial angiotension II has been implicated in glomerulosclerosis because it stimulates synthesis of mesangial matrix proteins, as shown by increases in growth factors as TGF-beta and inhibition of mesangial matrix degradation, as shown by decreased collagenase.[17] Probably not only angiotensin II, but also other vasoconstrictors may promote proliferative actions of growth factors. Endothelin-1 is one of the

most potent vasoconstrictors which also exerts its action on water and sodium excretion and acid-base balance. Stimulation of endothelin-1 receptors in mesangial cells may lead to mesangial cell proliferation and hypertrophy.[18] Mechanisms of renal damage in type 1 and 2 diabetes probably have multiple similarities. However, as stated previously, patterns of renal damage differ. Due to differences in patient characteristics and comorbidity between type 1 and type 2 diabetes, differences in pathophysiology of diabetic nephropathy exist. Type 1 diabetic patients are generally non-obese and young, and renal damage is mainly due to long-term exposure to hyperglycaemia. The onset of hypertension is closely associated with the onset of diabetic nephropathy in type 1 diabetes.[19,20] Interestingly, a familial predisposition to arterial hypertension increases the risk for development of diabetic nephropathy in type 1 diabetic patients.[19] Type 2 diabetic patients are generally older, have a higher BMI and more frequent additional morbidities as hypertension and dyslipidaemia. These comorbidities are thought to play an additional pathophysiological role in the development of diabetic nephropathy. Conversely, kidneys affected by these comorbidities may be more vulnerable to the detrimental effects of hyperglycaemia. Obesity itself is directly linked to renal dysfunction, independent of diabetes or hypertension. One of several possible mechanisms is that lower levels of adiponectin in obese patients result in increased oxidative stress. Oxidative stress causes podocyte damage and fusion of foot processes leading to the development of albuminuria.[21] Interestingly, obese type 2 diabetics are characterised by very low adiponectin levels, which are lower than in obesity per se.[22]

BIOMARKERS FOR DIABETIC NEPHROPATHY AND THE IMPORTANCE OF THE TUBULOINTERSTITIUM

Albuminuria is the most important biomarker for diabetic nephropathy, reflecting the extent of glomerular damage and mesangial matrix expansion. Albuminuria is a strong predictor for progression of renal disease and cardiovascular disease and mortality in diabetes.[23-26] Lowering albuminuria reduces renal and cardiovascular risk.[23-26] However, albuminuria is not a perfect biomarker. The randomised placebo-controlled Renin-Angiotensin System Study (RASS) investigated whether treatment with an AT1 receptor blocker (losartan) would prevent diabetic kidney disease in type 1 diabetic patients.[27] In this study kidney biopsies were taken at baseline and after five years of treatment. Although there was more occurrence of microalbuminuria during the study in the losartan group (17%) compared with the placebo group (6%), mesangial glomerular volume changes were similar in all groups as was the decline in renal function. The onset of microalbuminuria did not adequately reflect structural renal disease in this study. Experimental data in rats show that in spite of a reduction in albuminuria and blood pressure, pronounced progression of renal interstitial damage can be present.[28] And it is the extent of tubulointerstitial injury that ultimately determines the rate of renal function decline.[29] Of note, some diabetic patients develop biopsy-proven diabetic nephropathy in the absence of (micro)albuminuria.[30] Therefore, in some cases, therapy response to albuminuria and blood pressure can dissociate from renal interstitial damage. This indicates that better or additional tools for monitoring therapy response in diabetic kidney disease are needed. Biomarkers for interstitial damage could be valuable for this purpose and for predicting renal outcome. The predictive value of tubular injury markers for the onset of microalbuminuria or macroalbuminuria was evaluated in patients with type 1 diabetes mellitus participating in the Diabetes Control and Complication Trial (DCCT) in a nested case-control study.[31] Baseline urinary N-acetyl-β-D-glucosaminidase (NAG) as well as a rise in NAG were independently associated with the subsequent occurrence of both microalbuminuria and macroalbuminuria. This suggests that tubular alterations might either be a first sign of diabetic kidney involvement, and/or play a pathogenetic role in the development of diabetic nephropathy.

CARDIO-RENAL INTERACTION

Cardiovascular mortality and morbidity is the major threat for patients with microalbuminuria and diabetic nephropathy. An integrated approach for treating the heart and kidney dysfunction is advocated, since important interactions exist; these interactions are addressed as the cardio-renal syndrome.

The cardio-renal syndrome is a disorder of the heart and kidneys whereby acute or chronic dysfunction in one organ may induce acute or chronic dysfunction in the other organ, irrespective of the original cardiac or renal disease.[32] The association between heart and kidney failure is multifactorial, but haemodynamic factors play a major role as both organs are involved in homeostasis and management of extracellular and circulating fluid volume. On the one hand, the kidneys play a pivotal role in maintaining volume homeostasis via both vascular and tubular mechanisms. Low renal perfusion pressure activates baroreceptors in the vascular part of the juxtaglomerular apparatus in the kidneys, which activates the RAAS by stimulating these cells to release the enzyme renin. On the tubular level, volume depletion is detected by low sodium and chloride delivery to the macula densa. The macula densa in turn induces afferent

vasodilation, reducing vascular resistance and increasing renal perfusion (tubuloglomerular feedback mechanism). Sympathetic activation also stimulates renin release, leading to RAAS activation. On the other hand, reduction in cardiac output due to heart failure leads to a reduction in renal perfusion pressure. The kidneys respond by sodium and water retention, thereby increasing extracellular fluid volume and hence venous return. The increased venous return increases cardiac output (Frank-Starling mechanism), which restores renal perfusion pressure at the expense of volume retention. Furthermore, decreased cardiac output activates baroreceptors in the carotid sinus stimulating beta-adrenergic activity and thereby activating the RAAS. In addition, the cardio-renal syndrome may be aggravated by atherosclerotic changes and vascular damage in both the heart and kidneys as well as by hormonal and immunological factors.

TREATMENT GOALS

Treatment in diabetic nephropathy is aimed at deceleration of renal function loss as well as prevention or treatment of its (cardiovascular) complications. In current clinical practice, treatment is multifactorial and involves prevention or treatment of cardiovascular and renal risk factors (hypertension, albuminuria, glycaemic control, overweight, smoking, dyslipidaemia)[33] and secondary metabolic complications of renal failure (anaemia, mineral and bone disease, acidosis, malnutrition). Here we discuss some specific treatment goals for diabetic nephropathy (*table 1*).

Table 1. *Main pillars in the prevention and treatment of diabetic nephropathy*

Blood pressure (BP)	Type 1 (and young): the lower the BP the better with orthostatic symptoms limiting further decrease in BP
	Type 2 (and atherosclerosis), systolic BP between 120 and 130 mmHg
Albuminuria	Start treatment in patients with sustained urinary albumin excretion of >30 mg/day In patients with overt proteinuria treatment goal is <0.5 g/day
Interventions to reduce BP and albuminuria	
1.	Dietary sodium restriction: <100 mmol/day, < 6 gram salt/day
2.	Start RAAS blockade with ACEi or AT1 receptor blockade; aim for maximal dosage
3.	Addition of diuretic therapy: first choice loop diuretics, second choice thiazides (metabolic side effects as dyslipidaemia and hyperglycaemia)
4.	When proteinuria goal is not reached: add aldosterone receptor blockade (with strict monitoring of potassium)
5.	When blood pressure goal is not reached: add calcium re-entry blockers, beta-blockers, (alpha-blockers).
Glycaemic control	Young, well-informed patients, free of symptomatic atherosclerosis: HbA1c <6.5%
	Older, advanced renal damage, cardiovascular disease: HbA1c 7-7.5%
Dyslipidaemia	Total cholesterol <4.5 mmol/l
	eGFR >15 ml/min/1.73m^2: advise lipid-lowering treatment for reduction of cardiovascular events
	eGFR <15 ml/min/1.73m^2: lipid-lowering treatment not advised
Overweight	Advise all diabetic patients to lose weight if BMI >25 kg/m^2
Smoking	Advise all diabetic patients to quit smoking
Exercise	>30 minutes of exercise per day is recommended for all diabetic patients

Reduction of albuminuria

Diabetic patients have a substantial prevalence of (micro) albuminuria. Sustained microalbuminuria is associated with increased renal endpoints as well as cardiovascular morbidity and mortality in patients with longstanding type 1 diabetes (>5 years) or type 2 diabetes of any duration.[4] In line with this, lowering albuminuria predicts better renal outcomes in patients with diabetic kidney disease treated with RAAS blocking agents.[23-26]

Prevention of albuminuria, useful?

Because albuminuria predicts higher cardiovascular and renal risks and lowering existing albuminuria decreases this risk, one could hypothesise that preventing albuminuria lowers cardiac and renal risk. Therefore, trials have been undertaken to determine whether treating diabetic patients without albuminuria or signs of renal disease with RAAS-inhibiting agents will lower the risk of developing albuminuria and subsequently prevent cardiovascular and renal endpoints.

One such recent study was the European Randomized Olmesartan and Diabetes Microalbuminuria Prevention (ROADMAP) trial, which was performed in patients with type 2 diabetes.[34] New microalbuminuria developed in 8.2% of type 2 diabetic patients randomised to olmesartan compared with 9.8% of those receiving placebo, and the time to onset was also significantly longer in the olmesartan group. However, more cardiovascular events occurred in the olmesartan group. Lower blood pressure perhaps played a contributory role and we assume that some of these type 2 diabetic patients already had coronary atherosclerosis, which was as yet undetected. Prevention of albuminuria at the expense of too low blood pressures is thus undesirable in patients with type 2 diabetes. Therefore, RAAS-inhibiting agents in type 2 diabetic patients with normal blood pressure levels and without albuminuria are not indicated.

In this respect, type 2 diabetic patients may differ from type 1 diabetic patients, who might benefit from treatment to prevent microalbuminuria. As hypertension usually develops with the onset of kidney disease in type 1

diabetes, all primary prevention studies in type 1 diabetes have been performed in normotensive patients. Ramipril reduced the development of microalbuminuria compared with placebo in a subgroup of patients with type 1 diabetes from the micro-HOPE (Heart Outcomes Prevention Evaluation) study.[35] Moreover, perindopril prevented the development of microalbuminuria in normoalbuminuric patients with type 1 diabetes, even without effects on blood pressure.[36] However, as mentioned earlier, losartan did not prevent the development of microalbuminuria or mesangial glomerular volume changes, or the decline in renal function in type 1 diabetic patients (RASS study).[27] Thus, RAAS-inhibiting agents for primary prevention in normotensive normoalbuminuric type 1 diabetic patients is not justified. In theory, it may not be unreasonable to consider RAAS-inhibiting agents in a small subset of normotensive normoalbuminuric type 1 diabetic patients who are at high risk of developing nephropathy, such as those with a strong family history of diabetic nephropathy or hypertension in both parents. Future studies need to address this issue.

Glycaemic control

Long-term control of hyperglycaemia delays or prevents development of albuminuria and overt proteinuria.[37] Intriguingly, after pancreas transplantation, lesions of diabetic nephropathy can be reversed, although this takes more than five years of normoglycaemia.[38] The beneficial effects of strict glycaemic control persist in the long term even when glucose control is relaxed. This fascinating concept of metabolic memory is reported in trials as the Diabetes Control and Complications Trial (DCCT)[37] and the observational Epidemiology of Diabetes Interventions and Complications (EDIC) study.[39,40] Four years after finishing the DCCT study with a follow-up of 6.5 years, the difference in the median glycosylated haemoglobin values between the conventional-therapy and intensive-therapy groups (average, 9.1% and 7.2%, respectively) narrowed during follow-up (median during four years, was 8.2% and 7.9%, respectively; p<0.001). Nevertheless, the proportion of patients with new onset of microalbuminuria was still significantly lower in the former intensive-therapy group (5% of 601 patients versus 11% of 573 patients in the former conventional-therapy group).[40]

The other way around, it is believed that short-term hyperglycaemia, for example brief postprandial high elevations of glucose, may be sufficient to provoke renal injury in diabetes, probably also based on 'metabolic memory'. Recently, a potential role for epigenetic mechanisms in this metabolic memory was suggested.[41] Preliminary work in endothelial cells shows that transient episodes of hyperglycaemia can induce changes in gene expression that are dependent on modifications to histone tails (for example, methylation), and that these changes persist after return to normoglycaemia.[41] Moreover, clamping plasma glucose for just two hours at a high level results in increased urinary excretion of isoprostanes and TGF-beta, suggesting that the kidney undergoes oxidative damage and increased profibrotic growth factor expression.[42] The biochemical mechanism for this memory is not completely understood, but accumulation of advanced glycation end products (AGEs) as one of the carriers of metabolic memory and oxidative stress is possibly involved.[43] AGE accumulation can be assessed noninvasively by measuring skin autofluorescence and it predicts the development of diabetic nephropathy.[44,45] The cell biological basis of metabolic memory as well as the long-term effects of repetitive short-term peaks in blood glucose need further investigation.

The importance of tight glycaemic control once diabetic nephropathy has occurred is less straightforward. In a Canadian cohort study of 23,296 diabetic subjects with chronic kidney disease with a median follow-up time of 48 months, the association between levels of HbA1c stratified to the level of GFR was studied. In subjects with an eGFR between 30-60 ml/min/1.73m^2 an HbA1c <7% was associated with a 22% lower event rate of reaching ESRD compared with subjects with an HbA1c between 7-9%. In subjects with an eGFR between 15-30 ml/min/1.73m^2 no significant benefit of tight glycaemic control in subsequent subgroups was noted. Interestingly in this study high HbA1c levels of >9%, but also low levels <6.5% were associated with increased mortality rates.[46] The finding that a too strict glycaemic control is associated with increased mortality is in line with the results of a large intervention trial aiming at tight glycaemic control: the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial. In this study in type 2 diabetic patients with high cardiovascular risk, tight glycaemic control did not induce beneficial outcomes, but was associated with increased mortality.[47] It is assumed that these patients with established type 2 diabetes and major cardiovascular risk factors were more susceptible to the adverse consequences of hypoglycaemia. A subsequent analysis on renal endpoints at ACCORD's end showed that intensive glycaemic control resulted in a 20-30% reduction in the risk of new-onset microalbuminuria and macroalbuminuria, but without a reduction in the risk of doubling in serum creatinine or the development of ESRD.[48] Similar results were recently obtained by a post-hoc analysis of the Action in Diabetes and Vascular Disease (ADVANCE) study, in which 11,140 type 2 diabetic patients with an increased cardiovascular risk were included. Intensive glucose control reduced the risk of ESRD (20 compared with 7 events), new-onset microalbuminuria by 9% (1298 compared with 1410 patients), and new-onset macroalbuminuria by 30% (162 compared with 231 patients).[49] The most recent randomised

trial of intensified glycaemic control, the Veterans Affairs Diabetes Trial (VADT), enrolled 1791 military veterans with longstanding type 2 diabetes (mean duration 11.5 years), 40% of whom had known cardiovascular disease.[50] Patients were randomised to standard therapy versus intensified glycaemic control (HbA1c of 8.4% versus 6.9%). After a median of 5.6 years, there was no difference in the risk of mortality or microvascular endpoints, other than a reduced risk of progression of albuminuria; the risks of doubling of serum creatinine or ESRD were similar between groups.[50] In dialysis patients glycaemic control, measured as HbA1c level, is not associated with mortality.[51]

A recently published interesting editorial addresses the issue of the effects of glycaemic control on diabetic nephropathy in type 2 diabetes, and, more broadly, on patient survival and cardiovascular events.[52] As discussed, high-quality data from ACCORD, VADT and ADVANCE all demonstrate that tight glucose control (HbA1c 6-7%) will improve albuminuria-based surrogate outcomes, but only the post hoc analysis of ADVANCE[49] suggests that such an intensive strategy may reduce the clinically relevant outcome of ESRD. In contrast, tight glucose control (HbA1c <6.5%) increased mortality risk in the ACCORD study, probably related to the adverse effects of hypoglycaemia in patients with a high cardiovascular risk.[53] Taken together, intensive glycaemic control appears to have both risks and benefits. Tailored treatment with a more personalised approach aimed at the individual patient seems to be important. Tight glucose control is important in newly diagnosed type 1 diabetic patients, since they have a long time to develop diabetic kidney damage. Moreover, tight glucose control should only be advised to well-informed type 1 or 2 diabetic patients who are younger, at lower risk for hypoglycaemia, and free of symptomatic cardiovascular disease.[52] This is in contrast to older diabetics or subjects who already have more advanced renal and cardiovascular disease, in whom an HbA1c target of 7.5% might be sufficient.

Blood pressure

The ideal systolic blood pressure for patients with diabetes and chronic kidney disease would be between 120-130 mmHg. Systolic blood pressure is correlated with progressive decline in kidney function in patients with diabetes as shown by the UK Prospective Diabetes Study (UKPDS). There was a reduction of 13% in microvascular complications for every 10 mmHg decrease in systolic blood pressure.[54] However, the Irbesartan in Diabetic Nephropathy Trial (IDNT) showed an increase in all-cause mortality in patients with a systolic blood pressure below 120 mmHg.[55] The ACCORD trial, in patients with diabetes and pre-existing peripheral arterial or cardiovascular disease, showed no benefit but more adverse effects when aiming at strict blood pressure control of a systolic blood pressure below 120 mmHg.[53] The relation between blood pressure and cardiovascular morbidity and mortality in diabetic nephropathy seems to be J-curved. The worse outcome in diabetic subjects with low blood pressure is probably a reflection of relative hypoperfusion and/or hypoxia to major vascular beds as the heart and brain. Concerning the kidney, a decrease in blood pressure and thus glomerular pressure contributes to renoprotection by reduction of albuminuria and glomerular damage. However, too low perfusion pressure may result in renal hypoxia, tubulo-interstitial damage and as result in renal function decline. The optimal level of blood pressure lowering, where renal protection is outweighed by renal damage, has to be established.

How to treat diabetic patients with adequately controlled blood pressure but high residual albuminuria? Further lowering of albuminuria decreases cardiovascular risk. As for glycaemic control, tailored treatment with a more personalised approach aimed at the individual patient seems to be important. We propose that in young patients, especially those with type 1 diabetes: the lower the blood pressure, the better, with orthostatic symptoms limiting further increase in antiproteinuric treatment. On the other hand, especially in older patients with type 2 diabetes and a higher risk of atherosclerosis, systolic blood pressure targets should be higher. For whom and at which blood pressure level the downside of a low blood pressure outweighs the benefit of reduction of albuminuria is unknown. Unfortunately (as far as we know) this issue is not answered in subgroup analyses of these large trials aiming at strict blood pressure control.

Dyslipidaemia

Both diabetes and chronic kidney disease are associated with increased incidence of cardiovascular disease, with dyslipidaemia being an important factor in these associations. Current guidelines recommend treating nearly all diabetic patients with statins (HMG-CoA reductase inhibitors). The use of statin therapy in primary prevention in diabetics without elevated LDL levels has been studied in the Collaborative Atorvastin Diabetics Study (CARDS), showing a 37% rate reduction in cardiovascular events in 3.9 years median follow-up.[56] In patients with chronic kidney disease, a subgroup routinely excluded in large statin trials, it has long been debated whether statins should be used in primary prevention. Especially Die Deutsche Diabetes Dialysis (4D) study[57] and Aurora trial,[58] showing no benefit of statin use compared with placebo on cardiovascular outcomes in patients on dialysis, outlined the need for studies in subjects with chronic kidney disease. The Study of Heart and Renal Protection (SHARP) investigated whether simvastatin plus ezetimibe reduced renal and cardiovascular risk in 3023 patients on dialysis and 6247 patients with chronic kidney

disease in a setting of primary prevention.[59] During the median follow-up period of 4.9 years a 17% proportional reduction on major cardiovascular events was seen in the lipid-lowering group, with no evident differences in outcome between patients on dialysis and those who were not.[59] Subsequently performed meta-analysis shows some evidence that lipid-lowering therapy is effective in reduction of cardiovascular events in patients with chronic kidney disease at levels of eGFR >15 ml/min/1.73m.[2,60] In levels below that and in dialysis patients results are conflicting and lipid-lowering therapy is not advised.

In theory, use of statins could prevent renal damage by its antiatherosclerotic, anti-inflammatory and antioxidant effects.[61] However, secondary outcome measures in diverse statin trials show conflicting results regarding effects of statins on albuminuria and rate of renal function decline. The SHARP trial is the only large randomised controlled trial with prespecified renal endpoints. The use of lipid-lowering treatment did not reduce the rate of renal function decline nor progression to end-stage renal disease.[59] In summary, there is no evidence to support the use of statins for renoprotection only. A concern with statins that has recently been raised is their association with an increased risk of developing diabetes in the Women's Health Initiative cohort study.[62] Although bias by indication plays a role, this issue deserves more attention and further investigation.

CURRENT AND EMERGING TREATMENT APPROACHES

Based on the above-mentioned treatment goals a multifactorial approach in the treatment of diabetes and diabetic nephropathy could be advocated (*table 1*). The Steno-2 trial showed the success of such a multifactorial approach in patients with type 2 diabetes and microalbuminuria.[63] In this trial patients were treated during a mean treatment period of 7.8 years with either conventional therapy or an intensive regimen consisting of tight glucose control (target HbA1c <6.5%), RAAS blockade (regardless of blood pressure; target <130/80 mmHg), aspirin and lipid-lowering agents (target total cholesterol <4.5 mmol/l, fasting triglycerides <1.7 mmol/l). After 13.3 years of follow-up, the intensive regimen not only resulted in a 20% absolute mortality risk reduction, also diabetic nephropathy developed in fewer subjects (20 versus 37 patients), and ESRD in only one versus six patients. These results show that a multifactorial approach can slow the progression of diabetic nephropathy.

RAAS inhibition

Agents intervening in the RAAS are the mainstay in the management of diabetic nephropathy. Major evidence for this strategy is provided by the Captopril study in patients with type 1 diabetes and kidney disease[26] and the Reduction of Endpoints in NIDDM with Angiotensin II Antagonist Losartan (RENAAL)[24] and IDNT[25] study in patients with type 2 diabetes and kidney disease. The long-term benefits of ACEi and AT1 receptor blockade are mainly mediated by the reduction in systemic and intraglomerular blood pressure. In addition, these agents are thought to exert a specific antiproteinuric effect that cannot be fully attributed to the reduction in blood pressure.

Since inhibition of the RAAS by a single agent is incomplete, blocking the system at different levels simultaneously could be advocated. Dual blockade with both ACEi and AT1 receptor blockade or with a renin inhibitor further decreases albuminuria and has therefore temporarily been advocated as treatment for slowing renal disease. However, the ONTARGET study, a large (n=25,620) long-term follow-up (56 months) clinical trial recently reported the effects of dual RAAS blockade with ramipril and telmisartan on renal endpoints in patients with cardiovascular disease and a low renal risk. Despite a beneficial effect on microalbuminuria, dual blockade was associated with worse renal outcomes.[64] This may have been due to more hypotension.[64] Furthermore dual RAAS blockade induced more hyperkalaemia.[64] Recently the ALTITUDE study was stopped prematurely due to safety concerns.[65] This study evaluated the role of renin inhibition with aliskiren in addition to RAAS blockade in the prevention of cardiovascular events and hard renal endpoints in more than 8000 type 2 diabetic patients. Although blood pressure and albuminuria were reduced by aliskiren, the incidence of hyperkalaemia (potassium levels of >6 mmol/l) was higher. In addition, significant effects on primary cardiovascular and renal outcomes were lacking.[65] Based on the aforementioned studies, dual blockade with ACEi, AT1 receptor antagonists, or renin inhibitors is not recommended.

Several studies have shown that the addition of aldosterone receptor blockade to ACEi or AT1 receptor blockade can lead to further reduction in albuminuria. Classically, aldosterone exerts its effects on volume status by the regulation of sodium reabsorption through the mineralocorticoid receptor (MR) on epithelial sodium channels, which are located on cortical collecting duct cells in the distal nephron. Additionally, there is increasing evidence that aldosterone is directly involved in the development and progression of renal disease via nonepithelial MR-mediated effects. Aldosterone exerts profibrotic effects through increased production of TGF-beta, reactive oxygen species, PAI-1 and increased collagen gene expression and synthesis, which can be abolished by MR blockade.[66] RAAS blockade initially decreases circulating aldosterone levels, but suppression will not be sustained in 10-50% of patients,

a phenomenon called aldosterone breakthrough.[67] This is particularly the case during long-term treatment or during sodium restriction, which potentiates the adrenal response to angiotensin II. Thus many patients are exposed to high levels of a hormone with known profibrotic effects on the kidney. Furthermore, aldosterone breakthrough is associated with a poor response to antiproteinuric treatment and an enhanced decline of renal function in patients with diabetic nephropathy.[68,69] It is suggested that the worse clinical prognosis of patients with aldosterone breakthrough is due to direct effects of aldosterone. In line with this hypothesis, studies in patients with chronic kidney disease and early diabetic nephropathy show that MR blockade on top of ACEi and/or AT1 receptor blockade exerts added renoprotective effects.[68-70] Interestingly, the reduction in albuminuria induced by the addition of spironolactone to ACEi was related to aldosterone levels.[68] This suggests that aldosterone is a component of the renal damage that is associated with chronic kidney disease and that its inhibition by RAAS blockade can be incomplete. In spite of these encouraging results on albuminuria, long-term data on the efficacy of MR blockade on hard endpoints, for example the development of ESRD or patient survival, are still lacking.

Dietary sodium restriction and diuretic therapy

Despite the proven efficacy of RAAS blockade, the risk of renal and cardiovascular disease remains high, which is likely due to high residual blood pressure and/or albuminuria. Sodium status is an important determinant of the responses of blood pressure and albuminuria to RAAS blockade. ACEi and AT1 receptor blockers are largely ineffective during states of volume excess, either due to renal dysfunction, nephrotic syndrome or to increased sodium intake. Sodium restriction and diuretic treatment increase the top of the dose-response curve to RAAS blockade, and therefore a larger maximum response can be obtained.[71] Correction of volume overload, or induction of mild volume depletion by dietary sodium restriction, diuretic treatment or their combination, increases the therapeutic efficacy of RAAS blockade.[72,73] Interestingly, the addition of dietary sodium restriction to ACEi is considerably more effective than dual RAAS blockade with ACEi plus AT1 receptor blockade for the reduction of albuminuria and blood pressure in patients with overt proteinuria.[74] In this study sodium intake was reduced from a level that equals the prevailing sodium intake in the renal and general population (160-200 mmol sodium/day corresponding with 9.6-12 g salt/day) to a level conform current recommendations (<100 mmol/day, <6 g salt/day).[74,75] Accordingly, it should be feasible to implement the benefits of dietary sodium restriction in daily clinical practice. A recent study showed an association of sodium status with hard renal endpoints, which substantiates these short-term beneficial effects of dietary sodium restriction on albuminuria and blood pressure.[76] Data from the RENAAL and IDNT trials were merged and analysed retrospectively, showing that during AT1 receptor blockade lower dietary sodium intake was associated with lower albuminuria, less progression to ESRD and fewer cardiovascular events in patients with diabetic nephropathy.[76] Furthermore, compared with non-RAAS blockade based therapy, the positive treatment effects of AT1 receptor blockade on hard renal and cardiovascular outcomes were completely annihilated in subjects with the highest sodium intake.[76] This implicates that interventions to reduce dietary sodium intake will have the potential to greatly improve long-term renal and cardiovascular outcome in patients with diabetic nephropathy, particularly those patients who are treated with RAAS blockade.

Although the importance of sodium restriction seems to be evident, its importance is debated by some. A recent meta-analysis from Italy suggested more hospitalisation and increased mortality in patients with heart failure on a very strict sodium diet. However, while originally published in a high-impact journal, this paper was retracted due to incomplete and non-retraceable raw data.[77] We are not aware of any other report showing detrimental effects of a low-sodium diet.

Diuretic therapy with increased furosemide dosage together with the avoidance of excessive salt intake on top of dual RAAS blockade by ACEi and AT1 receptor blockade has been shown to decrease proteinuria in nephrotic patients (7 out of 18 had diabetic nephropathy).[78] Moreover, in albuminuric patients during high sodium intake the antiproteinuric as well as the blood pressure response to ACE inhibition was blunted, but could be restored by the addition of hydrochlorothiazide.[79] However, the practical problems with thiazides are their metabolic side effects, such as dyslipidaemia and hyperglycaemia, which is clearly undesirable in diabetic patients with an increased cardiovascular risk profile.

There is some evidence that the effects of sodium restriction and hydrochlorothiazide might not be equivalent, despite the fact that both act on sodium status. Thiazides mainly exert their antihypertensive effect by specific vascular changes rather than by volume depletion.[80] In an experimental study in rat, sodium restriction, but not diuretic therapy, diminished renal hypertrophy while blood pressure was similar.[81] Different modes of action of diuretics and sodium restriction are suggested by a randomised placebo-controlled study in 33 proteinuric patients.[72] Whereas, the addition of sodium restriction or hydrochlorothiazide to losartan was equally effective in reducing proteinuria, the effect of hydrochlorothiazide was associated with blood pressure response, while this was not the case for sodium restriction.[72]

NOVEL THERAPIES

In experimental studies several new targets and drugs for the treatment of diabetic nephropathy are being developed. It is beyond the scope of this review to provide a complete overview of these novelties. However, we want to highlight some of the most promising possible interventions.

Low vitamin D levels are associated with faster renal function decline. Experimental studies show that treatment with paricalcitol, a selective activator of the vitamin D receptor, decreases urinary albumin excretion and slows progression of kidney injury. Mechanisms probably include suppression of the RAAS, and anti-inflammatory and antifibrotic effects of vitamin D.[82,83] Recent experimental work shows that these beneficial effects especially exert a protective role in the apoptotic response of podocytes to hyperglycaemia.[84] The VITAL study, a short-term randomised controlled trial, investigated the effect of paricalcitol 1 or 2 μg per day on microalbuminuria in diabetic patients. After 24 weeks the patients using paracalcitol 2 μg showed a significant reduction in albuminuria ranging from -18% to -28%, with a favourable short-term safety profile.[85] Long-term studies with a special focus on long-term safety issues (risk for adynamic bone disease) are awaited.

The renal endothelin-1 system is activated in patients with diabetic nephropathy, linked to renal damage by its action on mesangial cell proliferation and hypertrophy.[18] In experimental studies, blocking endothelin-1 exerted renoprotective effects and a reduction in albuminuria was seen.[86] The endothelin-1 antagonist avosentan indeed reduced albuminuria in a randomised controlled trial in almost 1400 diabetic patients.[87] However, this trial was prematurely ended after a follow-up period of four months because of an increased incidence of cardiovascular adverse events, especially fluid overload and congestive heart failure.[87] Other endothelin-1 antagonists as atrasentan and sitaxsentan have been developed and appear to have fewer side effects and comparable albuminuria-reduction abilities. Additional trials using this class of drugs in diabetic nephropathy are ongoing.[88]

We have discussed the role of advanced glycation end products (AGEs) in the development of diabetic nephropathy. The AGE inhibitor pimagedine showed promising results in animal models and in a human study. In the ATION 1 study, 454 type I diabetic patients with nephropathy and retinopathy were treated with pimagadine during a follow-up period of 2-4 years. Pimagedine reduced albuminuria and the rate of renal function decline.[89] However, pimagedine did not reduce renal endpoints (doubling of serum creatinine). Further development of this AGE inhibitor was stopped due to safety concerns, primarily based on the non-specific actions of pimagedine.[90] Pyridoxine, another AGE inhibitor, has been tested in experimental studies, and seems to be well tolerated in humans.[91] The results of more trials using pyridoxine are being awaited. AGE crosslink breakers, a linked class of drugs able to cleave preformed AGE crosslinks, show promising results in experimental studies by showing improvement in structural morphological cardiac[92] and glomerular damage.[93] In small clinical trials the AGE-crosslink breaker alagebrium improved endothelial function and arterial compliance.[94] Clinical trials confirming these potential beneficial effects are needed.

CONCLUSION

To prevent diabetic nephropathy and cardiovascular mortality in patients with diabetes it is important to tailor treatment to the individual patient with individual treatment goals, depending on age, type of diabetes and diabetes duration. Aggressive treatment of glucose control and blood pressure might not always be best practice for every patient. The three main pillars in the treatment of diabetic nephropathy are albuminuria, blood pressure and glycaemic control with RAAS blockade being the cornerstone of treatment. To potentiate the effects of RAAS blockade, sodium restriction and/or diuretics can be added. Moreover, positive effects of aldosterone blockade have been shown.

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