

Preventive Strategies for Diabetic Nephropathy

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EPIDEMIOLOGY

Diabetes mellitus is a global epidemic affecting more than 150 million persons and it is expected that this number is likely to double by 2025¹. Diabetic nephropathy is the leading cause of chronic kidney disease in patients starting renal replacement therapy and is associated with increased cardiovascular mortality. Renal involvement in patients with diabetes is defined by the appearance of low but abnormal levels (≥ 30 mg/day, or $20 \mu\text{g}/\text{minute}$) of albumin in the urine. This stage of renal involvement has been termed as microalbuminuria or incipient diabetic nephropathy. The cumulative incidence of microalbuminuria in patients with type 1 diabetes was 12.6% over 7.3 years according to European Diabetes (EURODIAB) Prospective Complications Study Group² and 33% in an 18-year follow-up study from Denmark³. In the UK Prospective Diabetes Study (UKPDS) among patients with type 2 diabetes, the incidence of microalbuminuria was 2.0% per year and the prevalence 10 years after diagnosis was 25%⁴.

Without specific intervention, microalbuminuria usually progresses to the next stage of diabetic nephropathy – macroalbuminuria, or “overt” nephropathy – which is characterized by urinary albumin excretion ≥ 300 mg/day or $\geq 200 \mu\text{g}/\text{minute}$. It usually corresponds to total urinary protein excretion >0.5 g/day. Overt proteinuria usually occurs in 15 to 40% of patients with type 1 diabetes, with a peak incidence around 15 to 20 years of diabetes^{3,5}. In patients with type 2 diabetes, the prevalence is highly variable, ranging from 5 to 20 percent^{4,6}, if a patient has microalbuminuria, then the risk of progression to end stage renal disease (ESRD) is 20 to 40% within 15 to 20 years^{7,8}. If a patient has macroalbuminuria, then ESRD develops in approximately 50%

of cases within 10 years and in 75% within 20 years. In parallel, there is two-to-four fold increased risk for cardiovascular events and deaths for both conditions⁷.

STAGES AND CLINICAL CHARACTERISTICS

The natural history of diabetic nephropathy has been extensively studied in type 1 diabetes because it is normally possible to specify the exact time of onset. At first described by Mogensen, there are five distinct stages. Although renal structural changes and severity of target organ damage are similar in both types of diabetes, delayed diagnosis makes it difficult to identify various stages in the natural history of diabetic renal disease in type 2 diabetes. The course of diabetic nephropathy can be followed by two main variables: proteinuria and glomerular filtration rate (GFR). Various stages and their clinical relevance have been depicted in Table 1.

There is some evidence to suggest that the risk for developing nephropathy⁹⁻¹¹ and cardiovascular disease¹² starts when urinary albumin excretion (UAE) values are still within normoalbuminuric range. After 10 years of follow-up, the risk of diabetic nephropathy was 29 times greater in patients with type 2 diabetes with UAE values $>10 \mu\text{g}/\text{min}$ ¹¹. The same was true for patients with type 1 diabetes. This favours the concept that the risk associated with UAE is a continuum, as is the case with blood pressure levels. Possibly, values of UAE lower than those currently used for diagnosis of microalbuminuria should be established.

Although microalbuminuria has been considered a risk factor for macroalbuminuria, not all patients progress to this stage and some may regress to normoalbuminuria¹³. The initial studies in the 1980s demon-

Table 1: Diabetic nephropathy: Stages and main clinical characteristics

Stage	Description	Cut off values for albuminuria	GFR	Clinical relevance
1	Glomerular hypertension and renal enlargement	Normal	Increased by 20-50%	Blood pressure – usually normal. Reversible with diet control
2	Early glomerular lesions or silent stage with normal albumin excretion	Normal, however micro-albuminuria during exercise or poor metabolic control	Increased by 20-40%	Blood pressure – usually normal. Reversible with good control
3	Incipient diabetic nephropathy (Micro-albuminuria)	20-199 µg/min 30-299 mg/day 20-299 mg/g*	Still supranormal values, but predicted to decline with development of proteinuria	<ul style="list-style-type: none"> • Blood pressure – incipient increase • Dyslipidemia • Increased frequency of metabolic syndrome • Endothelial dysfunction • Associated with diabetic retinopathy, and cardiovascular disease
4	Clinical or overt diabetic nephropathy	≥200 µg/min ≥300 mg/day >300 mg/g*	Declines at a rate of 10 ml/min/year	<ul style="list-style-type: none"> • Hypertension • Dyslipidemia • Asymptomatic myocardial ischemia
5	End stage renal disease	Often some decline due to glomerulosclerosis	<10 ml/min	<ul style="list-style-type: none"> • Hypertension • Dyslipidemia • High prevalence of cardiovascular disease

*Protein-creatinine ratio in a spot urine sample

trated that ~80% of microalbuminuric type 1 diabetic patients progressed to proteinuria over a period of 6-14 years^{14,15}. In more recent studies, only 30-45% of micro-albuminuric patients have been reported to progress to proteinuria over 10 years¹³, may be as a result of more intensive glycemic and blood pressure control strategies.

SCREENING

As per the American Diabetes Association (ADA) guidelines (2006), annual test for the presence of micro-albuminuria should be performed in type 1 diabetic patients with diabetes duration of ≥ 5 years and in all type 2 diabetic patients starting at diagnosis, since ~7% of type 2 diabetic patients have albuminuria at the time of diagnosis. Serum creatinine should be measured at least annually for the estimation of GFR in all adults with diabetes regardless of the degree of UAE. The serum creatinine alone should not be used as a measure of kidney function, instead it should be used to estimate GFR and stage the level of chronic kidney disease (CKD). Patients should be referred to a nephrologist for evaluation and co-management when GFR reaches 30 ml/min, since there is evidence that nephrologist care may improve morbidity and mortality¹⁶.

PRIMARY PREVENTION (NORMOALBUMINURIC PATIENTS)

Control of Hyperfiltration

Hyperfiltration is the first abnormality in renal function in both types of diabetes, particularly in type 1 diabetes. Diabetic nephropathy occurs as a result of interplay of metabolic and hemodynamic factors in the renal microcirculation. Besides this, diabetic nephropathy is usually associated with hypertension which also aggravates the injury to the diabetic glomerulus. Hyperglycemia leads to spontaneous nonenzymatic reaction between glucose, lipids and proteins leading to formation of advanced glycosylated end products¹⁷. Several reactive substances have been postulated to be involved in the genesis of hemodynamic abnormalities. Angiotensin-II has several actions on the afferent and efferent arteriolar tone, mesangial contractility and tubular functions. Besides this, various cytokines have been implicated in triggering renal injury such as transforming growth factor β_1 (TGF β_1), platelet-derived growth factor (PDGF) and fibroblast growth factor (FGF).

It has been well documented that hyperfiltration predicts progression to microalbuminuria and overt

proteinuria. Hyperfiltration is best decreased by improved metabolic control. Newer strategies aimed at primary prevention should focus at intensive blood glucose control. Besides this, other known risk factors for development of nephropathy should be targeted such as hypertension, dyslipidemia and smoking.

Strict Blood Glucose Control

Clinical trials have consistently demonstrated that A1c levels <7% are associated with decreased risk for clinical and structural manifestations of diabetic nephropathy in type 1 and type 2 diabetic patients. In the Diabetes Control and Complications Trial (DCCT), intensive treatment of diabetes reduced the incidence of microalbuminuria by 39%¹⁸. It is interesting to note that patients randomized to strict glycemic control had a long-lasting reduction of ~40% in the risk for development of microalbuminuria and hypertension 7–8 years after the end of the DCCT (EDIC study)¹⁹. In the UKPDS, a 30% risk reduction for the development of microalbuminuria was observed in the group intensively treated for hyperglycemia²⁰. Moreover, in the Kumamoto Study, intensive glycemic control also reduced the rate of development of micro- and macroalbuminuria²¹. Therefore, intensive treatment of glycemia aiming at A1c < 7% should be pursued as early as possible to prevent the development of microalbuminuria.

Strict Blood Pressure Control

Hypertension is an important risk factor for the development and progression of diabetic nephropathy. Hypertension is common in diabetic patients, even when renal involvement is not present. About 40% of type 1 and 70% of type 2 diabetic patients with normoalbuminuria have blood pressure levels > 140/90 mmHg²². The effect of antihypertensive therapy on the development of nephropathy has been tested in several studies. In the UKPDS trial, a reduction of systolic blood pressure from 154 to 144 mmHg reduced the risk for the development of microalbuminuria by 29%²³. The Appropriate Blood Pressure Control in Diabetes (ABCD) Trial described a significant reduction in the rate of development of microalbuminuria in normotensive patients with type 2 diabetes on strict antihypertensive regimen (with no difference between nisoldipine and enalapril)²⁴ whereas there was no effect in the hypertensive cohort²⁵.

The role of ACE-inhibitors in the prevention of diabetic nephropathy in patients with type 1 diabetes without microalbuminuria has not been well studied.

The EUCLID study did not detect any difference in the rate of development of microalbuminuria in patients who had type 1 diabetes and were treated for 2 years with lisinopril compared with placebo²⁶. However, the use of perindopril for 3 years in normotensive, normoalbuminuric type 1 diabetic patients delayed the increase in albuminuria²⁷. On the other hand, in patients with type 2 diabetes, both ACE inhibitors and ARBs diminish the risk for diabetic nephropathy²⁸. A large scale multinational clinical trial, ROADMAP is going on to study whether an ARB can prevent the onset of microalbuminuria in patients with type 2 diabetes.

Blood pressure targets for patients with diabetes are lower (<130/80 mmHg) than those for patients without diabetes²⁹. In the Hypertension Optimal Treatment (HOT) study, a reduction of diastolic blood pressure from 85 to 81 mmHg resulted in a 50% reduction in the risk of cardiovascular events in diabetic but not non-diabetic patients³⁰.

SECONDARY PREVENTION (PATIENTS WITH MICRO- AND MACROALBUMINURIA)

The goal of secondary prevention is to retard the progression from micro- to macroalbuminuria, and the decline of renal function in patients with macroalbuminuria, and the occurrence of cardiovascular events. The principles of treatment are the same as those adopted for prevention of diabetic nephropathy, although multiple and more intensive strategies must be used.

Strict Blood Glucose Control

Epidemiologic studies have shown an increase in diabetic nephropathy with elevated HbA1c levels. The effect of strict glycemic control on the progression from micro- to macroalbuminuria and on the rate of renal function decline in macroalbuminuric patients is still controversial. In the DCCT trial, intensive glycemic control did not decrease the rate of progression to macroalbuminuria in patients with type 1 diabetes who were microalbuminuric at the beginning of the study^{18,31}. The Microalbuminuria Collaborative Study group also reported similar findings³². However, these studies^{31,32} were underpowered to detect an effect of intensified glycemic control on the progression from micro- to macroalbuminuria. Moreover, improvement of glycemic control, especially if associated with lower blood pressure levels, reduced the renal function decline in proteinuric type 1 diabetic patients³².

However, in patients with type 2 diabetes, microalbuminuria and even macroalbuminuria can be present

at the time of diagnosis. In these patients, very few studies have analyzed the role of blood glucose control on the progression of diabetic nephropathy. In the Kumamoto study, a reduction in the conversion from micro- to macroalbuminuria was observed with intensive treatment²¹. Although the effects of strict glycaemic control on the progression of diabetic nephropathy are not firmly established, it should be pursued in all these patients with an aim to achieve HbA1c level below 7 percent.

Choice of Antidiabetic Drugs

Some of the antihyperglycemic agents seem to be especially useful. However, before use of these drugs in proteinuric type 2 diabetic patients, one should take the level of renal function also into account. Sulfonylureas and their metabolites, except glimepiride are eliminated via renal excretion and should not be used in patients with decreased renal function³³. Metformin should not be used when serum creatinine is > 1.5 mg/dl in men and > 1.4 mg/dl in women due to increased risk of lactic acidosis³⁴. Repaglinide³⁵ and nateglinide³⁶ have a short duration of action, are excreted independently of renal function and have a safety profile in patients with renal impairment. However, in such patients, sulfonylureas and insulin secretagogues are usually not very effective due to the low endogenous production of insulin resulting from long duration of diabetes and there is risk of precipitating hypoglycemia. Thus most type 2 diabetic patients with diabetic nephropathy should be treated with insulin.

Role of Thiazolidinediones

Thiazolidinediones, a subclass of insulin sensitizing hypoglycemics, are peroxisome proliferator-activated receptor (PPAR) agonists. In addition to their hypoglycemic effect, they can decrease systolic blood pressure, improve endothelial function, and decrease triglyceride levels while increasing high-density lipoprotein cholesterol levels. They may act directly on the kidneys to favorably influence glomerular hemodynamics and prevent cellular injury^{37,38}. These potential beneficial effects have prompted recent preliminary trials of the effects of thiazolidinediones on renal function in patients with diabetic nephropathy. Nakamura et al³⁹ examined UAE, intima-media thickness of the carotid arteries, and pulse wave velocity in 45 normotensive patients with type 2 diabetes and microalbuminuria assigned to receive pioglitazone or one of two nonthiazolidinedione hypoglycemics, glibenclamide and voglibose, for 12 months. UAE,

intima-media thickness, and pulse wave velocity were significantly lower in the pioglitazone group than that in the other groups at 6 and 12 months. Pitrosch et al⁴⁰ similarly found that rosiglitazone treatment lowered albumin excretion in type 1 diabetic patients with microalbuminuria. Of note, treatment with rosiglitazone also decreased GFR. In contrast, Agarwal et al³⁸ found that pioglitazone taken for 4 months did not reduce proteinuria in a group of 44 type 2 diabetic subjects with overt nephropathy. One potential explanation of the difference in results is that thiazolidinediones are not effective when renal disease is established. More studies, however, are clearly required to assess the role of these agents in the treatment of diabetic nephropathy.

It should be kept in mind that in patients with diabetes and renal failure, measurement of HbA1c may be misleading. HbA1c levels may be elevated in patients with renal failure because of an increase in the rate of HbA1c formation, possibly as a result of uremic acidosis⁴¹. On the other hand, reduced RBC survival may lead to decrease in HbA1c level⁴².

Strict Control of Blood Pressure

Role of ACE-Inhibitors

In microalbuminuric type 1 and type 2 diabetic patients, several studies have demonstrated that treatment of hypertension, irrespective of the agent used, produced a beneficial effect on albuminuria⁴³. The renin-angiotensin-aldosterone system (RAAS) blockade with ACE-inhibitors or ARBs confers an additional benefit on renal functions. This renoprotective effect is independent of blood pressure reduction^{43,44} and may be related to decreased intraglomerular pressure and passage of proteins into the proximal tubules⁴⁵. These drugs decrease UAE and the rate of progression from microalbuminuria to more advanced stages of diabetic nephropathy.

A meta-analysis of 12 trials evaluating 698 non-hypertensive microalbuminuric type 1 diabetic patients showed that treatment with ACE inhibitors decreased the risk of progression to macroalbuminuria by 60% and increased the chances of regression to normoalbuminuria⁴⁶. In the Micro-HOPE study, which involved a large number of patients with type 2 diabetes, microalbuminuric patients who received ramipril had a reduced progression rate to overt proteinuria⁴⁷. In the ABCD trial, aggressive blood pressure control slowed progression to proteinuria in normotensive²⁴, but not in hypertensive patients with type 2 diabetes and microalbuminuria²⁵. The non-insulin dependent DIAbetes,

Hypertension, microalbuminuria or proteinuria, CARDiovascular events, and ramipril (DIABHYCAR) study⁴⁸, a randomized, controlled trial, however found that the use of low dose ramipril for 4 years did not prevent cardiovascular events, death or end stage renal disease in 4937 patients with type 2 diabetes, albuminuria and serum creatinine greater than 1.7 mg/dl. The DIABHYCAR results were notably different from those of the Micro-HOPE substudy⁴⁷ which found that ramipril caused a 25% reduction in the risk for the composite end point of myocardial infarction, stroke or cardiovascular death in 3577 subjects with diabetes. The different doses of ramipril used, 1.25 mg/day in the DIABHYCAR study and 10 mg/day in the HOPE study may explain the difference in results.

Role of Angiotensin-II Blockers

The increased activity of RAAS is an important pathogenetic factor in the development of nephropathy in diabetic patients. The main damaging effect of this system is the end product angiotensin II and its adverse effects are vasoconstriction, increase in aldosterone secretion, growth, fibrosis, thrombosis, inflammation and oxidation. Various trials have established the beneficial effects of ARBs in patients with diabetic nephropathy. The reduction of endpoints in NIDDM with the Angiotensin-II Antagonist Losartan (RENAAL) study investigated the effects of ARB, losartan in 1513 patients with type 2 diabetes and nephropathy⁴⁹. It was found that losartan reduced the relative risk of the primary composite end points as compared with the control group on conventional antihypertensive agents by 16%, reduced the incidence of doubling of serum creatinine by 25% and reduced ESRD by 28%. Irbesartan Diabetic Nephropathy Trial (IDNT) investigated the effects of irbesartan and amlodipine on the rate of progression of diabetic nephropathy in 1715 subjects with type 2 diabetic nephropathy⁵⁰. The results of this study were even more impressive than RENAAL study, however, in both the studies, there was no significant difference in relation to the risk of deaths, cardiovascular morbidity or mortality. The third trial, IRbesartan MicroAlbuminuria in hypertension patients with type 2 diabetes (IRMA) was carried out in 520 subjects with type 2 diabetes who were followed up for 2 years⁵¹. It revealed that irbesartan therapy was associated with reduction of relative risk of development of diabetic nephropathy by 39%. Based on these trials, the role of ARBs in patients with diabetic nephropathy has been firmly established.

ACE-I versus ARB Therapy

An important question which remains to be fully answered in the relative value of ACE-I versus ARB treatment. Based on various trials, American Diabetes Association (2006) has recommended that all patients with diabetes and hypertension should be treated with a regimen that includes either an ACE-inhibitor or an ARB except during pregnancy. If one class is not tolerated, the other should be substituted. If needed, to achieve blood pressure targets, a thiazide diuretic should be added. In addition, ACE-inhibitors have been shown to reduce severe cardiovascular disease. There is some evidence to suggest that ARBs have a smaller magnitude of rise in potassium compared with ACE-I.

The question of whether ACE-Is and ARBs have similar effects in patients with type 2 diabetes was approached by the recently reported Diabetics Exposed to Telmisartan and Enalapril (DETAIL) study⁵². The authors concluded that telmisartan is not inferior to enalapril in providing long-term renoprotection in patients with type 2 diabetes mellitus and early nephropathy. A further logical conclusion is that the moderate dose of ACE-I was at least as effective as the maximum commonly used dose of an ARB. The results were consistent with those of previous smaller studies suggesting that ACE-I and ARBs similarly reduce albuminuria and mortality⁵³ and support the notion that ACE-I and ARBs have similar overall effects.

Dual Blockage of RAAS

There is increasing evidence that angiotensin-II, the effector molecule of RAAS can be generated not only by the angiotensin-converting enzyme, but also by other pathways including chymase. Dual blockade of RAAS with both ACE-I and ARB has been suggested as superior to monotherapy in diabetic patients with microalbuminuria⁵⁴ and in diabetic nephropathy^{55,56} and in nondiabetic renal disease⁵⁷.

To date, the effects of dual blockade in diabetic nephropathy have been assessed only in short-term studies using reduction in proteinuria as an index of benefit. Fujisawa et al⁵⁸ compared the effect of half doses of candesartan and imidapril to full doses of each on albuminuria and blood pressure in 27 patients with type 2 diabetes and early nephropathy (urinary albumin excretion < 1 g/day and serum creatinine < 1.5 mg/dl). In comparison to use of the single agents, the combination therapy reduced albuminuria by about one third without changing the blood pressure. Similar positive

effects of combination therapy were observed in a study comparing the combination of enalapril and losartan to each agent alone⁵⁹. An analysis of three short-term crossover studies including 51 patients, by Jacobsen, et al⁶⁰, concluded that dual blockade reduces albuminuria by 37% while reducing systolic blood pressure by 7%, and diastolic blood pressure by 5%. In another study, Jacobson, et al⁶¹ found that dual blockade of RAAS is superior to the maximal recommended dose of ACE-I with regard to lowering of albuminuria and blood pressure in type 1 diabetes with nephropathy.

Together, these recent studies offered evidence favoring the use of combination of ACE-I and ARB in diabetic nephropathy. Long-term trials are needed, however, to confirm the superiority of combination therapy over single blockade in patients with diabetic nephropathy and in particular to compare the effect of combination therapy with the use of higher doses of single agents. There are many ongoing clinical trials involving ARBs. However, with an anticipated patient recruitment target of up to 5.5 years, ONTARGET (Ongoing Telmisartan Alone or in combination with Ramipril Global Endpoint Trial) is the largest ARB trial ever undertaken, which will further clarify the role of ACE-I and ARB in these cases. For the present, some authors have suggested that combination therapy be reserved for diabetic patients with uncontrolled albuminuria with or without hypertension despite maximal doses of single renin-angiotensin system blocking agents^{62,63}.

Role of Aldosterone Antagonists

Recent studies have suggested that aldosterone blockade has beneficial effects on the progression of cardiac disease beyond those achievable with conventional doses of ACE-Is^{64,65}. It has been shown, moreover, that in patients with diabetic nephropathy, maximum doses of ACE-Is or ARBs may not suppress plasma aldosterone levels⁶⁶. Presumably, aldosterone could therefore contribute to the progression of cardiovascular and renal disease during ACE-I and ARB treatment. This possibility has prompted investigation of the renal effects of superimposing aldosterone blockade on ACE-I and ARB treatment in patients with diabetic nephropathy. Sato, et al⁶⁷ initially reported that addition of spironolactone 25 mg/day to trandolapril in type 2 diabetic subjects with early nephropathy on ACE-I treatment reduced proteinuria without lowering the blood pressure. A subsequent study by the same investigators assessed the effect of adding spironolactone to ACE-Is in patients with a variety of renal

disease who had urinary albumin excretion of over 0.5 g/day despite treatment with an ACE-I for at least 10 months⁶⁸. Addition of spironolactone reduced albuminuria by 46% in the diabetic group and 29% in the nondiabetic group, again without lowering blood pressure. In a placebo-controlled crossover study of 21 type 2 diabetic patients with nephropathy, Rossing, et al⁶⁹ found that addition of spironolactone to an antihypertensive regimen including ACE-Is reduced albuminuria by 33%. However, in patients receiving aldosterone antagonists in addition to ACE-I or ARB, one should carefully look for development of hyperkalemia.

Role of Diuretics

A number of studies have suggested that the antiproteinuric effect of angiotensin converting enzyme inhibition is enhanced by reduction of extracellular fluid volume. Esnault et al⁷⁰ found that in 18 proteinuric patients (seven had diabetes mellitus) who were taking ramipril 5 mg and valsartan 80 mg per day, addition of furosemide further reduced proteinuria. Diuretic agents themselves may have an antiproteinuric effect. The recent Natrilix SR versus Enalapril Study in hypertensive Type 2 Diabetics with Microalbuminuria (NESTOR) study⁷¹, which enrolled 570 type 2 diabetic subjects with microalbuminuria and hypertension, found that the effect of receiving indapamide SR 1.5 mg daily is equivalent to receiving enalapril 10 mg daily for a year in reducing urinary albumin to creatinine ratio and blood pressure.

Role of Calcium Channel Blockers

Calcium antagonists are widely used as an adjunct to ACE-Is or ARBs for control of blood pressure in diabetic patients with nephropathy. Previous studies have yielded contradictory results, on the question of whether calcium antagonists offer renoprotection in addition to blood pressure reduction. In general, the non-dihydropyridine subclass has been more often recommended as renoprotective. This notion was supported by a recent study of 36 type 2 diabetic hypertensive patients with persistent microalbuminuria 1 year after treatment with ACE-I⁷².

Dietary Intervention

Meta-analysis of five studies involving a total of 108 patients dietary protein restriction slowed the progression of diabetic nephropathy in patients with type 1 diabetes⁷³. In another randomized controlled trial in

82 patients with type 1 diabetes and progressive diabetic nephropathy, a moderately low protein diet (0.9 g/kg/day) reduced the risk of end stage renal disease or death by 76 percent⁷⁴. Replacing red meat with chicken in the usual diet reduced UAE by 46% and reduced total cholesterol, LDL-cholesterol, and apolipoprotein B in microalbuminuric patients with type 2 diabetes⁷⁵. Based on various studies, it seems prudent to limit protein intake to 0.8 g/kg. The mechanisms by which a low protein diet may reduce progression of diabetic nephropathy are still unknown, but might be related to improved lipid profile and/or glomerular hemodynamics.

Dyslipidemia

Albuminuria is associated with an unfavorable lipid profile with higher concentrations of total cholesterol, LDL-cholesterol, total triglycerides, apolipoprotein B-1, and with an increase in atherogenic small dense LDL particles and reduced HDL-cholesterol levels⁷⁶. Higher cholesterol levels are associated with faster progression of renal disease⁷⁷. There is some evidence that lipid reduction by antilipemic agents might preserve GFR and decrease proteinuria in diabetic patients⁷⁸. In the Heart Protection Study, 40 mg simvastatin reduced the rate of major vascular events and GFR decline in patients with diabetes, independent of cholesterol levels at baseline, by 25%⁷⁹. Although there have been no large scale trials that lipid lowering therapy alters the rate of progression of renal disease, the strong association with cardiovascular disease suggests that lipid lowering therapy should be considered in patients with micro- and macroalbuminuria.

Anemia

Anemia may occur in patients with diabetic nephropathy even before the onset of advanced renal failure (serum creatinine <1.8 mg/dl), and it has been related to erythropoietin deficiency⁸⁰. Furthermore, anemia has been considered a risk factor for progression of renal disease and retinopathy. Besides this, erythropoietin has been found to interact with its receptor expressed in a large variety of nonhematopoietic tissues including kidneys to induce a range of cytoprotective cellular responses, including mitogenesis, angiogenesis, inhibition of apoptosis and promotion of vascular repair⁸¹. It is recommended to start erythropoietin treatment when hemoglobin levels are <11 g/dl. The target hemoglobin levels should be 11-12 g/dl, and the potential risk of elevation of blood pressure levels with erythropoietin treatment should be taken into account.

Role of Aspirin

Low-dose aspirin has been recommended for primary and secondary prevention of cardiovascular events in adults with diabetes. This therapy did not have a negative impact on renal function (UAE or GFR) in type 1 and type 2 diabetic patients with micro- or macroalbuminuria^{82,83}. However, the subgroup analysis of the Primary Prevention Project trial did not show a significant reduction in the occurrence of cardiovascular events in 1,031 diabetic patients using low-dose aspirin (100 mg/day)⁸⁴. Although this study was underpowered to analyze the effect on the development of cardiovascular events, these data raise the issue that diabetic patients could be less responsive to aspirin therapy (aspirin resistance). In fact, a recent study demonstrated a reduced response of platelets from diabetic subjects to treatment with aspirin (150 mg/day)⁸⁵. Therefore, diabetic patients might benefit from aspirin doses >100–150 mg/day or use of other antiplatelet agents such as clopidogrel.

Cessation of Smoking

Diabetics who smoke are at increased risk of microalbuminuria⁸⁶. In type 1 and type 2 diabetes, GFR fell twice as quickly in smokers as in nonsmokers and even in non-diabetic patients. Risk for progression to ESRD was much increased in smokers⁸⁷. However, the benefit of smoking cessation for renoprotection is not well appreciated by the patients and even the doctors.

MULTIFACTORIAL APPROACH

Patients with microalbuminuria frequently have other cardiovascular risk factors, such as hypertension and dyslipidemia. The beneficial effect of a multifactorial approach in preventing the development of proteinuria in diabetes was well documented in the Steno-2 study⁸⁸, where 160 microalbuminuric patients with type 2 diabetes were randomly assigned to receive standard diabetes care from the general practitioners or on intensive therapeutic program at the Steno Diabetes Centre, consisting of advice about an appropriate diet and exercise regimen, smoking-cessation program, intensive treatment of hyperglycemia, hyperlipidemia and hypertension, use of an ACE inhibitor or ARB (irrespective of blood pressure), use of antioxidants and use of aspirin. The targets were to achieve blood pressure levels <130/80 mmHg, fasting serum cholesterol <175 mg/dl, and A1c <6.5%. The primary end point was to reduce the progression to overt diabetic nephropathy; secondary end points were to limit the incidence and

progression of retinopathy and nephropathy. After 4 years of follow-up, patients who received intensive and multiple treatment had approximately 50 percent reduction of progression of microvascular complications [mean odds ratio (OR) 0.27 for nephropathy, 0.45 for retinopathy, and 0.32 for nephropathy]. In 2003, the authors published the results after 7 to 8 years of follow-up⁸⁹. The study showed a 55% reduction in the risk for the development of a composite end points consisting of death from cardiovascular causes, nonfatal myocardial infarction, revascularization procedures, nonfatal stroke and amputation in the multifactorial intervention group. Thus, a good management of diabetes, based on a multifactorial approach, represents the best strategy for prevention of various complications.

NOVEL THERAPEUTIC STRATEGIES

Many patients with diabetes have progressive nephropathy despite various therapeutic interventions mentioned above. Therefore, treatment targeting novel pathogenetic mechanisms may be beneficial. These have been listed in Table 2.

Table 2: Novel therapies for diabetic nephropathy

- Protein kinase C- β inhibition
- Inhibitors of advanced glycation end (AGE) products
- AGE cross link breakers
- Thromboxane antagonists
- Endothelin type A receptor antagonist
- Pirfenidone
- Antioxidants
- Thiamine

Protein kinase C (PKC)- β inhibitor: Preclinical studies have shown an important role for protein kinase C (PKC)- β in the pathogenesis of diabetic nephropathy. This signal transduction mediator induces a number of processes leading to renal injury that can be prevented by ruboxistaurin, a selective PKC- β inhibitor, in diabetic animals⁹⁰. Recently, it was also found to be effective in reducing albuminuria in human beings with type 2 diabetes and nephropathy⁹¹.

Inhibitors of advanced glycation end-products: Advanced glycation end-products (AGEs) have been implicated in the pathogenesis of glomerular injury in diabetes, hence attempts have been made to slow the progression of diabetic nephropathy by inhibiting AGE formation. In a recent study, A Clinical Trial In Overt

Nephropathy of Type 1 Diabetics (ACTION I), pimagidine, a second generation inhibitor of AGEs, reduced urinary protein excretion and the decline in GFR in proteinuric type 1 diabetic patients⁹². Besides this, treatment with ALT-711, a **cross-link breaker** of the AGEs, has been shown to result in a significant reduction in UAE, blood pressure and renal lesions in experimental diabetes⁹³.

Thromboxane antagonists: Few workers have suggested that platelet activation contributes to the pathogenesis of both the macrovascular and microvascular complications of diabetes^{94,95}. Platelets from patients with diabetes and from diabetic rats have been reported to synthesize more thromboxane than do normal platelets in response to a variety of agonists that induce deacylation of arachidonate from membrane phospholipids⁹⁵.

Endothelin type A receptor antagonists: Endothelin type A receptor antagonists have been shown to reduce albuminuria in animal models of diabetes⁹⁶. A randomized trial to assess the effect of avosentan, an endothelin receptor antagonist, in subjects with diabetes and nephropathy has been started and will be completed in 2009.

Pirfenidone: Pirfenidone, an antifibrotic agent, has been shown to be beneficial in animal models of diseases that involve scar formation, including pulmonary fibrosis and renal diseases characterized by glomerulosclerosis and interstitial fibrosis. Two randomized phase II trials are underway to evaluate its safety and efficacy in diabetic nephropathy.

Antioxidants: A causal relationship between oxidative stress, endothelial cell dysfunction and diabetic nephropathy has been established⁹⁷. Oxidative stress induces mRNA expression of NF κ B genes which in turn promotes production of proinflammatory proteins – TGF- β , fibronectin, laminin, elastin, IL-1, IL-6 and PDGF and inhibition of oxidative stress ameliorates all the manifestations associated with endothelial cell dysfunction and diabetic nephropathy.

Thiamine: High doses of thiamine and its derivative, benfotiamine have been shown to retard the development of microalbuminuria in experimental diabetic nephropathy, probably due to decreased activation of protein kinase C, decreased protein glycation, and oxidative stress⁹⁸. Decreased charge selectivity of the glomerular barrier, as a result of decreased glycosaminoglycan heparan sulfate content and loss of anionic charge on the glomerular basement membrane, is a specific

determinant of enhanced albumin ultrafiltration and albuminuria of diabetic nephropathy⁹⁹. In a rat model of diabetes induced glomerulosclerosis, administration of a modified heparan glycosaminoglycan prevented albuminuria, glomerular and tubular matrix accumulation and TGF β 1 mRNA overexpression¹⁰⁰. Very few studies have been conducted in humans.

SUMMARY

Diabetic nephropathy is presently the commonest cause of end stage renal failure in most of the countries and the prevalence continues to increase. There is sufficient evidence from the literature that tight control of blood glucose and blood pressure significantly reduces the risk of development of diabetic nephropathy. With the onset of albuminuria, good control of blood pressure especially with the use of inhibitors of renin-angiotensin-aldosterone system will delay the progression to end stage renal failure. Overall, good management of diabetes based on multifactorial approach represents the best strategy for prevention of various complications of diabetes.

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