

Volume No. 8

Symposium On Diabetes

Diabetic Nephropathy

Introduction

We, at Magnus Novo Nordisk, are in the forefront of diabetes care by not only providing excellent products but also creating awareness about diabetes. As leaders in diabetes care, we feel responsible to join hands with the medical fraternity to help detect diabetes and control it.

Symposium on diabetes is an effort towards disseminating information about various aspects of diabetes. Seventh in the series was on Cardiovascular Disease which highlighted the economic and physical burden imposed by the morbidity and mortality due to this macrovascular complication of diabetes.

In the current issue, Diabetic Nephropathy, a micro vascular complication of both Type 1 and Type 2 diabetes is discussed. As the leading cause of chronic renal failure, prevention of diabetic nephropathy is our best bet. Efforts directed towards preventing and/or delaying diabetic nephropathy by achieving tight glycemic control have met with promising results worldwide.

The staggering negative impact of renal failure mandates that aggressive therapy should be directed to prevent the onset of nephropathy and in those who have already developed nephropathy to delay its progression.

Through this quarterly publication Magnus Novo Nordisk promises to bring forth more information related to the practical aspects of diabetes. We are hopeful that you will find this series interesting and helpful in your day-to-day clinical practice.

Happy reading !

Diabetic Nephropathy

Diabetic nephropathy is a clinical syndrome characterized by persistent albuminuria (>300mg/24 h), a relentless decline in glomerular filtration rate (GFR), and raised arterial blood pressure.¹

Nephropathy is a major cause of illness and death in diabetes. Indeed, the excess mortality of diabetes occurs mainly in proteinuric type 1 and type 2 patients and results not only from end-stage renal disease (ESRD) but also from cardiovascular disease; the later particularly in type 2 patients.

Dramatic worsening of the prognosis of diabetic patients with proteinuria compared to diabetic patients without proteinuria and to the general population has been noted. The cardiovascular mortality of diabetic patients with proteinuria is about 4 times that of diabetic patients without proteinuria and 37 times that of the general population¹.

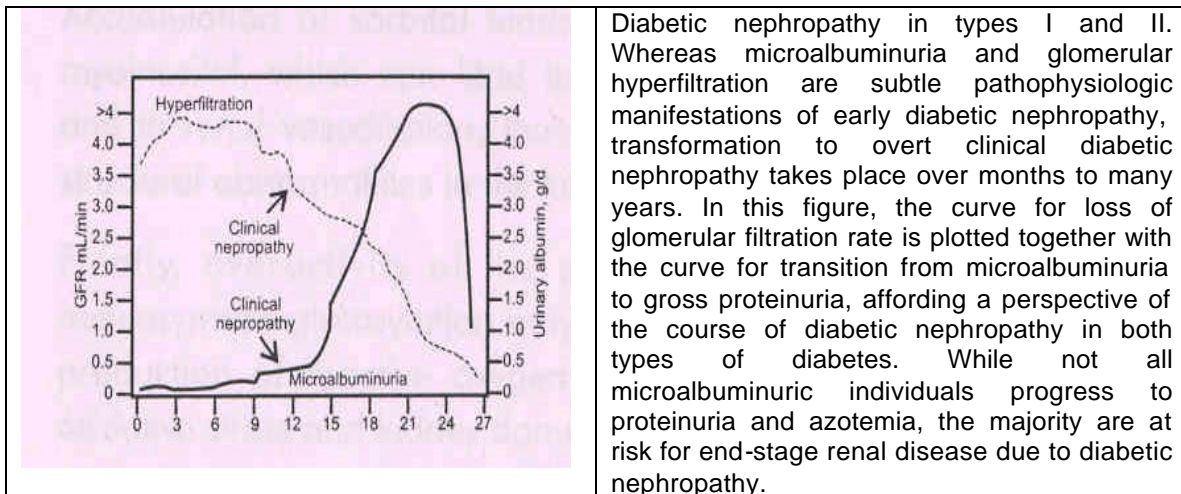
Both the incidence and the prevalence of ESRD caused by diabetes have risen each year over the past decade, according to reports from European, Japanese, and North American dominance of diabetes in ESRD is the 1997 report of the United States Renal Data System (USRDS), which noted that of 257, 266 patients receiving either dialytic therapy or a kidney transplant in 1995 in the United States, 80,667 had diabetes, a prevalence rate of 31.4%. Also, during 1995 (the most recent year for which summative data are available), of 71,875 new (incident) cases of ESRD, 28,740 (40%) patients were listed as having diabetes².

The direct cost of caring for persons with diabetes with ESRD is approximately \$5 billion per year in the United States alone, and the amount is rapidly rising. The indirect cost is of the some order of magnitude¹.

Although proteinuria had been demonstrated in diabetic patients since the 18th century, it was Bright who in 1836 postulated that albuminuria could reflect a serious renal disease specific to diabetes. One hundred years later, Kimmelstiel and Wilson described the nodular glomerular intercapillary lesions in patients with long-standing type 2 who had the clinical syndrome of heavy proteinuria and renal failure accompanied by arterial hypertension¹. Persistent albuminuria (>300 mg/24 h or 200 mcg/min) is the hallmark of diabetic nephropathy, which can be diagnosed clinically if the following additional criteria are fulfilled: the presence of diabetic retinopathy and the absence of any clinical or laboratory evidence of other kidney or renal tract disease. This clinical definition of diabetic nephropathy is valid in both type 1 and type 2 diabetes.

The earliest clinical evidence of nephropathy is the appearance of low but abnormal levels (>30 mg/day or 20 µg/min) of albumin in the urine, referred to as microalbuminuria.

Without specific interventions, ~80% of subjects with type 1 diabetes who develop sustained microalbuminuria have their urinary albumin excretion increase at a rate of ~ 10 - 20% per year to the stage of overt nephropathy or clinical albuminuria (<300 mg/24 h or >200 µg/min) over a period of 10 –15 years, with hypertension also developing along the way. Once overt nephropathy occurs, without specific interventions, the GFR gradually falls over a period of several years at a rate that is highly variable from individual to individual (220ml/min/year).



ESRD develops in 50% of type 1 diabetic individuals with overt nephropathy with 10 years and in >75% by 20 years.

A higher proportion of individuals with type 2 diabetes are found to have microalbuminuria and overt nephropathy shortly after the diagnosis of their diabetes, because diabetes is actually present for many years before the diagnosis is made and also because the presence of albuminuria may be less specific for the presence of diabetic nephropathy, as shown by biopsy studies. Without specific interventions, 20 – 40% of type 2 patients with microalbuminuria progress to overt nephropathy, but by 20 years after onset of overt nephropathy, only ~ 20% will have progressed to ESRD. Once the GFR begins to fall, the rates of fall in GFR are again highly variable from one individual to another, but overall, they may not be substantially different between patients with type 1 and patients with type 2 diabetes³.

Pathogenesis of Diabetic Nephropathy

Among the genetic, metabolic, and hemodynamic factors that appear to be most important in pathogenesis of diabetic nephropathy are hyperglycemia, hypertension, ethnicity, gender, family history, duration of diabetes, and cigarette smoking. These are likely significant in both type 1 and type 2 diabetes. Table 1 lists risk factors implicated in the development of diabetic nephropathy⁴.

Table 1 : Risk Factors For Diabetic Nephropathy ⁴	
Hyperglycemia	Ethnicity
Hypertension	Mexican-American
Microalbuminuria	Native American
Long duration of diabetes	African-American
Age	Asian
Family history	Male gender
Hypertension	Cigarette smoking
Cardiovascular disease	Genes
Nephropathy	- Insulin resistance
	- Angiotensin – converting enzyme polymorphism
	- Ion transport dysregulation
	- Hypercholesterolemia

Role of Hyperglycemia In The Initiation And Progression of Diabetic Nephropathy

Mechanisms of Hyperglycemic Damage⁴

A number of potential mechanisms exist by which poor glycemic control can damage the kidney and initiate or propagate the development of diabetic nephropathy, including

- hypertrophy and basement membrane thickening;
- increased endothelial cell permeability to albumin;
- increased production of vasodilatory prostaglandins, which contribute to renal hyper perfusion, intraglomerular hypertension, and increased hyper filtration.

Hyperglycemia also causes release of cytokines such as transforming growth factor-beta, by glomerular endothelial, epithelial, mesangial, and tubular cells, which results in mesangial hypertrophy.

Elevated glucose levels also cause production of advanced glycosylation end products, which alter structural proteins and cause vascular dysfunction, glomerular lesions, proteinuria, and renal failure.

Advanced glycosylation end products are, in fact, believed to play an important role in the pathogenesis of diabetic nephropathy and other complications.

Chronic hyperglycemia also increases the activity of the polyol pathway, which promotes and influx of glucose and accumulation of sorbitol in tissues such as the kidney, which do not require insulin for glucose uptake.

Accumulation of sorbitol leads to a depletion of intracellular myoinositol, which can lead to defects in cellular metabolism and to renal vasodilation, thus contributing to development of structural abnormalities in the kidney.

Finally, overactivity of the polyol pathway or increased nonenzymatic glycosylation may also lead to an increase in the production of reactive oxygen species, leading to increased oxidative stress and kidney damage via this mechanism.

Despite the demonstration that these molecular alterations occur, the basic question of why only certain diabetic individuals develop nephropathy is not understood. In type 1, it appears that there is a genetic predisposition to develop nephropathy because it has been shown that in certain families kidney failure results despite good glycemic control. Similarly the increased predilection of certain minority groups with diabetes mellitus to develop kidney disease also supports the role of genetics in the pathogenesis of diabetic nephropathy.

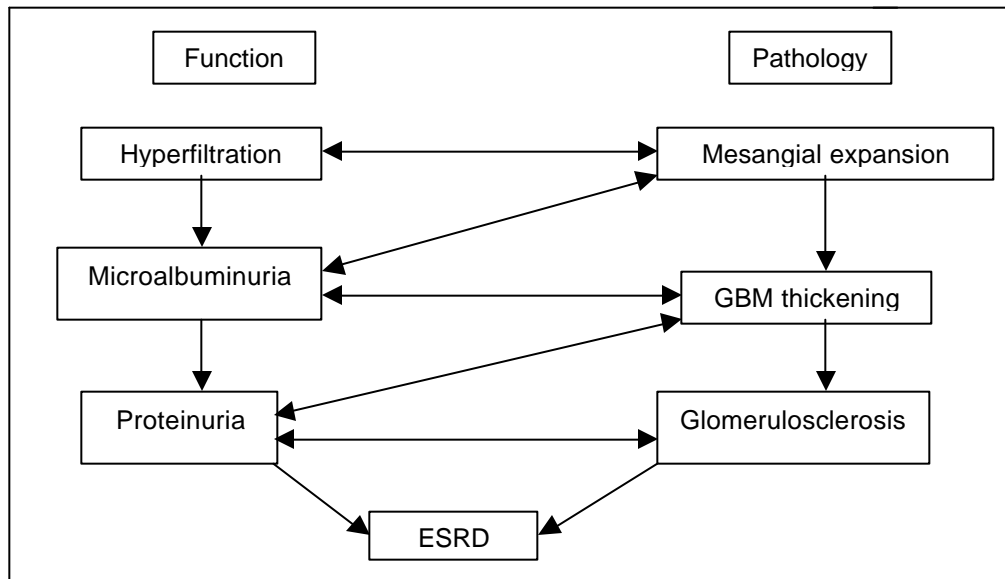
Natural History of Diabetic Nephropathy⁴

The progression of nephropathy in type 1 diabetes has classically been described as a series of stages in a relentlessly deteriorating course from normal renal function to ESRD, marked by the appearance of increasing amounts of albuminuria. These same stages apparently occur in type 2 diabetes. Increasing albumin excretion reflects histologic and functional abnormalities in the kidney.

Stage 1, clinically manifested as an increase in the GFR, is characterized by hyperfunction and hypertrophy of kidney tissue.

Stage 2, which occurs 2 to 3 years after the onset of diabetes, is characterized histologically by glomerular mesangial expansion, glomerulosclerosis, and basement membrane thickening, without clinically apparent disease.

Stage 3, which occurs 7 to 15 years after onset, is the stage of incipient nephropathy, with its hallmark an increase in urinary albumin excretion into the range of microalbuminuria. Microalbuminuria is the earliest laboratory evidence of nephropathy and occurs 5 to 8 years before the onset of overt proteinuria. An albumin excretion rate (AER) below 30 mg/d (20 mcg/min) represents normoalbuminuria; between 30 and 300 mg/d (200 mcg/min) is designated microalbuminuria; greater than 300 mg/d (200mcg/min) is termed microalbuminuria, clinical albuminuria, or gross or overt proteinuria. At this point, the urine protein test is positive with commercial albumin test sticks. During stage 3, the GFR is usually normal or slightly elevated, and intervention can reverse the albuminuria and halt or slow the progression of nephropathy.



Stages of nephropathy. The inter relationships between functional and morphologic markers of the stages of diabetic nephropathy are shown. Additional pathologic studies are needed to time with precision exactly when glomerular basement membrane (GBM) thickening and glomerular mesangial expansion take place. ESRD-endstage renal disease.

Stage 4, is overt nephropathy, characterized by proteinuria and a normal or slightly decreased GFR. Glomerulosclerosis continues during stages 3 and 4. Intervention during stage 4 can slow, but not reverse, the progression to renal failure. Without such intervention, the decline in renal function can be expected to occur at rate of approximately 1 ml/min per month, but there is wide individual variation. The rate of progression is increased if the individual is hypertensive or a cigarette smoker.

Stage 5, which occurs 20 to 40 years after onset of diabetes, is associated with a continuing decline in GFR and increasing blood pressure. Between 50% and 75% of patients who reach this point progress to ESRD within 10 to 18 years.

The onset of albuminuria within 5 years of diagnosis of type 1 diabetes, but not type 2, should be an alert to search for another cause of the kidney disease. In type 2 diabetes, the incidence of albuminuria at time of diagnosis of diabetes ranges from 3% to 30%. This incidence likely reflects the fact that most people with type 2 diabetes have had hyperglycemia for a number of years before diagnosis, so the early stages (stages 1 and 2) of nephropathy have already passed undetected. Finally, in type 1 diabetes, microalbuminuria and renal disease can still develop after as long as 30 years.

Screening For Albuminuria

A routine urinalysis should be performed at diagnosis in patients with type 2 diabetes. If the urinalysis is positive for protein, a quantitative measure is frequently helpful in the development of a treatment plan. If the urinalysis is negative for protein, a test for the presence of microalbumin is necessary. Microalbuminuria rarely occurs with short duration of type 1 diabetes or before puberty; therefore, screening in individuals with type 1 diabetes should begin with puberty and after 5 years' disease duration. Because of the difficulty in precise dating if the onset of type 2 diabetes, such screening should begin at the time of diagnosis. After the initial screening and in the absence of previously demonstrated microalbuminuria, a test for the presence of microalbumin should be performed annually.

Screening for microalbuminuria can be preformed by three methods:

- 1) Measurement of the albumin-to-creatinine ratio in a random spot collection;
- 2) 24-h collection with creatinine, allowing the simultaneous measurement of creatinine clearance; and
- 3) Timed (e.g., 4-h or overnight) collection.

Table 2: Definitions of abnormalities in albumin excretion³

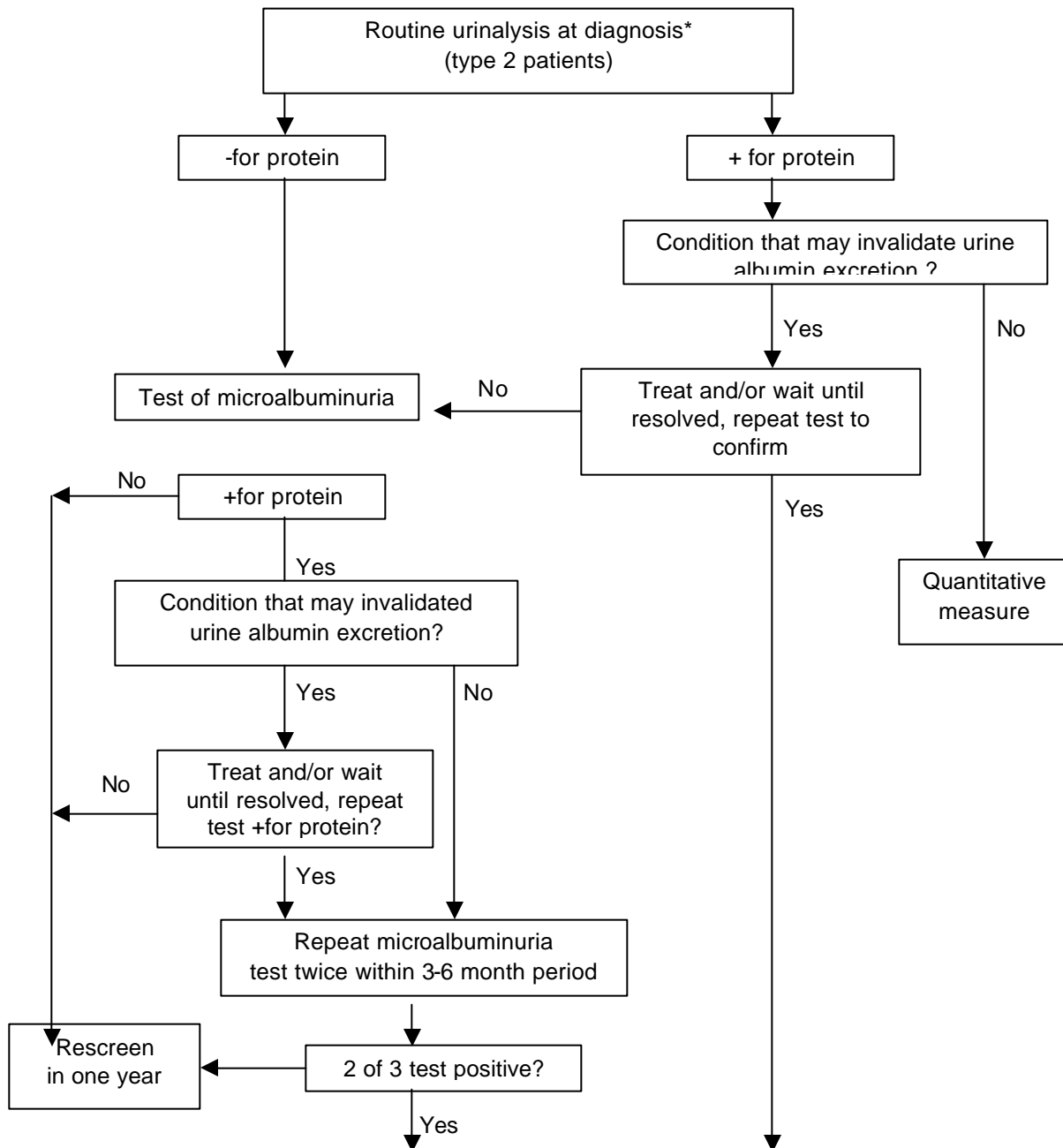
Category	24-h collection (mg/24h)	Timed collection (µg/min)	Spot collection (µg/mg creatinine)
Normal	<30	<20	<30
Microalbuminuria	30-300	20-200	30-300
Clinical albuminuria	>300	>200	>300

Because of variability in albumin excretion, two of three specimens collected within a 3 to 6 months period should be abnormal before considering a patient to have crossed one of these diagnostic thresholds. Exercise within 24 h, infection, fever congestive heart failure, marked hyperglycemia, and marked hypertension may elevate urinary albumin excretion over baseline values.

The first method is often found to be the easiest to carry out in an office setting and generally provides accurate information; first-void or other morning collections are preferred because of the known diurnal variation in albumin excretion, but if this timing cannot be used, uniformity of timing for different collections in the same individual should be employed. Specific assays are needed to detect microalbuminuria because standard hospital laboratory assays for urinary protein are not sufficiently sensitive to measure such levels. Microalbuminuria is said to be present if urinary albumin excretion is >30 mg/24 h (equivalent to 20 µg/min or a timed specimen or 30 mg/g creatinine on a random sample) (Table 2)³.

Short-term hyperglycemia, exercise, urinary tract infections, marked hypertension, heart failure, and acute febrile illness can cause transient

elevations in urinary albumin excretion. If assays for microalbuminuria are not readily available, screening with reagent tablets or dipsticks for microalbumin may be carried out, since they show acceptable sensitivity (95%) and specificity (93%) when carried out by trained personnel. Because reagent strips only indicate concentration and do not correct for creatinine as the spot urine albumin-to-creatinine ratio does, they are subject to possible errors from alterations in urine concentration. All positive tests by reagent strips or tablets should be confirmed by more specific methods. There is also marked day-to-day variability in albumin excretion, so at least two of three collections done in a 36 month period should show elevated levels before designating a patient as having microalbuminuria. An algorithm for microalbuminuria screening is given in Fig. 1



Microalbuminuria, begin treatment

Overt nephropathy, begin treatment

Figure 1 Screening for microalbuminuria.

* in type 1 diabetes, screening for albuminuria should begin with puberty and after 5 years' disease duration.

The role of annual urine protein dipstick testing and microalbuminuria assessment is less clear after diagnosis of microalbuminuria and institution of angiotension-converting enzyme (ACE) inhibitor therapy and blood pressure control. Many experts recommend continued surveillance both to assess response to therapy and progression of disease. In addition to assessment of urinary albumin excretion, assessment of renal function is important in patients with diabetic kidney disease.

Glycemic Control

The Diabetes Control and Complications Trial (DCCT), the United Kingdom Prospective diabetes Study (UKPDS), the Stockholm Intervention Study, and the Kumamoto study have shown definitively that intensive diabetes therapy can significantly reduce the risk of the development of microalbuminuria and overt nephropathy in people with diabetes. Thus achievement of excellent glycemic control should be the goal in this regard. However, individual patient characteristic should help determine mutually acceptable target.

Hypertension Control

In patients with type 1 diabetes, hypertension is usually caused by underlying diabetic nephropathy and typically becomes manifest about the time that patients develop microalbuminuria. In patients with type 2 diabetes, hypertension is present at the time of diagnosis of diabetes in about one-third of patients. The common coexistence of glucose intolerance, hypertension, elevated LDL cholesterol and triglycerides, and a reduction in HDL cholesterol, obesity, and susceptibility to cardiovascular disease suggests that they may relate to common underlying mechanisms, such as insulin resistance; and this complex is often referred to as syndrome X or insulin-resistance syndrome. Hypertension in type 2 patients may also be related to underlying diabetic nephropathy, be due to coexisting "essential" hypertension, or be due to a myriad of other secondary causes, such as renal vascular disease. Isolated systolic hypertension has been attributed to the loss of elastic compliance of atherosclerotic large vessels. In general, the hypertension in patients with both types of diabetes is associated with an expanded plasma volume, increased peripheral vascular resistance, and low rennin activity.

Both systolic and diastolic hypertension markedly accelerate the progression of diabetic nephropathy, and aggressive antihypertensive management is able to greatly decrease the rate of fall of GFR. Appropriate antihypertension intervention can significantly increase the median life expectancy in patients with

type 1 diabetes, with a reduction in mortality from 94 to 45% from 73 to 31% ,16 years after the development of overt nephropathy.

The primary goal of therapy for nonpregnant diabetic patients >18 years of age is to decrease blood pressure to and maintain it at <130 mmHg systolic and <85 mmHg diastolic. For patients with isolated systolic hypertension with a systolic pressure of >180 mmHg, the initial goal of treatment is to reduce the systolic blood pressure to <160 mmHg and to lower the systolic blood pressure by 20 mmHg for those with systolic pressure of 160-179 mmHg. If these initial goals are met and well tolerated, further lowering may be indicated.

A major aspect of initial treatment should consist of lifestyle modifications, such as weight loss, reduction of salt and alcohol intake, and exercise. In patients with underlying nephropathy, treatment with ACE inhibitors is also indicated as part of initial therapy. If after 46 weeks sufficient blood pressure reduction has not occurred, additional pharmacological therapy is indicated.

ACE Inhibitors

Many studies have shown that in hypertensive patients with type 1 diabetes, ACE inhibitors can reduce the level of albuminuria and can reduce the rate of progression of renal disease to a greater than other antihypertensive agents that lower blood pressure by an equal amount. Other studies have shown that there is benefit in reducing the progression of microalbuminuria in normotensive patients with type 1 diabetes and normotensive and hypertensive patients with type 2 diabetes.

Use of ACE inhibitors may exacerbate hyperkalemia in patients with advanced renal insufficiency and/or hyporeninemic hypoaldosteronism. In older patients with bilateral renal artery stenosis and in patients with advanced renal disease even without renal artery stenosis, ACE inhibitors may cause a rapid decline in renal function. Cough may also occur. This class of agents is contraindicated in pregnancy and therefore should be used with caution in women of childbearing potential.

Because of the high proportion of patients who progress from microalbuminuria to overt nephropathy and subsequently to ESRD, use of ACE inhibitors is recommended for all type 1 patients with microalbuminuria, to overt nephropathy and ESRD in patients with type 2 diabetes, the use ACE inhibitors in normotensive type 2 diabetic patients is less well substantiated. The effect of ACE inhibitors appears to be a class effect, so choice of agent may depend on cost and compliance issues.

Protein Restriction

The general consensus is to prescribe a protein intake of approximately the adult Recommended Dietary Allowance (RDA) of $0.8 \text{ g.kg}^{-1}.\text{day}^{-1}$ (~10% of daily calories) in the patient with overt nephropathy. However, it has been suggested that once the GFR begins to fall, further restriction to $0.6 \text{ g.kg}^{-1}.\text{day}^{-1}$ may prove useful in slowing the decline of GFR in selected patients. On the other hand, nutrition deficiency may occur in some individuals and may be associated with muscle weakness. Protein-restricted meal plans should be designed by a registered dietitian familiar with all components of the dietary management of diabetes.

Concurrent Care

Diabetic retinopathy is present in virtually all type 1 patients with nephropathy, whereas only 50% to 60% of proteinuric type 2 patients have retinopathy. Absence of retinopathy should require further investigation of nondiabetic glomerulopathies. Blindness due to severe proliferative retinopathy or maculopathy is approximately five times more common in type 1 and type 2 patients with nephropathy compared with normoalbuminuric patients. Macroangiopathy, as evidenced by stroke, carotid artery stenosis, coronary heart disease, and peripheral vascular disease, is two to five times more common in nephropathic patients.

Other standard modalities for the treatment of progressive renal disease and its complications (e.g., osteodystrophy) must also be used when indicated, such as sodium and phosphate restriction and use of phosphate binders. When the GFR begins to decline substantially, referral to a physician experienced in the care of such patients is indicated. Radiocontrast media are particularly nephrotoxic in patients with diabetic nephropathy, and azotemic patients should be carefully hydrated before receiving any procedures requiring contrast that cannot be avoided. There are three therapeutic choices for treatment of the diabetic patient with ESRD: transplantation (kidney only or kidney and pancreas), continuous ambulatory peritoneal dialysis (CAPD), and hemodialysis. Generally, the choice of therapy is tailored to the patient's desires and abilities.

Conclusion

The social and economic impact of renal replacement therapy is tremendous, particularly in diabetic patients with ESRD. The morbidity and mortality rates of diabetic patients on renal replacement therapy are higher compared with nondiabetics. A number of clinic studies provide strong evidence of the effectiveness of early detection and aggressive treatment of hyperglycemia and hypertension in delaying the onset of diabetic nephropathy and preventing its progression to ESRD.

Recent studies have now demonstrated that the onset and course of diabetic nephropathy can be ameliorated to a very significant degree by several

interventions, but these interventions have their greatest impact if instituted at a point very early in the course of the development of this complication.

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Experts Opinion

Dr. Sanjiv J. Shah

Good glycemic control can prevent or delay nephropathy in subjects with diabetes, however, genetic susceptibility to nephropathy and uncontrolled hypertension would also play an important role in development of nephropathy. On the contrary, some “lucky” diabetics do not develop nephropathy in spite of years of uncontrolled hyperglycemia.

Mumbai

Dr. Uday Phadke

Although nephropathy is a classic complication of type 1 DM of long duration, increasing numbers of end stage renal failure due to type 2 DM are now evident. Several studies both in type 1 and type 2 DM highlight that tight control of blood glucose and equally importantly blood pressure can retard or prevent the development of advanced renal failure.

Pune

Dr. K. Hari

In patients with Type 1 DM nephropathy develops in 30-40% patients within 20-25 yrs of diagnosis of diabetes. The incidence in Type 2 DM ranges between 2 – 16% in various studies. Due to rapid developments in the field of nephropathy, it is possible to identify diabetics who are at the risk of developing diabetic patient at risk of developing diabetic nephropathy are familial genetic predisposition, presence of clinical & biochemical markers.

Cochin

Dr. N. N. Asokan

The fact that 95% of the patients on dialysis and those who are waiting for renal transplantation are patients of diabetes is often forgotten. Hence it is of utmost importance especially in a country like India to increase the awareness of the complications of diabetes amongst doctors as well as public regarding the recognition of the stages of Diabetic Nephropathy and the importance of catching the patients young before they go in for Diabetic Nephropathy, which means even before the stage of microalbuminuria. One will be happy if they could be diagnosed during the stage of microalbuminuria if not during the hyper-filtrations stage earlier.

Kerala