# Diabetic Nephropathy in Indians - Long-Term Clinical Experience

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## INTRODUCTION

As diabetics live longer, they develop chronic complications such as retinopathy, nephropathy, neuropathy and increased risk of atherosclerotic disease. However, not all diabetics develop these complications - almost 25% remain free from all of these complications.

Diabetic renal disease is a life threatening microvascular complication characterised by presence of persistent proteinuria, hypertension and progressive decline in renal function. It predisposes to excess morbidity and mortality resulting from renal failure and cardiovascular disease. In developing countries, the high cost of treating end-stage renal disease precludes many such patients from availing of optimal therapy. Early identification of patients at high risk for diabetic nephropathy is therefore important to intensify the treatment and to modify the risk factors.

Non-insulin-dependent diabetes (NIDDM) is the most prevalent form of the disease in our country and constitutes 94-95% of diabetic population attending the diabetic clinic at any hospital [1]. All the cases reported by Kimmelstiel and Wilson [2] in 1936 were NIDDM and the histological changes of glomerulosclerosis are similar in both IDDM (insulin-dependent diabetes) and NIDDM. However, there are differences between these two types with regard to onset of proteinuria and its progression. Once clinical nephropathy is established, no known strategy exists that can stop or reverse the progression to End-Stage Renal Failure (ESRF). Effective treatment of hyperglycaemia and hypertension at an earlier stage before the onset of nephropathy can benefit in retarding further progression. The results of the Diabetes Control and Complications Trial (DCCT) have thrown the much needed light to emphasize the role of good metabolic control to prevent the development as well as the progression of albuminuria [3].

Epidemiology of Diabetic Renal Disease Diabetic renal disease has become the most common cause of ESRF and large numbers of these patients are entering renal replacement therapy. Diabetic nephropathy develops in 35% of patients with IDDM [4] and 3-15% of NIDDM patients [5]. In IDDM, the occurrence of proteinuria increases with the duration of diabetes with a maximum prevalence of 21 % after 20-25 years of diabetes and there is a low risk of developing nephropathy after 35 years. Over the past several years, decreasing proportion of diabetics with IDDM have developed ESRF reflecting the impact of enhanced blood pressure and glucose control on renal complications in diabetes.

A high prevalence of microalbuminuria and proteinuria in NIDDM is reported by many workers, being 20-40% and 5-15% respectively [6-9]. However, the incidence of renal failure is low and mortality in NIDOM with renal failure is largely from disability caused by large vessel disease [10j. A population study in Rochester, USA, by Humphrey et al [11] found similar rates of renal failure over 30 years in cohorts of 1832 NIDDM and 136 IDDM patients.

There is an increased prevalence of diabetic renal disease in certain ethnic groups including Asians, West Indians and Pima Indians [12, 13]. The Pima Indians have the world's highest reported incidence and prevalence of NIDDM and 47% albuminuria. Younger age at onset of diabetes and greater prevalence of hypertension in the Pima Indians are considered to be responsible for the early occurrence of renal disease.

The prevalence of renal involvement was studied by the author in 538 consecutive NIDDM subjects [6] (271 male and 267 females); the mean age of males was 55.4 ± 11.0 and the females 51.0 ± 10.5 years. Diabetic nephropathy was present in 8.9% of this population of NIDDM patients (Urinary Albumin Excretion (UAE) > 200 pg/min) and another 19.7% had microalbuminuria (MA) (UAE 20-200 µg/min). Since MA is recognized as a significant predictor of progress to clinical diabetic nephropathy as well as for premature cardiovascular mortality, identification of patients with MA is important. The age of the patients and known duration of diabetes were significantly higher in subjects with microalbuminuria and macroalbuminuria as compared to those in the normoalbuminuric group ($P < 0.001$) (Table 1). Predominance of males was striking in the macroalbuminuria group ($P < 0.001$). Other workers [14, 15] have also shown increased prevalence of clinical proteinuria and ESRF in males. It was also evident from our study [1] that significantly increased percentage of patients with macroalbuminuria had poor glycaemic control and hypertension.

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**Table 1**
**Clinical Data of 538 NIDDM patients according to Urinary Albumin Excretion**

| Characteristics | UAE µg/mm | | |
|---|---|---|---|
| | < 20.0 (384) | 20-200 (106) | > 200 (48) |
| Age (years) | 51.9 + 11.2 | 56.8 + 10.0 | 55.2 + 9.6 |
| Duration (years) | 7.1 + 6.6 | 8.9 + 7.2 | 11.6 + 7.8 |
| BMI-kg/m$^2$ | | | |
| Males | 22.9 + 3.3 (190) | 23.4+3.4 (51) | 21.4+3.6 (30) |
| Females | 24.5 + 4.2 (194) | 24.2 + 3.8 (55) | 22.9 + 4.5 (18) |
| Blood Glucose | | | |
| Fasting (mg/dl) | 138.0 + 42.8 | 145.4 + 46.4 | 159.3 + 70.5 |
| Post-prandial (mg/dl) | 216.8 + 66.7 | 228.3 + 67.3 | 255.4 + 86.5 |
| Blood Pressure | | | |
| Systolic (mm Hg) | 131.1 + 15.3 | 138.2 + 19.0 | 149.6 + 21.0 |
| Diastolic (mm Hg) | 83.6 + 8.0 | 86.1 + 9.1 | 90.4 + 10.9 |

Figures in parentheses indicate the numbers studied.

NIDDM patients represent a considerably more heterogenous population in terms of clinical presentation and onset of complications. Even though the prevalence rate of ESRF in NIDDM is about 1/l0th that of IDDM, there are more NIDDM patients with ESRF since the prevalence of NIDDM patients is much higher. Moreover, the exact time of onset of diabetes in NIDDM may be difficult to determine since the disease can exist without overt clinical manifestations for a considerable period of time.

A Finnish study [16] found that 20% of newly diagnosed NIDDM patients had albuminuria rates in the MA range or higher. A prevalence of persistent proteinuria of 8.2% at diagnosis of NIDDM is reported from the population of Minnesota USA [15] with subsequent incidence of 15.5 per 1000 patient years. In an earlier report from our centre [17] on 498 NIDDM patients with nephropathy, it was shown that the degree of renal failure and proteinuria showed a favourable pattern in relation to known duration of diabetes. In contrast to the observations that less than 5% of IDDM patients will have proteinuria in the first ten years, our study showed that 50% of patients with NIDDM with less than 10 years of known duration had proteinuria in the nephrotic range. Similar findings were reported from North India [14].

The lower rate of ESRF in patients with NIDDM may also be due to slower decline in GFR compared to IDDM. Ethnic differences in the development of ESRF have been suggested with an increased proportion of this complication in Asians, Afro-Caribbeans and Pima Indians. This may be attributed to increased prevalence of NIDDM with early onset of diabetes. The specificity of proteinuria and the diagnosis of diabetic nephropathy is much less in older NIDDM patients since other pathological conditions with increased proteinuria can co-exist. It is also shown that non diabetic renal disease occurs more frequently in NIDDM patients.

## Classification

## Development of diabetic renal disease.

The stages of development of diabetic renal disease is well documented in IDDM as described by Mogensen [18] while in NIDDM, the early stages are not well defined, as the onset of the disease is insidious and these patients can present with proteinuria. The five stages of development are as follows:

**Stage-1: Hyperfiltration-hypertrophy stage:** Renal hypertrophy and hyperfiltration are characteristic features of early renal involvement in IDDM and glomerular filtration rate (GFR) is more than 150 m/min. In contrast, the above findings have not been documented in NIDDM by our study [19] as well as by other workers. In 67 NIDDM patients, GFR was estimated using Technitium - 99 DTPA by the method devised by GATES. There was no evidence of hyperfiltration in the group of NIDDM with short known duration of diabetes.

**Stage-2:** In this stage there is structural glomerular changes without any change in renal function. UAE remains normal. Subjects with hyperfiltration and poor metabolic control are considered to develop nephropathy.

**Stage-3: Incipient nephropathy:** This stage is characterised by the presence of structural lesions of light microscopy and persistent UAE in it microalbuminuric range. Patients with MA have a very high risk of subsequent development of over nephropathy. GFR may be still preserved and may begin to show a decline as this stage progressed. This clinically important stage is evident in both IDDM and NIDDM and is a strong predictor of clinical diabetic nephropathy.

**Stage-4: Overt clinical nephropathy:** This stage characterised by proteinuria of more than 500 mg 24 hours, hypertension and subsequent fall in GF Retinopathy is almost always present. Once significant proteinuria develops, further progression of renal failure is fairly rapid and normally occurs in 5 years.

**Stage-5: End-stage renal failure (ESRF):** Management of diabetic patients with ESRF is complicated by the frequent co-existence of complications affecting other organ systems including proliferative retinopathy, cardiovascular disease, peripheral neuropathy or autonomic neuropathy. Renal replacement therapy is the choice of treatment for these patients. If contraindications to transplantation are present, a decision must be made regarding Chronic Ambulatory Peritoneal Dialysis (CAPD) versus haemodialysis.

## Risk Associations for the Development of Diabetic Nephropathy

Development of renal complications in diabetic subjects is attributed to both metabolic and genetic factors. The genetic hypothesis has been put forward to explain the familial clustering of diabetic nephropathy and increased incidence of parental hypertension in the siblings with nephropathy. Individuals with a genetic predisposition to hypertension are more likely to develop renal disease in the presence of hyperglycaemia. It was also shown that the risk diminished after 20-25 years of duration indicating that atleast some diabetic individuals have a genetic protection to this complication. The role of hyperglycaemia in the development of diabetic microvascular complication is now proved beyond doubt. The many epidemiological studies, animal model studies and other retrospective and prospective clinical trials have supported the glucose hypothesis and proved that hyperglycaemia is the major factor initiating the changes in the kidneys. The results of DCCT have clearly demonstrated that optimal glycaemic control maintained by intensive insulin therapy in IDDM can delay the onset and slow the progression of diabetic nephropathy [3]. The DCCT result can also be extrapolated to NIDDM providing a clear support for the clinical benefits of intensification of therapy in all types of diabetes.

The mechanisms responsible for the tissue damage caused by hyperglycaemia are the haemodynamic factor, glycosylation of the tissue proteins and increased activity of polyol pathway. Microvascular pressure and flow are increased in early diabetics. Elevated hydrostatic pressure is believed to be partly responsible for the leakage of protein and their deposition in the walls of arterioles and capillaries in the Kidney. Glycosylation of protein occurs in many tissues of the body including the lens, albumin, collagen, lipid proteins, nerve protein and haemoglobin. Glycosylation results in change in physical and chemical structure and causes alteration in function of tissue protein.

The protection to the development of diabetic nephropathy and its associated cardiovascular complications is explained most on the basis of metabolic control. However, genetic differences in the regulation of the biosynthesis of extracellular matrix may also explain individual differences in the compositional structure of matrix and thereby to susceptibility to nephropathy. The negative charge of the glomerular capillary wall produced by glycosialo proteins of heparin sulphate proteoglycans influences the leakage of macro molecules. Some individuals have differences in polymorphism to an enzyme system (N-Deacetylase) involved in heparin sulphate metabolism and this defective heparin sulphate metabolism has been shown to influence renal complications in a subgroup of patients.

## Urinary Albumin Excretion (UAE)

In a diabetic, the presence of albumin in the urine above the normal range is indicative of glomerular damage. There are a number of other causes of an increase in UAE in diabetic patients. UAE may increase during poor metabolic control which is reversible with adequate control. Other causes are urinary infection, essential hypertension and cardiac failure. Moderate exercise can increase UAE more rapidly in diabetics than non diabetics.

Measurement of smaller concentrations of albumin in the urine can be made by more sensitive methods such as immunoturbidometry, immunonephlometry and radio-immunoassay. The normal ranges for urinary albumin measured by RIA in our laboratory in 25 non diabetic healthy controls aged 25 to 55 years was 0.45 - 7.6 µg/min [5]. A value of 20 µg/min was chosen as the discriminating value between strictly normal and elevated or borderline level UAE and 200 µg/min as the upper limit of microalbuminuria. Since UAE varies with posture and with exercise, the evaluation should be carried out only on urine collected under standard conditions. Atleast 3 urine collections are recommended. Method of urine collection includes 24-hour urine, overnight and short term collection.

Patients with persistently Albustix positive urine in which other causes of increased UAE are excluded, corresponds to a UAE of more than 200 µg/min or more than 300 mg/24 hours and is termed clinical nephropathy. MA is diagnosed when UAE is more than 20 but less than 200 µg/min and this sub-clinical state of albuminuria is now recognised to predict clinical nephropathy and is a risk factor for cardiovascular disease in NIDDM.

Diabetic subjects with persistent MA progress to clinical nephropathy and in NIDDM, MA is a potent cardiovascular risk factor independent of hypertension and hyperlipidaemia. In 1984, Jarrett et al [22] and Mogensen [23] reported that MA is a predictor of increased mortality in NIDDM. In our study of NIDDM patients [6], significantly greater prevalence of complications with increasing UAE was a noteworthy finding (P< 0.1) (Table 2). In the presence of elevated blood pressure, abnormal arteriolar structure facilitates pressure transmission from systemic circulation to the glomerulus - thus raising the intraglomerular pressure. Dyslipidaemia has been found increasingly in both IDDM and NIDDM patients with MA. Presence of atherogenic lipid profile is an important contributor to the excess cardiovascular mortality described in patients with MA. Once overt nephropathy is established (UAE > 200 µg/min), progression of renal changes occurs with eventual ESRF in 5 to 7 years and this is associated with hypertension and abnormal lipid and haemostatic parameters. The mortality in proteinuric diabetic patients is several fold higher than in diabetic patients without proteinuria.

**Table 2**

**Association of Vascular Complications in NIDDM Subjects according to Urinary Albumin Excretion (Percentage)**

| Complications | UAE µg/min | | | |
|---|---|---|---|---|
| | < 20.0 (384) | 20-200 (106) | > 200 (48) | Total |
| Peripheral neuropathy | 48.7 | 60.4* | 72.9** | 53.2 |
| Coronary artery disease | 15.4 | 25.5* | 29.2** | 18.6 |
| Peripheral vascular disease | 0.5 | 0.9 | 2.1 | 0.7 |
| Cerebrovascular disease | 1.6 | 5.7* | 10.4** | 3.2 |
| Retinopathy | 7.5 | 12.0 | 50.0 | 14.5 |

Figures in parentheses indicate the numbers studied.
Compared to normals, *P < 0.05: **P < 0.01.

## Progression of Albuminuria

Factors known to influence the development and further progression of albuminuria include poor metabolic control, hypertension, smoking and genetic factors.

Poor metabolic control is associated with development of renal disease in normoalbuminuric patients. However, many patients may not develop renal disease inspite of increased $HbA_1$ for a long time.

NIDDM patients with essential hypertension and normoalbuminuria will remain the same without any progression. On the other hand, elevated blood pressure that develops during the phase of MA indicates a poor prognosis. In patients with proteinuria, many studies have shown that mean systolic blood pressure was the only factor which significantly determines the rate of decline in kidney function.

Hypertension was present in 36% of NIDDM patients in our study. Eighty percent of macroalbuminuric patients were hypertensive compared to only 16% of normoalbuminuric patients. Presence of hypertension in 47% of patients with MAwas noteworthy. GFR was found to be significantly lower in hypertensive diabetic patients compared to normotensives (P < 0.001) [19]. Baba et al [24] have also shown that GFR declined to 1.5 ml/min/month in diabetic patients with hypertension compared to a GFR decline of 0.08 ml/ min/month in normotensives.

A prospective study of a cohort of 481 NIDDM patients [25] was undertaken for a period of 5 years to evaluate the potential risk factors for the progression of albuminuria. Sixty two patients with normal UAE developed MA and 10 patients from the normoalbuminuric group and 24 from the MA group developed rnacroalbuminuria giving an incidence of 46.9/1000 person years and 58.9/1000 person years for normo and macroalbuminuria. The baseline UAE was significantly higher in those who progressed (Normo 8.5 ± 6 vs 5.3 ± 4 µg/min P < 0.001 ; micro 68.5 ± 57 vs 47.4 ± 34 µg/min P < 0.01 ). More patients in the progressors had baseline hypertension and significant increase in systolic blood pressure alone was seen during follow-up in patients who progressed from normo and microalbuminuric group (P < 0,\.05). Five, ten and seventy percent of the patients in normo, micro and macroalbuminuric group respectively died during the 5 years follow-up period. Fifty percent of the death were caused by acute myocardial infarction.

## Management

The present management strategy includes identification of subset of diabetic patients likely to develop nephropathy and to introduce therapeutic intervention at an appropriate time to prevent and slow the progression.

A screening programme for detection of MA is needed to identify the subset of diabetic patients at risk of developing nephropathy and early cardiovascular morbidity. All IDDM patients with more than 5 years duration and all NIDDM patients from the time of diagnosis of diabetes should have urine tested for albumin excretion at least once a year.

## Blood Glucose Control

The role of hyperglycaemia in the development of diabetic microvascular complication is now proved beyond doubt. The results of DCCT [3] has clearly shown that optimal glycaemic control can delay the onset and slow the progression of diabetic nephropathy.

Extrapolation of the results of DCCT to NIDDM subjects is justified because of the common input of chronic hyperglycaemia to the pathogenesis of these microvascular complications. A more aggressive approach to therapy is recommended in newly diagnosed NIDDM patients. Efforts to achieve normal blood glucose levels include risk factor reduction, diet, exercise and pharmacological agents. The results of the UK Prospective Study (UKPDS) will give definite information about the most effective and least risky therapy for newly diagnosed NIDDM patients.

## Blood Pressure Control

The effectiveness of blood pressure control with reduction of proteinuria and decrease in decline of GFR has been shown from many clinical studies [26, 27]. BP of less than 135/85 mmHg is recommended in these patients. Angiotensin Converting Enzyme Inhibitors (ACEI) have a specific role as reno-protective agents since they lower the intraglomerular pressure independent of systemic pressure changes. ACEI have been shown to improve renal function even in normotensive patients with MA.

A double blind controlled short period study on proteinuric NIDDM patients [28] showed that Captopril treatment resulted in reduction of proteinuria in a significant number of patients (mean reduction of 37%). Specific nephro-protective action of ACEI have prompted its use in the treatment of both incipient and overt nephropathy.

High protein diet has been shown to accelerate the progression of nephropathy and restriction of dietary protein to 0.5-0.6 gm/kg/day has been shown to retard the progression in patients with clinical nephropathy. In view of the adverse haemodynamic sequences of protein loading, patients at high risk of developing or of progression of nephropathy should be advised to avoid high protein diet. Diabetic patients should be advised also to refrain from smoking since smoking is shown to be a risk factor for microvascular disease.

In view of the high cost of treating end-stage renal disease with its associated complications, early identification of patients at high risk for nephropathy is important so that treatment can be intensified. Presence of risk indicators such as hypertension, dyslipidaemia and insulin resistance should be identified and treated. The stage of MA appears to be responsive to intervention therapy since many clinical studies have shown the effectiveness of post-primary intervention measures in arresting or delaying the progression from MA to established nephropathy. Treatment of established renal disease can only delay the onset of ESRF. Our ultimate aim should therefore be the prevention of the transition from normoalbuminuria to MA in diabetic subjects who are at high risk of diabetic renal disease and cardiovascular disease.

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