ORIGINAL ARTICLE

ROLE OF DURATION OF DIABETES IN THE DEVELOPMENT OF NEPHROPATHY IN TYPE 2 DIABETIC PATIENTS

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ABSTRACT

Introduction: Diabetes has now become the most common single cause of end stage renal disease and about 40% of diabetic patients develop nephropathy. The present study was conducted to find out the relation between duration of diabetes & development of renal disease.

Methodology: The study was conducted in 120 patients with Type 2 diabetes. Three groups were selected with 40 patients in each group – with diabetes of <5year duration, 5-10year duration and >10year duration. 40 normal healthy adults were included in the control group. Parameters like BP, blood urea, serum creatinine, urine microprotein were compared with controls.

Results: As duration increases, there is impairment of renal function as evidenced by increase in blood urea, serum creatinine & microproteinuria. Statistically significant increase in BP was also observed with increase in duration.

Both metabolic & hemodynamic factors play a decisive role in the development of nephropathy. AGEs, PDGF, TGFβ, VEGF, and Angiotensin II etc. stimulate growth & fibrotic factors leading to renal damage.

Conclusion: Screening for microalbuminuria will allow early identification of patients with nephropathy. It has been shown that meticulous glycemic & bloodpressure control can slow the progression of diabetic nephropathy. Developing countries like India with its large burden of diabetes should evolve strategies for prevention of its secondary complications.

Keywords: Microproteinuria, nephropathy, Type2 diabetes.

INTRODUCTION

The incidence of diabetes mellitus in human population has reached epidemic proportions worldwide. It is estimated that ten years down the lane, one in every five diabetics will be an Indian[1].People with type 2 diabetes develop severe renal and cardiovascular complications prematurely, especially those with high urinary albumin excretion.[2] However, the greater risk of dying from associated coronary artery disease in the older population with type 2 diabetes may prevent many with earlier stages of nephropathy from progressing to ESRD. As therapies and interventions for coronary artery disease continue to improve, however, more patients with type 2 diabetes may be expected to survive long enough to develop renal failure. Nelson et al[3] identified multiple factors contributing to the initiation and progression of diabetic nephropathy including proteinuria, hyperglycemia, hypertension, genetic susceptibility, ethnicity, high protein intake and familial predisposition to renal disease.

Duration of diabetes is a very important factor in the development of diabetic nephropathy as demonstrated in several studies. Rudberg et al[4], in a study of adolescents with a mean duration of disease of 10.9 years, found that the duration of disease was an important factor in the overall severity of glomerulopathy. Overt nephropathy caused by glomerulosclerosis first appears 10-15 years after the onset of IDDM and after 5 to 10 years in patients with NIDDM[5]. Nelson et al selected 364 Pima Indians aged 35 years older with type 2 diabetes and proteinuria. Of these 364 subjects, 95 developed ESRD. The cumulative incidence was 40% at 10 years and 61% 15 years after the onset of proteinuria. They found out that the incidence of ESRD attributed to diabetic nephropathy increased from 0 cases / 1000 person-years at 0-5 years to 40.8 cases/ 1000 person- years at greater than or equal to 20 years duration of diabetes. Longer the duration of diabetes, higher the frequency of diabetic nephropathy.

Studies from different centres agreed that microalbuminuria is a strong predictor of subsequent development of overt diabetic nephropathy as manifested, typically by overt proteinuria, hypertension and ultimately declining GFR progressing toward ESRD. Microalbuminuria is defined as the persistent excretion of albumin in urine at rates that are above the normal range but below values detected by conventional methods including ordinary urinary dipsticks[6] i.e., urinary albumin losses persistently between 20 and 200μg / minute. Microalbuminuria predicts renal disease in diabetic Pima Indians[7], a group that tends to develop NIDDM at a relatively young age. More than a decade ago, Mogensen[8] reported that overt nephropathy developed within 9 years in 22% of patients with NIDDM who had microalbuminuria at baseline. The cumulative four year incidence of macroalbuminuria among patients who initially had microalbuminuria in the study of Nelson et al[9] was 37%; this is in agreement with the results of Ravid et al[10] who found that the cumulative 5 year incidence of macroalbuminuria was 42% in young Jewish patients with NIDDM and microalbuminuria at baseline. The patients in the study by Nelson et al and Ravid et al were approximately 20 years younger than those in the earlier study by Mogensen (40 to 45 years vs. 60 to 65 years). Differences in race and in various other risk factors mentioned previously for progression from microalbuminuria to macroalbuminuria probably have an important role as well. Although the GFR did not change in the Pima Indians with NIDDM who initially had microalbuminuria, a reduction in Kidney function, reflected by an increase in the serum creatinine concentration, was reported by Ravid et al. The same discrepancy has been described in normotensive patients with IDDM and microalbuminuria, suggesting that valid information on the glomerular filtration rate can be obtained only by measurement of a marker, such as insulin or iothalamate. Information about changes in the glomerular filtration rate in hypertensive patients with NIDDM or IDDM and macroalbuminuria is scanty.

Evidence also suggests that diabetic nephropathy can be secondary to long term metabolic abnormalities present in diabetes. Recent clinical evidence suggests that poor glycemic control leads to the development of diabetic lesions and proteinuria. On the other hand, some diabetic patients may go for years without nodular lesions despite poor glycemic control. Thus genetics as well as other factors may also play a role in this disorder. Hypertension promotes kidney dysfunction in patients with NIDDM or IDDM and diabetic nephropathy[11].The microvascular complications of diabetes mellitus are responsible for a substantial proportion of associated morbidity and mortality. Fortunately, recent evidence indicates that improved glycaemic and blood pressure control can slow and perhaps even stop the development of nephropathy in diabetic patients.

Although diabetic nephropathy is not clinically apparent in the early years of diabetes, biochemical screening should be performed annually, beginning at the time of diagnosis, in patients with type 2 diabetes, since they may have had asymptomatic disease for years before hyperglycemia was detected. If the relation between duration of diabetes and development of diabetic nephropathy could be established, screening of early signs of nephropathy provide an opportunity for early treatment which has been shown to preserve renal function ensuring that patients with diabetes will live longer and have better lives .So the present study was aimed at finding out the relation between duration and development of nephropathy in type 2 diabetics.

MATERIALS AND METHODS

The study was conducted in a total of 160 subjects of which 40 were included in the control group. There were 70 males and 50 females with type 2 diabetes and 24 males and 16 females as normal subjects. Approval for the study was obtained from institutional ethics committee. Diabetic patients who attended the diabetic clinic OP of Medical College Hospital were chosen for the present study. Those with debilitating illness were excluded from the study. Patients who developed diabetes after 30 years of age were considered to have type 2 diabetes. Diabetic patients with microproteinuria were considered to have nephropathy. Though hypertension was defined according to World Health Organization as a blood pressure $\geq$ 140/90 mm of Hg, diabetic patients with blood pressure $\geq$ 120/70 mm of Hg are associated with increased cardiovascular event rates and mortality.

Defined groups of patients with diabetes of less than 5 year duration, 5-10year duration and more than 10year duration were selected. A detailed history was taken according to the proforma. Blood pressure was measured with the subject in the sitting position.

The control group consisted of 40 normal healthy adults who were the bystanders from various wards. They had no history of diabetes or hypertension.

Blood samples were collected for estimation of blood urea and serum creatinine. Patients were asked to provide a random morning urine specimen. Microproteinuria from a random urine sample has been identified as a reliable and valid means of estimating albumin excretion in clinical settings [12,13]. The various tests with blood samples and urine were done in clinical biochemistry laboratory of Medical College Hospital.

Statistical analysis

The relationship of development of proteinuria in diabetes with duration of the disease was analysed using chi square (x^2) test. The mean levels of systolic blood pressure; diastolic blood pressure; blood urea and serum creatinine in each group were compared with the normal group. To find out the statistical significance of difference in means in each group, the p value was found out for each group.

RESULTS AND DISCUSSION

The results are tabulated in tables with standard deviations in brackets

Table 1: Comparison of normal group with diabetes of < 5 year, 5 -10 year and more than 10 year duration

Variables	Normal	< 5 year	5-10 year	> 10 years
Mean Serum creatinine (mg%)				
Male	0.95(0.25)	1.163(0.713)	1.41(0.90)	2.522(2.33)
Female	0.923(0.22)	1.15(0.734)	1.25(0.77)	1.85(1.42)
p value				
Male		Not significant	<0.050	< 0.010
Female		Not significant	Not significant	< 0.050
Mean Blood urea (mg%)				
Male	28.1(8.79)	35.38(12.87)	40.66(7.86)	55.66(30.43)
Female	28.6(10.00)	37.84(16.32)	43.06(6.61)	49.578(28.07)
p value				
Male		<0.050	< 0.001	<0.001
Female		Not significant	<0.001	<0.010
Mean Systolic BP (mm of Hg)				
Male	123.9(5.75)	127(14.1)	133.67(14.03)	141.33(18.65)
Female	120.1(6.95)	135(18.1)	134.13(12.27)	154.31(20.9)
p value				
Male		Not significant	<0.010	<0.001
Female		<0.01	<0.001	<0.001
Mean Diastolic BP (mm of Hg)				
Male	79.16 (5.20)	82.8(8.26)	86(7.32)	88(6.48)
Female	77.87(5.30)	84.5(5.30)	83.25(8.61)	94.73(8.7)
p value				
Male		Not significant	<0.001	<0.001
Female		<0.001	<0.010	<0.001

Diabetic nephropathy is a clinical hall mark of microangiopathy and is the most important single disorder leading to renal failure in adults[14]. The earliest clinical evidence of nephropathy is the appearance of low but abnormal levels of albumin in the urine and the patients with microalbuminuria are referred to as having incipient nephropathy. In addition to its being the earliest manifestation of nephropathy, albuminuria is a marker of greatly increased cardiovascular morbidity and mortality for patients with type 2 diabetes. Thus, the finding of microalbuminuria is an indication for screening for possible vascular disease and aggressive intervention to reduce all renal and cardiovascular risk factors.

Table 2: Table showing number of subjects with proteinuria in the different groups

Group (yr)	Proteinuria	No proteinuria	X^2, P value
Male			
< 5	5	16	17.26,
5 – 10	7	17	<0.001
> 10	17	4	
Total	29	37	
Female			
< 5	5	14	12.65,
5 – 10	5	11	<0.010
> 10	15	4	
Total	25	29	

The pathogenesis of diabetic nephropathy is complex and involves the interplay of many different factors. An interaction between genetic predisposition and hyperglycemia induced hemodynamic and metabolic changes sets the stage for kidney injury. Hemodynamic factors such as activation of the renin-angiotensin-aldosterone and endothelin systems occur. In response, secretion of profibrotic cytokines, such as transforming growth factor β1 (TGF-β1), is increased. The interactions between hemodynamic and fibrotic cytokines, such as angiotensin II and TGF β1 causes further hemodynamic changes to occur, such as increased systemic and intraglomerular pressure leading to hyperfiltration in the kidneys of diabetic patients and thus may cause structural injury. The addition of hypertension to their hemodynamic alterations worsens the glomerular damage, particularly in combination with impairment of autoregulation, which is commonly present in diabetes. The degree of metabolic control affects the development of diabetic glomerulosclerosis. Metabolic pathway involvement, among other features, leads to nonenzymatic glycosylation, increased protein kinase C (PKC) activity, and abnormal polyol metabolism. Advanced glycosylation end products adversely affect glomerular permeability and the accumulation of macromolecules within the glomerulus.

Achieving the best metabolic control (A1c <7%), treating hypertension (<130/80 mmHg or <125/75 mmHg if proteinuria >1.0 g/24 h and increased serum creatinine), using drugs with blockade effect on the renin-angiotensin-aldosterone system, and treating dyslipidemia (LDL cholesterol <100 mg/dl) are effective strategies for preventing microalbuminuria, in delaying the progression to more advanced stages of nephropathy and in reducing cardiovascular mortality in patients with type 1 & type 2 diabetes.

In the present work, the variation in blood urea, serum creatinine, urine microprotein and blood pressure levels in diabetics of varying duration of diabetes were compared to the normal subjects. It was observed that there was a significant relation between blood urea, serum creatinine, microproteinuria and blood pressure with the duration of diabetes.

The diabetes control and complications trial revealed the association of long duration of diabetes with the development of diabetic nephropathy. A significant correlation between the increasing duration of diabetes and development of microproteinuria was documented by Kathryn et al[15] and Knowler WC et al [16]. The present study confirmed and extended the frequent occurrence of microproteinuria with increasing duration of diabetes. Similar results were observed in the studies of Nelson RG et al and Dasmahapatra A et al[17] and Klein R et al. [18]

In the present study, serum creatinine and blood urea levels were found to be increasing with the duration of diabetes. Serum creatinine was increased in 55.6%, males and in 64.3% females with diabetes of more than 10 year duration. Sameer Huraib et al obtained similar results. A reduction in kidney function, reflected by an increase in blood urea and serum creatinine concentration was reported by Ravid et al[19].

There is a strong epidemiological connection between hypertension in diabetes and adverse outcomes of diabetes. Clinical trials demonstrate the efficacy of drug therapy versus placebo in reducing these outcomes. The UKPDS and HOT trial demonstrated improved outcomes in patients assigned to lower blood pressure targets. In the U.K.Prospective Diabetes study, each 10 mm Hg decrease in mean systolic blood pressure was associated with reduction in risk of 13% for microvascular complications related to diabetes. Optimal outcomes in the HOT study were achieved in the group with a target diastolic blood pressure of 80mm Hg (achieved 82.6mm of Hg). Therefore, a target blood pressure goal of < 130/80 mm of Hg is reasonable if it can be safely achieved. MICRO HOPE study and PREMIER study group[20] had demonstrated a favourable effect of angiotensin converting enzyme inhibitors on the renal and cardiovascular outcomes in diabetics.

Clinical expression of diabetic nephropathy follows a predictable course starting with proteinuria and terminating in end stage renal disease. Screening for microalbuminuria will allow the identification of patients with nephropathy at a point very early in its course. Risk factor modification, renal function monitoring and combined therapies are the current integrated approaches to manage patients with diabetic kidney disease.

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