DIABETIC NEPHROPATHY - STRATEGY OF MANAGEMENT

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ABSTRACT

End stage renal failure in type 2 diabetes is a medical catastrophe. Better understanding of diabetic nephropathy and its management is the need of the hour. Studies conducted at our centre on South Indian type 2 diabetic patients thrown light on various aspects of nephropathy, its relation with hyperglycemia and hypertension. A familial aggregation study showed that siblings of probands with diabetic nephropathy had higher prevalence of nephropathy (33%). The probands also developed diabetes, hypertension and coronary heart disease at a younger age when compared with probands without diabetic nephropathy. A positive association was established between D' allele of ACE gene and diabetic proteinuria (80.2% of nephropathy vs 57% of non-albuminuric subjects). A study was conducted to determine the effect of ACE – inhibitors (ACEI) in 109 proteinuric patients. The results showed that the beneficial effect of ACEI on the progression of nephropathy might be independent of its anti hypertensive effects. A six-year follow-up was conducted in 410 newly registered type 2 patients. 43% of patients with mild proteinuria developed nephropathy during the study. This study also validated that expected protein excretion was an inexpensive test, which could be used in developing countries for serial assessment of renal function. Early detection of renal impairment is very essential. Aggressive management of diabetes and hypertension can prevent diabetic kidney disease.

KEY WORDS : ACE gene polymorphism; Angiotensin converting enzyme inhibitors; Diabetic nephropathy; Familial aggregation and type 2 diabetes mellitus.

INTRODUCTION

End stage renal failure in type 2 diabetes is a medical catastrophe of worldwide dimensions (1). Diabetic nephropathy and its management are discussed under the following headings.

1. Magnitude of the problem
2. Familial aggregation studies
3. Genetic studies
4. ACE Inhibitor therapy
5. Studies on progression of renal disease

MAGNITUDE OF THE PROBLEM

Mani M.K, 1988, had shown the prevalence of diabetic nephropathy among 4837 patents with chronic renal failure to be 30.3%, chronic interstitial nephritis 23% and chronic glomerulonephritis in 17.7%, respectively (2). In India, only less than 5% of patients with End Stage Renal Failure (ESRF) receive renal transplantation, because only a few centres have the facilities for renal transplantation. Cadaveric kidney transplantation is yet to pick up and there is non-availability of related donors.

The patients with longer duration of diabetes, poor glycemic control and raised blood pressure, have a major risk of developing diabetic nephropathy. Therefore it is important to screen these high risk patients and intervene at the microalbuminuria stage to prevent ESRF

FAMILIAL AGGREGATION STUDIES

Familial Aggregation of Diabetic Kidney disease in Type 2 Diabetes in South India (3).

Two groups of diabetic siblings of type 2 diabetic patients matched for age, body mass index and duration of diabetic mellitus were studied. Group A comprised of siblings of probands with diabetic nephropathy and retinopathy [n=30, M:F = 20:10] and Group B were siblings of probands without diabetic nephropathy or microalbuminuria [MAU] [n=30, M:F=14:16]

Table 1: Prevalence of associated complications in the study groups.

	SIB A	(n=30)	SIB B	(n=30)
Proteinuria	22	(76.7%)	1	(3.3%)
Mau	7	(26.7%)	1	(3.3%)
Macro Proteinuria	15	(50%)	0	
Retinopathy	10	(33.3%)	2	(6.7)
Retinopathy + Nephropathy	10	(33.3%)	0	
Neuropathy	4	(13.3%)	2	(6.7%)
IHD	3	(10%)	2	(6.7%)
PVD	1	(3.3%)	0	
HTN	9	(30.0%)	5	(16.7%)
PU with HTN	7	(23.3%)	0	

P=0.023 by Fisher's exact probability test. Intergroup differences in IHD

PU= Proteinuria MAU= Microalbumiuria, IHD= Ischemic heart disease, PVD = Peripheral vascular disease, HTN = Hypertension, SIB = Siblings

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Table1 shows that persistent proteinuria was present in 15 (50%) siblings in Group A and none is Group B. MAU was detected in 26.7% (n=7) in Group A and 3.3% (n=1) in Group B (P=0.057). Thus a total of 22 out of 30 cases in Group A had albuminuria. Occurrence of retinopathy was found to be significantly higher in Group A that Group B (33.3 vs 6.7%, $x^2 = 5.1$ p = 0023)

Younger age at onset of Nephropathy in Type 2 Diabetic offspring with Familial Aggregation of Nephropathy: (C. Snehalatha, V. Vijay, K. Shina, A. Ramachandran, - Unpublished Data)

The objectives of this study were to a). analyse the effect of familial predisposition to hypertension, coronary heart disease and diabetes, on the occurrence of diabetic nephropathy. b) to study whether the familial inheritance had an influence on the age at diagnosis of diabetic nephropathy in the probands. Among the probands, 305 did not have diabetic nephropathy (NDH) (Group 1) and 195 had diabetic nephropathy (DN) (Group 2). The two groups had comparable age, duration of diabetes and BMI

Table 2: Comparison of the Family History of Various Diseases in the Study Groups

	Group NDH (n=305)		**Group DN (n=195)**			
Family history	**n**	**%**	**n**	**%**	**X^2**	**P value**
DM	186	61	154	79	16.87	<0.001
HTN	119	39	127	65	31.84	<0.001
CHD	64	21	37	19	0.186	0.666
DN	19	6.2	35	17.9	15.76	<0.001

DM= Diabetes mellitus, HTN=Hypertension, CHD=Coronary heart disease
DN=Diabetic nephropathy. NDH = Non diabetic nephropathy

Patients with diabetic nephropathy had significantly higher rates of positive family histories of diabetes, hypertension and diabetic nephropathy. Rates of family history of coronary heart disease (CHD) were similar in both groups.

Table 3: Age at onset of Diabetes and other Complications in the Two Study Groups.

	DM	**HTN**	**CHD**	**DN**
	Age of diagnosis (years)			
NDH Families				
Offspring	44.1 ± 7.6*	48.7±6.0*	52.5±5.8	
	(454)	(134)	(55)	
Parents	57±9.8	57.4±12	63±10.7	68.7± 8.7
	(189)	(88)	(66)	(15)
DN Families				
Offspring	42±7.7***	45.1±6.2***	48.1±6.1	51±5. 7
	(337)	(235)	(66)	(211)
Parents	53.6±11.7	56±8.8	58.8±9.8	59±5. 7
	(136)	(89)	(30)	(31)

P<0.001 compared with the respective group of parents. ** P < 0.001 compared with NDH. Numbers in brackets show the numbers studied. NDH = Non diabetic nephropathy DN=Diabetic nephropathy.

Probands with diabetic nephropathy developed diabetes, hypertension (HTN) and CHD at a younger age than the probands without diabetic nephropathy. This study in a large group of type 2 diabetic probands, confirmed the existence of a strong familial aggregation of a diabetic nephropathy in Indians. It also showed that family history of diabetic nephropathy, diabetes and hypertension had independent association with diabetic nephropathy in the probands (Table 2 and Table 3).

GENETIC STUDIES

To study the association of ACE gene Polymorphism and diabetic nephropathy in South Indians subjects. (Vijay Viswanathan, Yanqing Zhu, Karthik bala, Stephen Dunn, C. Snehalatha, A. Ramachandran, Kumar Sharma – In press)

The Ace gene polymorphism is believed to have a significant impact on the progression of diabetic nephropathy. The ACE encoded by a gene located on chromosome 17. Bi allelic ACE polymorphism is characterized either by the absence (deletion 'D') or presence (insertion 'I') of a 287 base pair ACE repeat sequence inside intron 16. Patients with DD or ID genotype have less fall in blood pressure and

albuminuria when treated with ACEI than those with the II genotype. Patients with DD genotype have greater fall in GFR

The study was done in 109 South Indian type 2 diabetic patients. Group 1 consisted of diabetic nephropathy subjects (n=86) and Group 2 had subjects with normoalbuminuria (n=23). Group 1 and 2 had a similar age, BMI, duration of diabetes and duration of hypertension.

Table 4: Clinical details and distribution of ACE genotypes in the study groups.

	Group 1		**Group 2**	
	(Nephropathy patients) n=86		**(Non-Albuminuric patients) n=23**	
Age (years)	56.7 ±8.9		56.7 ± 9.3	
BMI kg/m^2	25.9±4.2		25.7±3.5	
Duration of diabetes (yrs)	13.4±6.9		13.2±5.1	
Duration of HTN(yrs)	6.1±3.5		5.7±3.8	
ACE genotype	**n**	%	n	%
Id	45	52.3	8	35
DD	24	27.9	5	22
II	17	19.8	10	43.5*
'D' allele	69	80.2	13	57**

**X^2 =4.27, p=0.04 vs Group 1; **X^2=4.27, P=0.004 vs Group 1.*

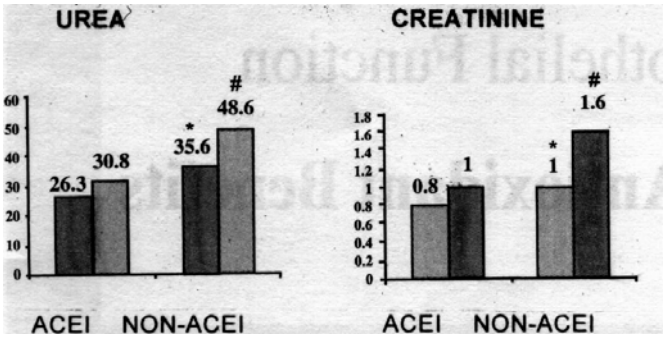
Table 4 shows that D allele was present in 80.2% in Group 1 compared to 57% in group 2. This study has shown a positive association between the D'allele (ID and DD genotype) of the Ace polymorphism and diabetic proteinuria is South Indian type 2 diabetic patients.

ACE INHIBITOR THERAPY

Effect of Angiotensin Converting Enzyme inhibitors (ACEI) on proteinuria in Type 2 Diabetes. (Dr. Vijay Viswanathan – In press)

This study was undertaken to determine the effect of ACE inhibitors in patients with diabetic nephropathy in South Indian diabetic population. Group A consisted of patients who had taken ACEI regularly (n=34) and Group NA consisted of patients with proteinuria who had not taken ACEI at all (n=44). The mean period of follow-up was four years for Group A and three years for NA Group. The patients in the NA group were on the following anti hypertensive drugs, Calcium blockers (n=23), betablockers (n=4), combination of calcium and betablockers (n=8). Nine patients had note taken any anti-hypertensive.

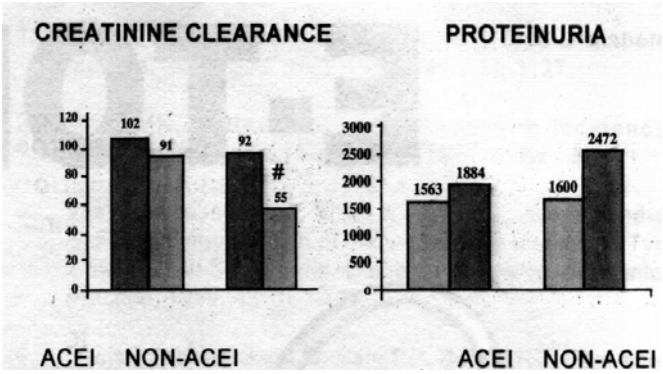
Figure 1 : Effect of ACE-Inhibitors on Urea and Creatinine



 # = Initial vs Follow-up

The rise in blood urea from the initial to the follow-up was significantly higher in the NA group than in Group A during the study period, Similarly the rise in serum creatinine was also significant higher in the NA group.(Fig 1)

Figure 2 : Effect of ACE-Inhibitors on Creatinine clearance and proteinuria



 # = Initial vs Follow-up

The fall in creatinine clearance was significant greater in NA group than in the Group A. In the study we have found that ACE inhibitors significantly reduce the rate of decline in creatinine clearance.(Fig 2)

We found that systemic BP did not differ between patients treated with ACEI and non ACEI group of baseline and at follow-up. This finding supports the hypothesis that the beneficial effect of ACEI on the progression of nephropathy may be independent of its anti-hypertensive effects (4).

STUDIES ON THE PROGRESSION OF RENAL DISEASE

Evaluation of a simple random urine test for prospective analyses of proteinuria in Type 2 Diabetes: a six year follow-up study (5).

410 newly registered type 2 diabetes patients who had annual follow-up for six years, who selected (M:F 263:147). Expected protein excertion (EPE) was calculated by estimation of protein/creatinine (P/C) ratio in a random urine sample.

Table 5: A Prospective study of kidney function using P/C ratio

	No proteinuria < 150mg/d	**Mild 150-500mg/d**	**Nephropathy > 500mg/d**
Baseline proteinuria	83.4%	12.9%	3.7%
At follow up	67.3%	15.6%	17.1%

Conversion to nephropathy	
No proteinuria	6.7%
Mild proteinuria	43.4%

Table 5 shows the changes that occur in the status of kidney function over a period of six years. Conversion of nephropathy was greater in patients with mild proteinuria at baseline. Thus EPE was found to be useful in serial evaluation of kidney function.

Table 6: Prevalence of Retinopathy in the four groups

	Normal		**Normal to proteinuria**		**Proteinuria both periods**		**Mild Proteinuria to Proteinuria**	
	n	**%**	**n**	**%**	**n**	**%**	**N**	**%**
Base line	5	2	1	3.1	9	60	4	17.4
Follow up	10	4	24	75	12	80	19	83
X^2	1.0				0.63		17	
P value	0.29				0.42		<0.001	

Table 6 shows that during the follow-ups, a large percentage of patients who developed persistent proteinuria from mild proteinuria at baseline also developed retinopathy.

This study validates an inexpensive test that can be used in developing countries for serial assessment of renal function on an out patient basis.

CONCLUSION

An early detection of renal impairment in diabetes and aggressive management of diabetes and hypertension can prevent diabetic kidney disease.

REFERENCES:

1. Ritz E. Nephropathy in patients with Type 2 diabetes mellitus. N. Eng. J. Med. 1999; 341 (15): 1127

2. Mani MK. Patterns of renal disease in indigenous populations in India. Nephrology 1998; 4: S4 – S7.

3. Vijay V, Snehalatha C, Shina K, Lalitha S, Ramachandran A. Familial aggregation of diabetic kidney disease in Type 2 diabetes in South India. Diabetes Research and Clinical Practice, 1999; 43: 167-171.

4. Lewis EJ, Hunsicker LG, Bain RP, Rohde RD. The effect of angiotensin – converting - enzyme inhibition on diabetic nephropathy. N Engl. J. Med. 1993; 329: 1456-1462.

5. Vijay Viswanathan, Snehalatha Chamukuttan, Shina Kuniyil, Ramachandran Ambady. Evaluation of a simple, random urine test for prospective analyses of proteinuria in Type 2 diabetes: a six year follow-up study. Diabetes Research and Clinical Practice. 2000; 49: 143 – 147.