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Diabetic Nephropathy (An Epidemiological and Clinical study)

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Introduction

Diabetes Mellitus is the most common cause of end - stage renal disease today (1). Renal failure from diabetic nephropathy is found in approximately 35% of the patients admitted to renal replacement programs in the United States and 15% in Europe (2). At the time of admission about 70% of patients are on Insulin therapy (this must not be confounded with the type of diabetes). Type 2 Diabetes is particularly common in elderly and black patients. In the past few years, both in United States and in Europe there has been a dramatic increase of the proportion of diabetic patients admitted to hospitals because of Renal Failure. This is in part due to: 1)The advancing age of the general population with the attendant increased prevalence of type 2 Diabetes. 2)Better survival of Diabetic patients in the preuremic stage and 3) Relaxation of admission policies.

In any case, Diabetic Nephropathy continues to be a major challenge to clinical Nephrologist as it is, at least in part a preventable condition.

The potential presence of proteinuria in Diabetic patients was first recognised by Cotugno in Bari in 1764. Renal lesion and Renal Failure in the Diabetic patient were described by Royer in 1840 (Paris). The specific Renal lesion of Diabetes (i.e. Nodular Glomerulosclerosis) however was only recognised in 1936 by kimmelstiel and Wilson (Boston). It took another two decades before in 1952 Lundbaek (Aarhus) recognised the Renal lesion as one specific facet of a more generalised problem: Microangiopathy of Diabetes Mellitus.

Materials and Methods.

During the years 1996 - 1997 we studied in a retrospective way all the Diabetic patients hospitalised in the University Hospital Center of Tirana. The total number of Diabetics hospitalised in this period was 493. From those, 256 had Diabetes Type 1 and 237 had Diabetes Type 2. **Table 1**

Table 1. Patients hospitalized with dianetes. (1996-1997)

	N.	Percent
D. Type 1	256	51,9
D. Type 2	237	48,1
D. Total	493	100

The division in 2 types was made according to the World Health Organisation in which Type 1 or Insulin Dependent Diabetes Mellitus is characterised by the abrupt on set of symptoms, insulinopenia, dependence on injected insulin for life and proneness to ketoacidosis. Patients with Type 2 Diabetes Mellitus are often overweight, have initial normal or high circulating insulin levels and exhibit insulin resistance to

skeletal muscle, of all diabetic patients we have selected only those complicated by Diabetic Nephropathy. Those were 149 patients and they make 30,2% of all Diabetic patients studied. **Table 2**

Table 2. Prevalence of Diabetic Nephropathy

	N.	Percent
D.N. Type 1	84	32,8
D.N. Type 2	65	27,4
D.N. Total	149	30,2

We defined clinically a patient as having Diabetic Nephropathy when it was found the presence of persistent proteinurial (> 0.5 gr./24 h.). This entity was considered also when it was associated with concomitant retinopathy and elevated Blood pressure, but without urinary tract infection, other renal diseases or heart failure. (3). We did not studied in our Diabetic Patients the early phase of DN, the so called "Incipient Nephropathy" because we have not performed the measurement of subclinical increases in Albumin excretion that are termed Microalbuminuria (4).

We have studied the frequency of DN according to the type of Diabetes. We observed also the age and sex of patients with DN in all groups. Beyond that it was studied the level of Blood Pressure and the prevalence of patients with High blood Pressure. Also the Retinopathy was studied and correlations were made between Retinopathy and Nephropathy. It was investigated further the frequency of Nephrotic range proteinuria, the presence of Hematuria and alterations of Lipids in DN.

An important problem was that of Renal functional Deterioration and its prevalence among patients with DN. The role of different factors on progression of renal failure were studied and their correlations were discussed.

Results and Discussion

It was found that the prevalence of DN in all type 1 Diabetic patients, was 32,8% while in typer 2 Diabetic patients, the prevalence of DN was 27,4%. (see Table 2). Till now there are at least two major cohort studies that describe the prevalence and incidence of DN in Insulin Dependent Diabetic patients (6.7.8.) In fact the prevalence of Nephropathy increases with duration of Diabetes to a peak of 21% after 20 - 25 years and then declines to about 10% in patients who have had Diabetes for 40 years or more. Only a small proportion of patients (4%) develop Nephropathy within 10 years of Diabetes.

In our patients with DN of type 1 Diabetes, the mean duration of Diabetes was 9.95-+ 8.07 years. Even other authors give importance to the duration of Diabetes in the expression of the incidence of DN. So it was observed that after a lag time of approximately 5 years, the annual incidence of DN rises rapidly over the next 10 years, to a peak after 15 to 17 years and then declines progressively (3). In fact the paucity of new cases of DN among the long standing diabetic patients would support the view that this complication occurs in most of the susceptible individuals earlier in the course of Diabetes. So the cumulative incidence clearly indicates that only a proportion of juvenile diabetic patients will ever develop Nephropathy.

In the group of type 2 Diabetic patients, the prevalence of DN was 27,4% which is lower than that of type 1 Diabetic patients. In European Diabetic patients the overall prevalence of proteinuria in exess of 500 mg/24 h. was reported to be aproximately 16% (9). Is was observed in some non European ethnic groups, that there is also a tendency for the prevalence to increase with the duration of Diabetes though this does not seem to apply to all populations. Of interest is the observation that as many as 62% of European Diabetic patients have been found to maintain normal protein excretion even after 16 years of Diabetes (10). Recent data from Europe shows a 57% cumulative frequency of proteinuria after 25 years of Diabetes (11). Reports of non - insulin dependent diabetic patients of Japanese (12) and of Pima Indians (13) indicate that the incidence rate of Nephropathy as measured by persistent proteinuria, rises with the duration of Diabetes, with a cumulative risk of proteinuria of 50% after 20 years of Diabetes.

The mean age of all our patients with diabetic nephropathy was 53.0+14.58 years, while we observed a significant difference in two types of Diabetes. **Table 3**

Table 3. Age and sex of patients with D.N.

	Age (years)	SD	Males	Percent	Females	Percent
D.N. Type 1	48,15	16,71	45	53,6	39	46,4
D.N. Type 2	58,71	10,18	27	41,5	38	58,5
D.N. Total	53,0	14,58	72	48,3	77	51,7

In type 1 DN the mean age was 48.15+16.71 years and in type 2 the mean age was 58.71+10.18 years. This difference is related to the different age at the diagnosis of those two types of Diabetes. Actually it is known that age at diagnosis significantly influences indidence of Nephropathy. So it was observed that Nephropathy develops more slowly in individuals who manifest Diabetes before the age of 10, than in those diagnosed after puberty (7). The higher incidence is seen (44%) in subjects who develop diabetes between the age of 11 and 20 years (8). Patients who deve lop Diabetes after the age of 20 have a lower cumulative incidence of Nephropathy at around 35%. Current age has been found by some authors (7), but not by others (8) to influence the incidence of proteinuria with a maximal risk in the age interval 18 - 35 years and a rapid decline in incidence after age of 35 years regardless of duration of Diabetes (15). But this discrepancy in fingings may be partly related to the different age groups of the cohorts studied.

The study of sex predominance in our patients with DN shows in general that females: males ratio is 49% vs 51%, but while in type 1 DN there is a predomination of males over the females (53.6% vs 46.4%), in type 2 Diabetes it was observed just the opposite (41,5% males vs 58.5% females). This is not found by other authors (14). We observed the origin of our patients with DN and found that 81.2% of them were townsmen and only 18.8% were peasants. This occurs in a country like Albania where more than 60% of the population lives in the countryside.

Table 4

Table 4. Origin of patients with D.N.

	N.	Townsmen	Percent	Peasants	Percent
D.N. Type 1	84	64	76,2	20	23,8
D.N. Type 2	65	57	87,7	8	12,3
D.N. Total	149	121	81,2	28	18,8

In type 2 DN the prevalence of patients originated from the cities is greater than in type 1 DN (87.7% vs 76.2%).

It exist a link between DN and the level of arterial blood pressure Raised blood pressure as well as cumulative exposure to diabetes are important determinants of renal involvement in Diabetic patients. This is particularly true in type 2 Diabetes. Those who develop proteinuria had a higher prevalence of Hypertension before onset of persistent proteinuria than those who did not (10). In all our patients with DN we found increased systolic blood pressure in 35.5% and inxreased diastolic blood pressure in 12.7% of them. **Table 5**

Table 5. Blood pressure in patients with D.N.

			Increased BP	
	mm Hg.	S.D.	Nr.of pt	Percent
S.B.P.	140,4	26,37	53	35,5
D.B.P.	86,6	9,84	19	12,7

Dividing the findings of high blood pressure according to the type of Diabetes, is results that in type 1 Diabetes increased systolyc blood pressure was found in 26 patients (30.9%), while increased diastolyc blood pressure was found in 7 patients (8.3%). **Table 6**

Table 6. Patients with increased S.B.P. (>140 mmHg) and increased D.B.P. (>90mmHg)

	Increased S.B.P.	Percent	Increased D.B.P.	Percent
D.N. Type 1	26	30,9	7	8,3
D.N. Type 2	27	41,5	12	18,4

In type 2 DN the respective fingings were 27 patients (41.5%) with increased systolyc blood pressure and 12 patients (18.4%) with increased diastolyc blood pressure. We have also noticed that all patients that have progressed in the stage of renal insufficiency are practically hypertensive. This finding has been observed also by other authors (16, 17). The association of DN with high blood pressure may be multifactorial but some serious studies suggested that familiar predisposition to raised arterial blood pressure may be a possible contributing factor to susceptibility to nephropaty in Diabetes. So, parents of insulin - dependent Diabetics with proteinuria were found to have significanlty higher arterial pressure than matched parents of non proteinuric diabetic patients (18). Studies of red cell sodium - lithium countertransport which are genetically determined and associated with the risk of Essential Hypertension, have been found to be higher in proteinuric diabetic patients than in matched long - term normo - albuminuric controls (19,20).

In a study of short term Diabetic patients without clinical proteinuria but with arterial hypertension, those with higher rates of sodium - lithium countertransport were more insulin resistant and had higher albumin excretion rates, increased total body exchangeable sodium, enlarged kidneys and left ventricular hypertrophy (21).

It seems to be the Diabetic Hypertensive patient with high sodium lithium countertransport who dislplays albuminuria, left ventricular and renal hypertrophy and insulin resistance that have been related to renal and vascular injury (22, 23). Anyway, the above metioned mechanism of a genetic presisposition to primary hypertension that predisposes also to nephropathy is more suitable for the type 1 Diabetic patient. In this type of Diabetes there is a presisposition to sodium retention and this explains why hypertension of diabetic patient is uniquely susceptible to sodium restriction and treatment to diuretics. Plasma renin is usually low in hypertensive diabetic patient. But more sophisticated analyses clearly showed that circulating angiotensin 2 levels are inappropriate to the prevailing level of blood pressure and exchangeable sodium. But anyway two of our elderly patients with type 2 Diabetes were in a supressed activity of renin system probably because of the "hyporeninemic hypoaldosteronism" as they had caracteristically the signs of hyperkalemia and metabolic acidosis. We suggest that the recognition of this condition is particularly important in the patient who is scheduled to receive angitensin - converting enzyme (ACE) inhibitors, because such patients are prone to develop hyperkalemia.

The relation between hypertension and nephropathy is more complex in type 2 Diabetes. In most patients the onset of chemically overt type 2 Diabetes is preceded by years and decades of elevated blood pressure. In these patients the presence of insulin resistance and the associated "metabolic syndrome", characterised by central obesity, dyslipidemia and elevated insulin levels is important since it predisposes the patient to atherosclerosis. Concluding, while the hyperglicemia is the major determinant for the risk of development of diabetic nephropathy, blood pressure on the other hand is the major determinant for the rate of progression of nephropathy once overt proteinuria is present. The causal role of hypertension for progression has been substantiated by studies that document that antihypertencive medication reduces albuminuria and attenuates the rate of loss of GFR in Diabetic patients with nephropathy.

Proteinuria is the most characteristic feature of diabetic nephropathy. Of all patients of our study, 18 cases (12%) had nephrotic range proteinuria. We did not find a significiant difference of heavy proteinuria between type 1 diabetic patients and type 2 diabetic patients (11.9% vs 12.3%). **Table 7**

Table 7. Retinopathy and heavy proteinuria in D.N.

	Retinopathy		Proteinuria > 3g/24h	
	N.	Percent	N.	Percent
D.N. Type 1	80	95,2	10	11,9
D.N. Type 2	36	55,4	8	12,3
D.N. Total	116	77,8	18	12,0

Recent studies have demostrated that the proteinuria of the late stages of overt nephropathy is

probably the result of a defect in size selectivity properties of glomerular membrane. But it is likely also that the charge selectivity defects persist at this stage of advanced nephropathy. Heavy protein excretion and nephrotic syndrome are related to a poorer renal outcome (24).

As a rule the development of persistent proteinuria is followed by progressive decline of the GFR to End - stage Renal Failure.

Retinopathy was studied by fundo - scopic examination. Retinopathy was observed in 80 patients (95.2%) of type 1 diabetes and in 36 patients (55.4%) of type 2 diabetes (Table 7). In total retinopathy was present in 116 patients (77.8%). In different recent studies diabetic retinopathy is present in virtually all insulin dependent diabetic patients with nephropathy (25, 26, 27). Some authors suggest that the absence of retinopathy should lead to careful consideration of other non - diabetic causes for proteinuria and renal desease (3).

In our study we have found that in uremic stages of renal disease, retinopathy was severe with new vessel formation. In one patient the disease was complicated by blindness. Blindness was extremely common in the past among the diabetic patients with renal failure, nowadays this has become less frequent with improvement of anti - hypertensive treatment and prophylactic laser coagulation.

While almost all patients of type 1 Diabetes with Nephropathy have retinopathy, the reverse is not true: the retinopathy even of proliferative kind may occur in the absence of proteinueria and renal disease up to one third of patients with proliferative retinopathy may be free of proteinuria (3). The exact reasons for this discrepancy in manifestations of microvascular disease are not clear but epidemiological evidence suggest that retinopathy and nephropathy are associated with different enviromental determinants, the former being more closely related to a history of poor blood glucose control and the latter showing a stronger association with bloof pressure. We can't explain the lower frequency of retinopathy in our patients with type 2 Diabetes, but even others has found retinopathy present in 47 to 63% of non - insulin dependent diabetics with persistent proteinuria (29, 30).

We found the presence of microhematuria in 87 patients with type 1 and type 2 diabetic nephropathy (58.3%). It has been claimed that those with microhematuria have a higher prevalence of concomitant non - diabetic renal disease, however it is sure that microhematuria can occur in proteinuric diabetic patients as part of the diabetic nephropathy syndrome and in the absence of other renal conditions. Microhematuria is of little use in distinguishing non - diabetic renal disease (31).

Dyslipidemia is a common finging in patients with diabetic nephropathy. We found increased levels of serum cholesterol in 59 patients (44.7%) and increased levels of serum tryglicerides in 52 patients (39.4%). **Table 8**

In general patients with type 2 diabetes had higher levels of cholesterolemia (57.6% vs 33.8%) and of trigficerides (44.1% vs 35.15) than patients with type 1 diabetes. Some authors observed dyslipidemia particularly in type 2 diabetes even whem renal function was normal and glycemia was well controlled. This may result from the common presence of insulin resistance and later on dyslipidemia is further aggravated by the onset of nephropahty. In some recent studies elevated triglycerides and low HDL levels were protent predictors of cardiac death (2).

Table 8. Increased Cholesterolemia (>220mg%) and Triglycerides (>165mg%)

	Increased Cholesterolemia		Increased Triglycerides	
	N.	Percent	N.	Percent
D.N. Type 1	25	33,8	26	35,1
D.N. Type 2	34	57,6	26	44,1
D.N. Total	59	44,7	52	39,4

Last we studied the presence of deteriorated renal function in patients with diabetic nephropathy. **Table 9**

Table 9. Increased level Uremia (>40mg%) and creatininemia (>1,5mg%)

	Increased Uremia		Increased Creatinine	
	N.	Percent	N.	Percent
D.N. Type 1	46	54,7	9	10,7
D.N. Type 2	28	43	4	6,1
D.N. Total	74	49,6	13	8,7

It is known that the development of persistent proteinuria is followed by progressive decline of GFR to end stage renal failure. In patients with diabetic nephropathy taking to antihypertensive medication, GFR decreases at an average rate of 10 ml/min/year, but the rate of loss of GFR varies markedly between individuals. We found increased levels of creatininemia in 13 patients (8.7%) and increased levels of uremia in 74 patients (49.6%). The number of patients with renal failure was greater in insulin dependent diabetics than in non - insulin dependent diabetics. In general, once the renal insufficiency develops, the adequacy of blood glucose control has a limited impact on progression. The level of diastolic blood pressure has been found to be correlated with the rate of progression of established diabetic nephropathy and serum creatinine concetration have been reported to rise sooner in those proteinuric patients with the highet blood pressure levels (32).

Today the average time between the onset of persistent proteinuria and end - stage renal failure has been considerably extended with the early use of more intensive treatment for hypertension (3). Concluding as nearly as 35% of newly diagnosed end - stage renal disease is a result of diabetes in some developed countries and as experts predict that diabetes will be the primary cause for 50% of ESRD in a near future, we hope that our study is a small contribution in the enormous efforts made by the physicians to resolve this great problem of our society.

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