CHAPTER 4

Diabetic Nephropathy in Type 2 Diabetes

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When dialytic therapies became readily available in the United States (USA) in the late 1960s, the diagnosis of diabetes was considered a contraindication to receiving end-stage renal disease (ESRD) therapies. It is ironic that diabetic nephropathy (DN) is now the leading ESRD diagnosis of patients entering ESRD programs in the USA, as well as most of the Western world. Also, as an ESRD diagnosis, it is increasing in incidence at a more rapid rate than any other ESRD diagnosis.[1] It is unknown if this growth is related to actual increases in the incidence of DN, or to an increased identification of patients as ESRD therapies become more readily available.

Classic teaching has promulgated the notion that type II diabetes carried a relatively benign renal prognosis. A tour of a haemodialysis unit in most parts of this country would demonstrate that nothing could be farther from the truth. Still, the exact percentage of type II patients that develop nephropathy is unknown for most populations. Even when patients are tracked, patients with ESRD secondary to type II diabetes may be misclassified as hypertensive renal disease, or type I diabetics because of the usage of insulin. The Pima Indians, a group of Native Americans who live in the Gila River Indian Community in the desert of Arizona and in which accurate longitudinal data are available, have nephropathy rates that may even exceed that of patients with type I diabetes (50% after twenty years of type II diabetes).[2,3]

RISK FACTORS

Genetic: Nephropathy does not affect all ethnic groups equally with

Caucasians having the least risk, Hispanics and African Americans having a higher risk than Caucasians, and Native Americans and Asian/Pacific islanders having the highest risk. The incidence rate for diabetic ESRD in the United States for 'Whites' (Caucasians and Hispanics) is one fourth that of African Americans and one sixth that of Native Americans.[1] The ethnic breakdown of the incidence of type II diabetes is unknown except for whites versus African Americans with African Americans being at least twice as likely to have type II diabetes than whites.[4] This does not explain the four-fold difference in diabetic ESRD incidence rate between these two ethnic groups. In fact one study demonstrated that the incidence of diabetic ESRD was almost three times higher in African Americans than whites, even after adjustment for the higher prevalence of diabetes in the African American population.[2]

One extreme example of this genetic predisposition for both type II diabetes and diabetic nephropathy comes from data collected on Pima Indians. Seventy percent of Pima adults develop type II diabetes. Diabetic renal disease is common with an incidence of diabetic ESRD (essentially all type II) twenty times greater than that for the general population of the United States. There is a greater chance of a Pima having an ESRD death than a cardiovascular disease death![2,3]

Length of diabetes and age: The longer a patient has diabetes, the greater the risk of developing nephropathy. However, when patients with type II diabetes are matched for years of diagnosis of diabetes, patients diagnosed after age 50 had a higher prevalence and degree of microalbuminuria (76% and 93 mg/g creatinine respectively) than those diagnosed before the age of 40 (38% and 38 mg/g creatinine).[2]

Gender: The male to female incidence ratio of ESRD secondary to diabetes is 1.1 even though women are diagnosed with diabetes at a rate 1.5 times that of men, suggesting diabetic males are at greater risk of developing nephropathy.[2]

Hypertension: Type II diabetic patients that have an elevated blood pressure in the pre-proteinuric state have an increased risk of developing proteinuria compared to normotensive type II patients. However, this must be interpreted with caution. The onset of nephropathy for this purpose should not be defined by clinical onset (proteinuria) since histologic ultrastructural evidence of nephropathy many precede proteinuria by many years and these histologic changes may be accompanied by physiological alterations that lead to

hypertension. Still, the presence of hypertension in a Pima Indian, even before the diagnosis of diabetes, is associated with a higher rate of albuminuria after the diagnosis of diabetes.[2,3]

Hyperglycaemia: In the Appropriate Blood Pressure Control in Diabetes Trial (ABCD), poorer diabetic control was found in patients with nephropathy. The majority (70%) of the patients in this study were white with 11% African American and 15% Hispanic. In a study from Germany where the majority of type II patients are Caucasian, the level of postprandial glucose in the preproteinuric stage did not predict the subsequent development of proteinuria.[5] In the African American type II diabetic population, studies have failed to demonstrate an association of the level of blood glucose control to the likelihood of a patient having nephropathy. On the other hand, the risk of nephropathy correlated strongly to blood glucose control in studies in Native American Indians.[2]

Cigarette Smoking: In type II patients with newly diagnosed diabetes, albuminuria was found in 8.2% of smokers and in 7.3% of former smokers, however it was present in only 2.1% of non-smokers.[2]

Insertion/deletion polymorphism of the angiotensin-converting enzyme (ACE) gene: The gene that codes for angiotensin converting enzyme exists in two polymorphic forms depending on the presence (insertion: I) or absence (deletion: D) of a 287 base pair fragment. Humans may carry both insertion genes: II, one of each: ID, or both deletion genes: DD. The levels of ACE in Caucasians with the DD allele is twice that of those with the II allele. Those with ID allele have intermediate levels. There are conflicting results concerning a patient's risk of developing nephropathy based on their ACE ID genotype although patients with the DD genotype progress to ESRD the fastest while those with the II genotype progress the slowest.[2]

NATURAL HISTORY

There are five stages that have been defined in the course of type I DN and it is useful to discuss the natural history of the type II DN in the context of these stages (**Table 1**). Since the onset of type II diabetes is usually not known, the time of onset of each of these stages in relation to the years of diabetes will not be provided.[2,6,7]

Table 1: Comparison of the Five Stages of Nephropathy in Patients with Type I and II Diabetes

Stage	Diabetes	Onset	Findings		
			Kidney Volume	**Glomerular Size**	**GFR**
1	Type I	At Diagnosis	Increased	Increased	Increased
	Type II		Increase or NL	Increased or NL	Increased, but only compared to age matched controls
			BM	**Mesangium**	
2	Type I	Years 2–5	Thickened	Expanded	
	Type II		Thickened	Expanded	
			Microalbuminuria		**BP**
3.	Type I	Years 5–15	Prevalence only 20% but majority of those (80%) progress to stage 4		Usually normal but increased over baseline
	Type II		Higher prevlance (40%) but minority of those (20%) progress to stage 4		Usually elevated
			BP	**Nephrotic syndrome**	**Fall in GFR**
4.	Type I	Years 10–20	Usually Elevated	Often present	2–10 ml/min/year
	Type II		Usually Elevated	Often present	5–10 ml/min/year
			ESRD		
5.	Type I	Years 20–	High mortality rate, improved with transplantation		
	Type II		High mortality rate, often excluded from transplantation		

GFR = glomerular filtration rate, BM = Basement membrane, BP = Blood pressure, ESRD = End-stage renal disease, NL = normal

THE ASSOCIATION OF NEPHROPATHY TO RETINOPATHY

In type II patients that have biopsy proven diabetic glomerulosclerosis, retinopathy by fundus photographs is present in only 56–75% of patients. Therefore the caveat of lack of retinopathy suggesting non-diabetic renal disease in the type I diabetic does not hold true for type II diabetes.[2,8]

HISTOLOGY IN TYPE II PATIENTS WITH PROTEINURIA

The lesions of nodular (KW) and diffuse glomerulosclerosis (DGS) described by Kimmelstiel and Wilson in 1934 were in patients with type II diabetes.[9] The vast majority of patients with type I diabetes, proteinuria and retinopathy will have diabetic nephropathy as an explanation for the proteinuria. There are a number of reports for type II diabetes that have challenged this, claiming that 30-60% of these patients, when biopsied, will have a renal histopathologic diagnosis other than diabetic nephropathy, or will have another lesion in addition to diabetic nephropathy. A summary of prospective studies is presented in **Table 2.** The criteria for biopsy as well as the means by which these studies have interpreted the histology may have lead to an overestimation of non-diabetic glomerulopathy in type II patients with proteinuria. The data from Schwartz *et al* where only 6% of patients had a non-diabetic renal disease may be a more accurate representation of the prevalence of this condition.[2,8]

PREVENTION AND INTERVENTION

Improved hyperglycaemic control: The Diabetes Control and Complications Trial (DCCT) has not been repeated in the type II population. The United Kingdom Prospective Diabetes Study (UKPDS) is designed to answer this question but the results are not yet available.[10] A 6 year prospective study from Japan evaluated the effects of intensive glycaemic control (mean HgbA1 values of 7.1%) compared to conventional glycaemic control (mean HgbA1 levels of 9.4%) in 110 type II diabetic patients. Despite

Table 2: Histology in Patients with Type II Diabetes and Proteinuria[2,8]

		Histology		
Author	**# of Patients**	**DG**	**DG & Other**	**Other**
Lipkin	82	61%	9%	30%
Parving	35	77%		23%
Gambara	52	37%	33%	30%
Schwartz	34	94%		6%

DG = Diabetic glomerulosclerosis

the small cohort size of this study, the investigators found significant benefit for both end-points, retinopathy and nephropathy, in both cohorts in the patients receiving intensive management (**Table 3**).[11]

Achieving tight control is not without risk. Patients in the DCCT were younger, less obese, normotensive, had more normal lipid profiles, and had less cardiovascular disease at baseline than do most patients with type II diabetes. Aggressive antihyperglycaemic treatment, especially when this requires insulin in the type II patient, may exacerbate some of these pathologic conditions.

Hypertensive treatment: Prospective studies on the natural history of type I DN demonstrated that hypertension accelerates the loss of GFR in patients with established type I diabetic nephropathy, and the rate of loss of renal function can be attenuated with antihypertensive agents. This work will not be repeated in the type II population because it would be unethical to prospectively not treat hypertension in a population of patients with such a high risk of cardiovascular disease. Still, despite this lack of data supporting a role of lowering blood pressure in the hypertensive type II patient with nephropathy, it seems prudent if not obvious, to do so.[2]

ACE Inhibitors: ACE inhibitors (ACEi) slow progression of nephropathy through mechanisms that are independent of their effect on systemic blood pressure (renoprotection). In patients with type I diabetes, this has been extensively demonstrated in patients with both microalbuminuria and overt nephropathy.[12] Data on their effects in patients with type II diabetes is sparse and renoprotection (GFR preservation independent of blood pressure) has

Table 3: Results of Intensive Management of Blood Glucose in Patients with Type II Diabetes[11]

	Prevention Cohort		Progression Cohort	
Insulin Regimen	**Retinopathy**	**Nephropathy**	**Retinopathy**	**Nephropathy**
Intensive	8%	8%	19%	12%
Conventional	32%	28%	44%	32%

Numbers represent cumulative percentages of patients developing or progressing with microangiopathy

only been definitively demonstrated in patients with microalbuminuria (**Table 4**).11 However, this may reflect inadequate powering of these studies, either by size[14,15] or study length.[15] Although data for the use of ACEi in type II DN are not as conclusive as that for type I DN, it seems reasonable to screen type II patients for overt proteinuria as well as microalbuminuria and to initiate ACEi, even if patients are normotensive.

The use of ACEi was well tolerated in these studies. Whether or not this will hold true in a large population of patients with type II diabetes and overt nephropathy is unknown. Large well controlled studies are currently underway. Hyperkalaemia may be exacerbated by ACEi and acute renal failure secondary to functional (small vessel) or structural (large vessel) renal artery stenosis may also be expected in some patients. Therefore, patients should be under close initial observation, at least until more data is available concerning efficacy and safety.

Calcium Channel Blockers: Unlike ACEi where the antiproteinuric effect appears to be a class related effect, different antiproteinuric responses have been reported depending on the calcium channel blocker (CCB) being used. Diltiazem has been shown to reduce proteinuria to a similar degree as ACEi. Nifedipine on the other hand has been shown to increase proteinuria in some series of type II diabetic patients. There are no long term studies looking at

Table 4: ACE Inhibitors in Type II Diabetic Nephropathy[2,13,14,15]

Study	Nephropathy*	Treatment	Period	Blood Pressure	Results
Ravid[13]	MA	ACEi vs placebo	5yr	Same in both grps	↓ proteinuria with ACEi ↓ rate of creatinine rise with ACEi
Lebovitz[14]	MA & ON	ACEi vs placebo	3yr	Lower with ACEi	↓ GFR loss with ACEi in MA grp only
Nielsen[15]	ON	ACEi vs Beta Blocker	1yr	Same in both grps	↓ proteinuria with ACEi GFR loss same in both grps

*MA = microalbuminuria, ON = overt nephropathy

preservation of renal function with CCBs. There may be a role for some of these agents in proteinuric diabetic patients that cannot tolerate ACEi. In addition, the combination of ACEi (lisinopril) and CCB (verapamil) has been demonstrated to lower proteinuria to a greater degree than the ACEi alone.[2,16] Reports of increased cardiovascular morbidity in type II diabetics with hypertension have brought to question the safety of these agents in this population.[17] These results are by no means ubiquitous and further study will hopefully define their safety profiles in specific populations, receiving specific CCBs.[18]

Diet: The Modification of Diet in Renal Disease Study (MDRD) did not study diabetic patients although one study in type I diabetics demonstrated that aggressive protein restriction (0.7 gm/kg/day) decreased the rate of deterioration in renal function to one fourth the rate of non-protein restricted (1.1 gm/kg/day) patients.[2] This study has not been repeated in type II diabetics nor is it clear that protein restriction to this degree is safe in the older type II population.

SUMMARY

With type II diabetes now the leading cause of ESRD in many parts of the world, we must focus attention on manoeuvres that might prevent or delay onset, or slow progression to ESRD. Although there are differences between the nephropathy associated with these two types of diabetes, there are more similarities than dissimilarities. It therefore seems reasonable to take a similar clinical approach when treating both type I and type II diabetic patients with renal disease.

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