Bahrain Medical Bulletin, Volume 18, Number 2, June 1996

Editorial

EARLY DIABETIC NEPHROPATHY

Roger K Ferguson, FACP, FACC, FCCP*

Diabetes mellitus is becoming commoner in almost all parts of the world. Diabetic renal disease represents one of its most devastating complications. Physicians and health care workers often ask the following questions about its early recognition, prevention and treatment.

1. **What is the importance of diabetic kidney disease**?

Among the huge worldwide population of diabetic patients, renal disease is a significant and all-too-common complication. Nephropathy, characterised by albuminuria and a decreasing glomerular filtration rate (GFR), will develop in more than 40 % of those with type 1 or insulin dependent diabetes mellitus (IDDM)[1]. In type 2 or non-insulin dependent diabetes (NIDDM), nephropathy is less prevalent (5-10 %), but affects as many patients because it is far more common (nearly 90 % of all diabetics)[2]. Type 1 diabetes usually begins at an earlier age than the adult onset type 2 diabetes and is believed to result from a different cause.

Among type 1 diabetics, renal failure and its complications represent the most common cause of death[3], a risk nine times that of patients without this complication. One third of all new dialysis patients have diabetic nephropathy and more than a third of patients who receive renal transplantation[4]. The economic costs of caring for patients with end-stage renal disease (ESRD) are staggering (more than US $6 billion annually in the USA), but the costs in terms of human misery and suffering are worse. Hence, prevention or slowing the progression of diabetic nephropathy is not only desirable but, as will be seen, seems to be increasingly possible.

2. **What is the pathogenesis of diabetic nephropathy**?

Complications of diabetes appear to result mainly from its concomitant hyperglycaemia although other metabolic abnormalities probably play a role. Glucose reacts

---

* Professor & Head
Division of Internal Medicine
College of Medicine & Medical Sciences
Arabian Gulf University
State of Bahrain

non-enzymatically with proteins in vivo to form advanced glycosylation end-products (AGE's). Glycosylated peptides, which accumulate first in blood and then at a faster-than-normal rate in tissues, contribute primarily to the microvascular complications of diabetes mellitus[5]. Associated metabolic alterations such as changes in growth hormone and insulin-like growth factors also may contribute but the fact is that increases in circulating AGE's parallel the severity of the renal functional impairment of diabetic nephropathy[6]. Indeed, glycosylated haemoglobin of less than 7.5 % implies a low risk of developing nephropathy[7].

Thus, via glycosylation, hyperglycaemia damages glomeruli by causing molecular disorganisation followed by thickening of the glomerular basement membrane (GBM) and mesangial collagen matrix. These in turn lead to increased intraglomerular pressures and altered sieving properties of the GBM. How the structural changes bring about the albuminuria is not fully understood. One (the Steno) hypothesis postulates that damage to the GBM and mesangium result from the decreased density and sulfating of heparin sulfate proteoglycans[8]. These in turn cause a loss-of-charge selectivity and leakage of serum albumin across the barrier.

Glycosylation too sets in motion oxidising forces and the release of free radicals that can injure cells and membranes. Prolonged hyperglycaemia also can lead to the accumulation of sorbitol which can disrupt membrane integrity through depletion of myoinositol. Finally, sieving of protein itself may aggravate the injury.

Haemodynamic factors also contribute to the process, particularly in type 1 disease. Alterations in several vasoactive control systems such as glucagon and growth hormone, angiotensin II and norepinephrine may be harmful to glomerular capillaries. Hyperglycaemic consequences are afferent arteriolar vasodilatation, relative efferent constriction, augmented glomerular capillary blood flow and heightened filtration[9]. Diabetic kidneys may be particularly susceptible to these forces.

Genetic predisposition to hypertension also has been implicated in the evolution of diabetic nephropathy, but thus far no candidate gene has been identified[10]. Having a parent with hypertension increased the risk of nephropathy fourfold above patients who did not have hypertensive parents. Risk of nephropathy appears to vary with ethnicity[11,12]. It develops in 5-10 % of Caucasian patients with NIDDM, whereas among other racial groups e.g. Latinos and African-Americans, the incidence of renal insufficiency is 50 % or more. These groups are also more prone to develop hypertension and diabetes mellitus. Taken together, the evidence points to a strong connection between a genetic predisposition to hypertension and the evolution of clinical diabetic nephropathy[11,13].

Hyperglycaemia and hypertension therefore appear to be the prime risk factors in the development of diabetic renal disease. On the other hand, even some patients with poor glycaemic control seem to be protected against the development of nephropathy, perhaps again due to genetic factors. Hence, the need arises for a marker of identifiable risk for the early detection of those patients who are at risk for both nephropathy and other vascular complications.

3. **What is the cause of diabetic nephropathy?**

The first indication that diabetes is affecting the kidneys is a supranormal GFR that may exceed 150 ml/min (normal is up to 120 ml/min). Although it occurs in NIDDM, this hyper filtration is more often detectable in IDDM. If a renal biopsy was performed around this time, it would reveal glomerulomegaly that is the hallmark of diabetic nephropathy. Over the next two to five years the capillary GBM and mesangium will thicken because of the accumulation of collagen in reaction to injury, leading to focal than diffuse glomerulosclerosis. As the glomerulosclerosis develops and becomes more diffuse, the glomerular capillaries will begin to leak protein.

This initial manifestation called 'microalbuminuria' even though this is a misnomer in that the albumin molecules are normal in size. The term refers rather to the amount of albumin (ranging from 130 to 300 mg a day) sieving across the glomeruli. This is the earliest external manifestation of diabetic renal disease, and which can now be detected as the hallmark of incipient nephropathy.

Systemic blood pressure will begin to rise more or less concurrently upon the appearance of microalbuminuria in a diabetic patient. As the blood pressure raises further, glomerulosclerosis progresses and urinary albumin excretion increases. When it exceeds 300 mg per day, the process becomes largely irreversible with present management strategies. Up to this point, GFR generally remains normal or supernormal but once the albuminuria approaches 1000 to 3000 mg a day, the GFR will begin a progressive decline of about 1 ml a month, leading to renal failure.

When the urinary albumin excretion exceeds 3000 mg a day, nephrotic syndrome appears and, in a third of the patients, the classic Kimmelstiel-Wilson syndrome. Most patients reach end-stage renal failure within 10 years after the onset of albuminuria. Although nephropathy may evolve gradually over those years, the clinical course is fairly predictable.

4. **What other factors influence the rate of progression of diabetic nephropathy**?

Hypertension. Systemic hypertension is known to accelerate the course, resulting in an earlier decline in renal function and a worsening of the proteinuria. All studies agree that elevated blood pressure constitutes a risk factor for diabetic glomerulopathy[14]. Diabetic kidneys may be particularly vulnerable to the adverse effects of hypertension because of the afferent vasoconstriction that ordinarily occurs in essential hypertension. Systemic pressures are transmitted more directly into the glomerular capillaries, resulting in greater intraglomerular hypertension. The best argument that this is true is that lowering blood pressure often attenuates the microalbuminuria associated with the hyperfiltration[15].

Dyslipidemias. Adverse changes in lipoproteins and apolipoproteins are also more common in patients with persistent microalbuminuria[16,17]. They are often a result of poorly controlled hypertension. Indeed, NIDDM patients are more likely to die from macro vascular complications than from diabetic nephropathy[16].

Dietary Protein. High protein content in the diet can exaggerate the hyper filtration and albuminuria of diabetic animals and patients[17]. The same increases in GFR and renal blood flow occur in normal humans with an acute protein load[18]. In addition, patients with renal failure who consume normal or high amounts of protein have more symptoms and signs of uremia than those who consume restricted amounts of protein.

Smoking. In one study cigarette smoking was considered to be the most important factor for progression of both incipient and overt diabetic nephropathy[19]. Smoking increased the levels of carboxyhaemoglobin and fibrinogen and enhanced platelet aggregation resulting in tissue hypoxia and vascular damage. It may also raise blood pressure acutely, thereby adversely affecting kidney function.

5. **How can we detect diabetic nephropathy?**

The finding of protein by routine dipstick analysis (> 300 mg/L) established clinically overt diabetic nephropathy. At this point urinary albumin excretion already exceeds 150 to 200 mg a day (20-200 ug/min). Although the serum creatinine and urea nitrogen levels are usually in the normal range, the GFR will have already begun to fall and many patients will also demonstrate elevation of the blood pressure. Once nephropathy develops the progression to ESRD is inexorable and predictable in this group of patients.

A renal biopsy with microscopic evaluation of the glomeruli could, of course, detect disease earlier, but this is impracticable in most patients and unreliable in others. Thus, the best current predictor of diabetic nephropathy

is the presence of persistent microalbuminuria[20,21]. This preclinical phase, termed incipient nephropathy, is also the best predictor of other cardiovascular complications including diabetic retinopathy[22].

Prevalent microalbuminuria is usually defined as the presence of microalbuminuria in two of three consecutive specimens. Its detection is now practical thanks to the development of more sensitive assays and dipsticks for screening. Semi-quantitative dipsticks can detect albumin levels of 20-200 mg/L on random urine specimens[23]. Quantitative urinary albumin excretion can be measured using newer radio-immunoassay and turbidimetric assay techniques[24]. They have proven useful in detecting microalbuminuria.

6. **What can we do to prevent diabetic nephropathy**?

The current challenge in the care of diabetic patients is to find strategies to minimize the development of diabetic complications. Based on the pathogenesis, of course, the prime consideration in preventing complications is the control of hyperglycaemia. In contrast to patients with overt nephropathy, patients with incipient nephropathy have been benefited by strict glycaemic control. A central role for hyperglycaemia is supported by studies that demonstrate not only that glomerular changes and proteinuria are present in animals and humans with surgically induced diabetes, but that those changes can be reversed through maintaining euglycaemia. Data also exist showing that diabetic renal disease can still develop in diabetics who undergo renal transplantation, but that successful pancreas transplantation can prevent or halt glomerulopathy.

But the most powerful confirmation of the value of glycaemic control is the North American Diabetic Complications and Control Trial (DCCT)[25]. At least in IDDM complications including microalbuminuria and renal disease could be prevented or delayed by tight control of blood sugar. Though it is true that there was a higher incidence of hypoglycaemia due to the aggressive treatment, this could be alleviated by self-monitoring of blood glucose and improved insulin regimens[26]. Monitoring glycosylated haemoglobin also is a way of measuring longer term success in reducing hyperglycaemia[26,27]. Presumably, similar results will be obtained in controlled trials of NIDDM, given the better drugs we have available today.

7. **How should we treat incipient diabetic nephropathy?**

Once incipient nephropathy is detected by testing for persistent microalbuminuria, how should we intervene to prevent the evolution of the kidney disease? Detection as such should deliver a message to patient and physician that it is time for more rigorous treatment of hyperglycaemia using weight control, exercise and diet as well as improved monitoring of glucose. But the microalbuminuria itself merits specific therapy as does any associated hypertension, since both are detrimental and may contribute to deterioration of renal function. Fortunately, one class of drugs has been found effective on both counts.

The angiotensin-converting enzyme (ACE) inhibitors block the production of angiotensin II and reduce the synthesis of aldosterone, thus withdrawing vasoactive and volume components that may be activated in hypertensive disorders. The ACE inhibitors have been shown to be useful in controlling blood pressure and decreasing urinary albumin excretion in patients with early or established nephropathy[28,29]. Moreover, three long-term controlled trials using ACE inhibitors reported that progression to overt nephropathy (proteinuria and/or decreased GFR) may be delayed and possibly halted even in normotensive patients with IDDM and NIDDM who have microalbuminuria[30,31]. These results suggest that some of the beneficial effects of ACE inhibitors may be independent

of systemic antihypertensive effects and may be caused in part by increased efferent vasodilatation in the kidneys. Whether this is a specific effect remains unproven, but nonetheless the ACE inhibitors offer an effective means of slowing the decline in renal function even in normotensive patients[32].

All ACE inhibitors appear capable of these Reno protective effects and some have been shown to maintain them for as long as three years[33]. In addition, as a class of antihypertensive agents they appear to have an excellent side effect profile advantageous to the diabetic patient. Other blood-pressure lowering drugs, such as calcium entry blockers, can reduce microalbuminuria but are more hetergenous in this aspect[34].

The ACE inhibitors, moreover, are metabolically 'neutral' with respect to lipid and carbohydrate metabolism. A few studies suggest that ACE inhibitors may even increase insulin sensitivity in some patients. This is especially noteworthy because insulin resistance and hyperinsulinaemia are independent risk factors for cardiovascular disease[35].

8. **How effective can we expect the treatment of early diabetic nephropathy to be?**

Recent surveys suggest that the incidence of diabetic nephropathy may be decreasing; earlier and more effective treatment of hypertension probably accounts for this trend[1-4]. Better monitoring and improved treatment of diabetes mellitus could be expected to result in a similar outcome now that we know the benefits of tight control of hyperglycaemia[25]. With newer technology and improved education prevention of diabetic complications should be more attainable. Finally, early detection of microalbuminuria and intervention with effective therapy also could prevent the progression of incipient nephropathy to renal failure and allay the need for dialysis and transplantation. Again, newer knowledge and methods make this feasible. However, governments, and health care workers need to promote attitudes and undertake efforts that will lead to significant improvement in the care of diabetic patients.

CONCLUSIONS

Today ample information and means exist to significantly alter the course of diabetes mellitus in the majority of patients[36]. Clinical and basic researches during the past decade have dramatically altered our concepts concerning the causes and natural history of diabetes. Not only can we detect the complications earlier but now are able to identify individuals at high risk and should be able to alter the course of the disease(s). There is even the promise that in future we may be able to prevent them, which of course is the ultimate goal.

REFERENCES

1. Knowler WC, Kinzelman CL. Population comparisons of the frequency of diabetic nephropathy. In: Mogenson EE, ed. The Kidney and Hypertension in Diabetes Mellitus. Boston:Martinus Nijhoff, 1988: 25-32.

2. Bellard DJ, Humphrey LL, Metton JJ, et al. Epidemiology of persistent proteinuria in type II diabetes mellitus. Diabetes 1988;37:405-12.

3. Parving HH, Hommel E. Prognosis in diabetic nephropathy. Br Med J 1989;299:230-3.

4. Krolewski AS, Warsham JH, Christlieb AR. The challenging natural history of nephropathy in type I diabetes. Am J Med 1985;78:785-94.

5. Brawnlee M, Gerami A, Vlassara H. Advanced glycosylation end products in tissue and the biochemical basis of diabetic complications. N Engl J Med 1988;318:1315-21.

6. Makita Z, Radoff S, Rayfield EJ, et al. Advanced glycosylation and products in patients with diabetic nephropathy. N Engl J Med 1991;325:318-26.

7. Dahl-Jorgensen D, Bjoro T, Kierulf P, et al. Long term glycemic control and kidney function in insulin dependent diabetes mellitus. Kidney Int 1992;41:920-3.

8. Borch-Johnsen K, Anderson PK, Deckert T. The effect of proteinuria on relative morbidity in Type 1 (insulin-dependent) diabetes mellitus. Diabetologia 1985;14:369-
79.

9. Kasiska BL, Kalil RSN, Ma JZ, et al. Diabetic nephropathy: hemodynamic basis and implications for isease management. Ann Intern Med 1993;118:129-38.

10. Borch-Johnsen K, Norgaard K, Hommel E, et al. Is diabetic nephropathy an inherited complication ? Kidney Int 1992;41:719-22.

11. Selby JV, Fitz Simmons SC, Newman JM, et al. The natural history and epidemiology of diabetic nephropathy: implications for prevention and control. JAMA 1990;263:1954-9.

12. Hawthorne VM. Preventing the kidney disease of diabetes mellitus: public health perspective. Ann J Kid Dis 1989;13:1-6.

13. Seaquist ER, Goetz FC, Rich S, et al. Familial clustering of diabetic kidney disease. N Engl J Med 1989;320:1161-5.

14. Mauer SM, Sutherland DER, Steffes MW. Relationship of systemic blood pressure to nephropathy in insulin dependent diabetes mellitus. Kidney Int 1992;41:736-40.

15. Taguma Y, Kitamoto Y, Futaki G, et al. Effect of captopril on heavy proteinuria in azotemic diabetics. N Engl J Med 1985;313:1617-20.

16. Fein FS. Heart disease in diabetes. Cardiovasc Rev Rep 1982;3:877-95.

17. Zatz R, Meyer TW, Remmke HG, et al. Predominance of haemodynamic rather than metabolic factors in the pathogenesis of diabetic lomerulonephropathy. Proc Natl Acad Sci USA 1985;82:5963-7.

18. Bosch JP, Lew S, Glabman S, et al. Renal hemodynamic changes in humans: response to protein loading in normal and diseased kidneys. Am J Med 1986;81:809-15.

19. Sawicki PT, Didjurgeit V, Mulhauser I, et al. Smoking is associated with progression of diabetic nephropathy. Diabetes Care 1994;17:126-31.

20. Viberti GC, Hill RD, Jarrett RJ, et al. Microalbuminuria as a predictor of clinical nephropathy in insulin dependent diabetes mellitus. Lancet 1982;1:1430-2.

21. Abbott KC, Sanders LR, Bakris GL. Microalbuminuria in non-insulin dependent diabetes mellitus. Implications for renal survival. Arch Int Med 1994;154:146-54.

22. Mogensen CE. Microalbuminuria predicts clinical proteinuria and early mortality in maturity-onset diabetes. N Engl J Med 1984;310:356-60.

23. Spooren PFMJ, Lekkerkerker JFF, Vermes L. Micral-Test9; a quantitative dipstick test for microalbuminuria. Diabetes Res Clin Pract 1992;18:83-7.

24. Holtmann N, Gider WG. New turbidimetric assay for microalbuminuria. J Clin Chem Clin Biochem 1989;27:589-93.

25. The Diabetes Control and Complications Trial Group. The effect of intensive insulin treatment on the development and progression of long-term complications in insulin dependent diabetes mellitus. N Engl J Med 1993;329:977-86.

26. Gebhart SSP, Wheaton RN, Mullens RE, et al. A comparison of home glucose monitoring with determinations of hemoglobin A1c, total glycated hemoglobin, fructosamine and random serum glucose in diabetic patients. Arch Int Med 1991;151:1133-7.

27. Nathan DM, McKitrick C, Larken M, et al. Glycemic control in diabetes mellitus: have changes in therapy made a difference ? Am J Med 1996;100:157-63.

28. Bjorck S, Mulec H, Johnsen SA, et al. Renal protective effect of enalapril in diabetic nephropathy. Br Med J 1992;304:339-43.

29. Lewis EJ, Hunsicker LG, Bain RP, et al. The effect of angiotensin-converting enzyme inhibitors on diabetic nephropathy. N Engl J Med 1993;329:1456-62.

30. Mathiesen ER, Hommel E, Giese J, et al. Efficacy of captopril postponing nephropathy in normotensive insulin dependent diabetic patients with microalbuminuria. Br Med J 1991;303:81-7.

31. Ravid M, Savin H, Jutrin I, et al. Long-term stabilizing effect of angiotensin-converting enzyme inhibition on plasma creatinine and on proteinuria in normotensive type I diabetic patients. Ann Int Med 1993;18:577-81.

32. Remuzzi G, Ruggenenti P. Slowing the progression of diabetic nephropathy. [editorial] N Engl J Med 1993;329:1496-7.

33. Bakris GL. Angiotensin-converting enzyme inhibitors and progression of diabetic nephropathy. [editorial] Ann Int Med 1993;18:643-4.

34. Ferguson RK, Nyomba BL. Crossover comparison of captopril and amlodipine in incipient diabetic nephropathy. Int J Diab 1995;3:128-32.

35. Ferguson RK. Insulin resistance and hypertension. In: Sharma AK, ed. Diabetes Mellitus and its complications. Delhi: Macmillan, 1993:92-100.

36. Ferguson RK. Diabetes in the 90's: prospects and challenges. Int J Diab 1993;1:5-6.