Review Article

Retarding the Progression of Diabetic Nephropathy in Type 2 Diabetes Mellitus: Focus on Hypertension and Proteinuria

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Abstract

Introduction: There is a worldwide pandemic of type 2 diabetes mellitus and approximately one-third of these individuals will develop diabetic nephropathy. Coupled with their increased risk for cardiovascular disease, these individuals pose an enormous economic and social burden to all countries. This review will discuss therapeutic strategies, aimed at control of blood pressure and proteinuria, to prevent or retard the development of diabetic nephropathy. Methods: Studies that involved patients with type 2 diabetes with albuminuria (microalbuminuria or proteinuria) and/or hypertension and/or renal impairment were included in this review. The PubMed Medline database was used as the source of data. Results: Blood pressure control is paramount in reducing cardiovascular risk and the development of diabetic nephropathy. The target blood pressure is <130/80 mm Hg in all patients with type 2 diabetes. Angiotensin receptor blockers (ARBs) are the preferred first-line agents while angiotensin-converting enzyme (ACE) inhibitors can be considered in those with microalbuminuria and normoalbuminuria. Reduction in proteinuria retards the progression of nephropathy and should be considered as a goal on its own. Dual therapy with an ACE inhibitor and ARB can be considered in patients with severe proteinuria or uncontrolled hypertension. Conclusion: Important strategies to prevent or retard the progression of diabetic nephropathy in type 2 diabetes include excellent blood pressure control with an aggressive approach to reduce microalbuminuria or proteinuria. The drugs of choice are the ARB and the ACE inhibitor.

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Key words: ACE inhibitors, Angiotensin receptor blockers, Microalbuminuria

Introduction

The prevalence of type 2 diabetes mellitus continues to climb at an alarming rate and the World Health Organisation predicts that the number of people affected with diabetes will more than double from the current 170 million to 370 million by the year 2030.[1] Approximately one-third of these individuals will develop diabetic nephropathy.[2] Coupled with their increased risk of cardiovascular disease, these individuals will pose a significant burden on the healthcare system of all countries. A similar situation is occurring in Singapore where the crude prevalence of diabetes is 9%[3] and is one of the highest in the Asia-Pacific region. Diabetic nephropathy accounted for 47.2% of all new patients starting on dialysis in the year 2000 in Singapore and was the highest in the Asia-Pacific region.[4]

Over the last few years, several large trials involving patients with type 2 diabetes in different stages of nephropathy have been conducted. Together with the recent release of updated guidelines for the treatment of hypertension from major authorities in the field, it appears appropriate to review the treatment strategies in type 2 diabetes with a focus on preventing diabetic nephropathy.

This paper will review the following strategies targeted at retarding the progression of renal disease in diabetic nephropathy: (1) control of blood pressure, (2) control of microalbuminuria/proteinuria and (3) combination therapy with angiotensin-converting enzyme inhibitors (ACE inhibitors) and angiotensin receptor blockers (ARBs). Other strategies that have been recommended, but not discussed in this paper, include dietary protein restriction and lipid-lowering therapies.[5]

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Clinical Features of Diabetic Nephropathy

The first sign of renal involvement is the presence of persistent microalbuminuria (24-hour urinary albumin excretion of 30 to 300 mg/day) and this stage is known as incipient nephropathy. This occurs in 20% to 40% of patients 10 to 15 years after the onset of diabetes. Unfortunately, the onset of disease in type 2 diabetes is often difficult to ascertain and it is not uncommon for patients with type 2 diabetes to already have persistent microalbuminuria when they present for the first time with diabetes. Progression to macroalbuminuria or proteinuria (urinary albumin excretion >300 mg/day; urine dipstick positive for protein) occurs in 20% to 40% of patients 15 to 20 years following the onset of diabetes and this stage is also known as overt nephropathy. Following this, the creatinine clearance deteriorates at an average rate of 10 to 12 mL/min/year in untreated patients and hypertension develops.[6] Once they develop end-stage renal disease (ESRD), the 5-year survival rate is dismal; e.g., this rate was reported as 6% in Germany and 27% in Australia.[7]

In type 2 diabetes, the microalbuminuria is seldom reversible, unlike type 1 diabetes, and is probably a sign of endothelial dysfunction that is not only confined to the kidney.[8] Forty per cent to 50% of type 2 diabetics with microalbuminuria die from cardiovascular disease, emphasising the notion that microalbuminuria is a harbinger of vascular disease and that apart from reno-protective strategies, reduction of all cardiovascular risk factors in this cohort of patients is practically mandatory.[9,10]

Proteinuria in diabetes may occur as a result of non-diabetic glomerular disease and this can occur in as many as 20% of patients.[11] Clinical clues that suggest non-diabetic renal disease include an acute presentation of renal disease and the presence of an active urinary sediment containing red blood cells and casts. Although the presence of retinopathy is strongly associated with the presence of nephropathy in type 1 diabetes, this association is less predictable in type 2 diabetes. One study found that only 56% of patients with nephropathy exhibited retinopathy.[12] Hence, while the presence of retinopathy supports the diagnosis of diabetic nephropathy in type 2 diabetes, the absence of retinopathy does not exclude diabetic nephropathy.

Control of Blood Pressure

Arterial hypertension is frequently present in patients with type 2 diabetes, even in the absence of proteinuria or renal disease, and probably constitutes the metabolic syndrome that is characterised by insulin resistance, obesity, dyslipidaemia and hypertension. A study employing ambulatory blood pressure monitoring found that 60% of patients newly diagnosed with type 2 diabetes were hypertensive.[13]

While hypertension may not be a definite sign of nephropathy in type 2 diabetes, it is a risk factor for the development of nephropathy and subsequent progression of the renal disease. Early treatment of hypertension is important in preventing cardiovascular disease and the progression of diabetic renal disease and retinopathy[14] and the benefit of tight blood pressure control may be as great or greater than strict glycaemic control.[15] Two recent excellent reviews by Snow et al[16] and Vijan et al[17] detail the effects of blood pressure control on cardiovascular and microvascular complications and the rationale for choosing the antihypertensive agents.

Target Blood Pressure

The target blood pressure in patients with diabetes with or without renal disease is lower than usual to allow maximal protection. In the Hypertension Optimal Treatment (HOT) Study,[18] patients were randomly assigned target diastolic blood pressures of 90, 85 and 80 mm Hg and the group assigned to a target of 80 mm Hg achieved a significantly lower relative risk for cardiovascular death and major cardiovascular events compared to the group assigned the target of 90 mm Hg. Recently, the major consensus groups[19-23] have published their recommendations on the guidelines for treatment of hypertension and have unanimously recommended a target blood pressure of <130/80 mm Hg for diabetic patients (Table 1).

Table 1. Recommended Target Blood Pressures and Initial Therapy in Diabetic Patients

Consensus Group	Target BP (mm Hg)	Initial therapy
Canadian Hypertension Society (2004)[19]	<130/80	ACE inhibitor/ARB/Thiazide (in those without albuminuria)
American Diabetes Association (2003)[20]	<130/80	ACE inhibitor/ARB
National Kidney Foundation – CKD (2004)[21]	<130/80	ACE inhibitor/ARB
World Health Organisation/ISH (2003)[22]	<130/80	ACE inhibitor/ARB
7th Report of the Joint National Committee (JNC 7) (2003)[23]	<130/80	ACE inhibitor/ARB

ACE inhibitor: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; CKD: chronic kidney disease; ISH: International Society of Hypertension

Pharmacological Therapy

In order to achieve the target blood pressure of <130/80 mm Hg, randomised studies have shown that an average of 3.2 antihypertensive medications is required.[24] Angiotensin II receptor blockers are the preferred first-line agent, as 2 recent major trials have demonstrated. In the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) study,[25] 1513 hypertensive diabetic patients with nephropathy and renal impairment were randomly assigned losartan or placebo. There were minimal blood pressure differences between the 2 groups and the losartan group had a 16% risk reduction of its composite primary end point (doubling of serum creatinine, end-stage renal disease, death). The Irbesartan Diabetic Nephropathy Trial (IDNT)[26] used 1715 patients with similar characteristics to those in the RENAAL trial and randomised them to treatment with irbesartan, amlodipine or placebo. Here again, the investigators were able to demonstrate a 20% risk reduction in the composite renal end point. In both trials, the higher doses (losartan 100 mg and irbesartan 300 mg) were more effective than the lower doses (losartan 50 mg and irbesartan 150 mg).

Apart from their antihypertensive properties, some of the ARBs appear to have other beneficial metabolic and anti-inflammatory effects. Losartan has the unique effect of being a uricosuric agent.[27] Losartan and irbesartan also demonstrate anti-platelet activity (losartan at therapeutic doses), as do valsartan and telmisartan at higher doses.[28,29] Both these effects are advantageous in patients with renal disease.

An area of recent concern with the use of ARBs is its possible potential to increase the risk of myocardial infarction. This was highlighted in a recent editorial in the *British Medical Journal*[30] where the results of the Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial[31] were reviewed and showed that the ARB, valsartan, produced a statistically significant 19% relative increase in a secondary end point of myocardial infarction (fatal and non-fatal) when compared to amlodipine. The editorial also commented that careful evaluation of the current evidence showed that the ARBs are either neutral or increase the rates of myocardial infarction despite their beneficial blood pressure-lowering effects. While the jury is still out on this new development, clinicians need to be alerted to follow the literature closely on this aspect, especially with the recent emphasis on the sharing of all potential side effects, no matter how trivial, with patients.[32]

The role of ACE inhibitors in type 2 hypertensive diabetic patients with nephropathy is less well established as studies have generally been small and of short duration. However, one large study was the MICRO-HOPE (Heart Outcomes Prevention Evaluation) Study[33] which evaluated a subgroup of 3577 type 2 diabetic patients who were enrolled in the HOPE study. These patients had no clinical proteinuria and were randomly assigned to ramipril 10 mg daily, placebo or vitamin E. The combined primary outcome was a reduction in myocardial infarction, stroke or cardiovascular disease and the group assigned to ramipril showed a 25% risk reduction compared to the placebo group. There was a 34% risk reduction of overt nephropathy (secondary end point). The drawback of this study is that it is a subgroup analysis.

To resolve the issue as to whether an ACE inhibitor or ARB is the preferred first-line agent in patients with type 2 diabetes and nephropathy, a recent trial evaluated a head-to-head comparison of an ARB, telmisartan (80 mg) and enalapril (20 mg) [Diabetics Exposed to Telmisartan and Enalapril Study (DETAIL)].[34] The study enrolled 250 diabetic patients with hypertension and increased urinary albumin excretion and the primary end point was a change in the glomerular filtration rate. After a follow-up of 5 years, telmisartan was found to be equivalent to enalapril in providing long-term reno-protection. Hence, it appears that in type 2 diabetic patients with incipient nephropathy, there is clinical equivalence between an ACE inhibitor and ARB.

Frequently, as earlier mentioned, additional anti-hypertensive agents are required to achieve the blood pressure goal and both low-dose thiazide diuretics (12.5 mg to 25 mg) and/or calcium channel blockers (CCBs) have useful additive effects with the renin-angiotensin system (RAS) blockers.[24] Apart from their blood pressure-lowering effects, the combination of a RAS blocker with a thiazide and CCB also abrogates the common side effects of hypokalaemia (from the thiazide) and oedema (from the CCB).

There has been concern about the use of dihydropyridine CCBs in patients with diabetes as 2 relatively small trials, the FACET (Fosinopril versus Amlodipine Cardiovascular Events Trial)[35] and ABCD (Appropriate Blood Pressure Control in Diabetes)[36] trials using amlodipine and nisoldipine, respectively, suggested increased cardio-vascular complications when compared with an ACE inhibitor. It was presumed that the difference represented a benefit from the ACE inhibitor rather than an increased risk with the dihydropyridine CCB. Moreover, major hypertension trials, such as the HOT trial,[18] found no evidence of increased cardiovascular events with the use of a long-acting dihydropyridine CCB in diabetic patients and similar safety results were also reported in a recent meta-analysis evaluating 14 studies using CCBs in hypertensive diabetic patients.[37] Despite the initial concern about the CCBs, they are powerful antihypertensive agents and remain an important component in the antihypertensive regimen of the diabetic patient.

Beta-blockers can also be considered additive antihypertensive agents despite concerns about the masking of hypoglycaemia and exacerbation of peripheral vascular disease. They have the ability to reduce cardiovascular events and mortality and have additive blood pressure-lowering effects with most agents when the patient has a baseline pulse of more than 80 beats per minute.[38] In the UK Prospective Diabetes Study (UKPDS) of patients with type 2 diabetes, atenolol was found to be as effective as captopril in blood pressure lowering and protection against microvascular disease.[15] Carvedilol, a combined non-selective beta- and alpha-1 adrenergic antagonist, may be superior to other beta-blockers as it has been shown to be metabolically neutral.[39]

In summary, the first-line antihypertensive agent in patients with type 2 diabetes and hypertension (with or without nephropathy) is an angiotensin II receptor blocker. ACE inhibitors may be considered as an alternative for patients with hypertension and incipient nephropathy (increased albumin excretion). Additional antihypertensive agents are frequently required to bring the blood pressure down to the target of <130/80 mm Hg and would include low-dose thiazide diuretics and/or CCBs.

Control of Microalbuminuria and Proteinuria

Microalbuminuria is associated with an increased risk of diabetic nephropathy and the progression of renal disease in type 2 diabetes and it is also an independent predictive risk factor for cardiovascular disease.[40] It is recommended that the urine be screened for microalbuminuria/proteinuria on an annual basis in all patients with type 2 diabetes.[40] This allows early identification of the patients at risk so that early intervention can be instituted.

Although the presence of proteinuria has traditionally been viewed as a marker of renal injury, recent data suggest that proteinuria may actually be an independent modifiable risk factor for the progression of renal disease in both diabetic and non-diabetic renal disease. There is evidence that suggests that the proteins filtered by the glomerulus cause injury to the tubulointerstitium, leading to tubulointerstitial fibrosis and renal impairment.[41] Therefore, therapeutic measures that reduce proteinuria should retard the progression of renal disease and this has been shown in a number of trials in patients with type 2 diabetes with overt nephropathy, where a reduction of proteinuria >30% below baseline was associated with better preservation of renal function.[42-45] In a recent large trial [Irbesartan in Patients with Type 2 Diabetes and Microalbuminuria (IRMA II)],[46] 590 patients were randomised to receive either placebo or the ARB, irbesartan, at 150 or 300 mg daily. There were no significant differences in the blood pressure between the various study groups. At the end of 2 years, overt nephropathy developed in 15% of patients on placebo, 10% of those on 150 mg of irbesartan and 5% of those on 300 mg of irbesartan. Urinary albumin excretion increased in the placebo group but dropped by 6% in the irbesartan 150 mg group and fell by 46% in the irbesartan 300 mg group. Similarly, restoration to normoalbuminuria occurred in 20% of patients on placebo, 24% of the irbesartan 150 mg group and 34% of the irbesartan 300 mg group. ACE inhibitors and ARBs have most often been used in these trials and have been shown to be effective in reducing albuminuria. However, non-dihydropyridine CCBs have also been shown to be effective in reducing albuminuria.[43]

While most trials have enrolled hypertensive patients with microalbuminuria, there have been a number of trials where normotensive patients with type 2 diabetes and microalbuminuria have been evaluated. Ravid et al[47] randomised 94 normotensive patients with type 2 diabetes and microalbuminuria to receive either enalapril or placebo. The trial was double-blinded for the first 5 years and open for the last 2 years. At the end of the 7-year follow-up, there was an absolute risk reduction of 42% for nephropathy in the enalapril group. In another larger study [Appropriate Blood Pressure Control in Diabetes (ABCD)],[48] 480 normotensive patients with microalbuminuria were randomised to receive either the CCB, nisoldipine or enalapril and also were randomised to receive moderate versus intensive blood pressure control. Over the 5-year follow-up period, intensive therapy resulted in slowing of the progression from incipient to overt nephropathy, decreased the progression of diabetic retinopathy and also the risk of stroke when compared with the group with moderately controlled blood pressure. There was no difference between the two drugs. These trials showing benefit in even normotensive diabetic patients supports the notion that the blood pressure target should probably be lower than usual in diabetic patients. It also supports the practice of early detection and treatment of patients at risk for developing progressive diabetic nephropathy.

From a slightly different angle, the BENEDICT (Bergamo Nephrologic Diabetes Complications Trial) trial[49] studied the effect of the ACE inhibitor, trandolapril versus verapamil, used either singly or in combination, versus a placebo, on preventing microalbuminuria in type 2 diabetics who were hypertensive but had normal urinary albumin excretions. There were 1204 patients who were followed up for a median of 3.6 years and the ACE inhibitor, trandolapril, used either singly or in combination with verapamil, prevented the onset of microalbuminuria when compared with placebo. The effect of verapamil alone was similar to placebo.

Therefore, although blood pressure control remains the cornerstone of treatment in the management of diabetic

nephropathy, more emphasis should now be placed on the early detection and treatment of microalbuminuria as recent trials have shown that the onset of overt nephropathy can be averted or delayed. The drug of choice is an ARB or ACE inhibitor. The ACE inhibitor is also the drug of choice in hypertensive patients with type 2 diabetes and normoalbuminuria as it can prevent the development of microalbuminuria. In patients with overt nephropathy (with proteinuria), more attention should be focused on the degree of proteinuria and drug therapy should be maximised to reduce the proteinuria to a target of at least 30% below baseline in order to retard the progression of renal disease. Here again, the ARB is the drug of choice. An important point to remember when using either an ACE inhibitor or ARB is that the effects are dose-related and therefore the maximum recommended dose should be administered whenever possible.

Dual Therapy – ACE Inhibitor and Angiotensin Receptor Blocker

The ACE inhibitor prevents production of angiotensin II by blocking the enzyme responsible for converting angiotensin I to angiotensin II. However, there are alternative metabolic pathways for the production of angiotensin II and these include chymase, glucose and a high-salt diet. Hence, angiotensin II levels are not completely suppressed with ACE inhibitors. The other beneficial effect of an ACE inhibitor is the prevention of breakdown of the vasodilator bradykinin (bradykinin is responsible for the development of cough in susceptible individuals). The ARB on the other hand, blocks the deleterious effects of angiotensin II by blocking its access to the angiotensin II-type 1 receptor. It has no effects on the bradykinin pathway. It is postulated that combination therapy with an ACE inhibitor and ARB is beneficial and the effect additive in that it allows:

1. complete blockade of the renin-angiotensin system and
2. an increase in vasodilatation through an increase in bradykinin.

There have been a number of studies evaluating the effect of dual therapy on reduction of proteinuria in both diabetic (type 1 and 2) and non-diabetic renal disease. Two studies enrolled patients with type 2 diabetes. The Candesartan and Lisinopril Microalbuminuria (CALM) study[50] randomised 199 patients with type 2 diabetes, microalbuminuria and hypertension to receive 12 weeks of monotherapy with either candesartan (16 mg daily) or lisinopril (20 mg daily), followed by another 12 weeks of monotherapy or combined therapy. Both the blood pressure and also urinary albumin excretion were significantly reduced in patients on the combination therapy compared to monotherapy with either drug. In a smaller study of 18 patients with type 2 diabetes, hypertension and overt nephropathy (proteinuria >1 g/day), Rossing et al[51] studied the effect of adding candesartan (8 mg daily) to existing drug regimens that included optimal doses of ACE inhibitors on blood pressure and proteinuria. After the 8-week cross-over study period, the dual therapy was found to significantly reduce blood pressure and proteinuria. Although the current studies are limited by short observation periods and the use of the surrogate end point of proteinuria, there is accumulating evidence, from both diabetic and non-diabetic trials, that combination therapy is useful in patients with severe proteinuria and/or uncontrolled hypertension.[52] Small increases in potassium, and a consistent decrease in haemoglobin in patients on dual therapy, have been observed. Hence, patients on dual therapy require close monitoring of the serum creatinine, potassium and haemoglobin.

Recommendations for the Prevention of Diabetic Nephropathy in Type 2 Diabetes

1. *Blood pressure control*: Excellent blood pressure control is a priority in reducing cardiovascular risk and progression of renal disease. The target blood pressure for hypertensive diabetic patients with or without nephropathy is <130/80 mm Hg. An average of 3.2 antihypertensive medications is required to achieve the target blood pressure in most patients.
2. *Antihypertensive agents*: An ARB is the first-line agent for treatment of hypertension in patients with incipient nephropathy (microalbuminuria) or overt nephropathy (clinical proteinuria) with/without renal impairment. An ACE inhibitor may be considered as first-line in hypertensive patients with incipient nephropathy and also in those with normoalbuminuria. The maximum dose of the drug should be prescribed where tolerable to achieve the optimal effect. A low-dose thiazide (12.5 to 25 mg daily) and/or a CCB are recommended as second-line therapy because of their synergistic effects with the ACE inhibitor or ARB.
3. *Microalbuminuria*: Microalbuminuria is a risk factor for progressive renal disease and cardiovascular disease. An annual screen for microalbuminuria is recommended in all patients with type 2 diabetes. Treatment of microalbuminuria can prevent the onset of overt nephropathy. Either an ACE inhibitor or ARB can be used in patients with microalbuminuria with or without hypertension.
4. *Proteinuria*: Proteinuria is also an independent risk factor for progressive renal disease and treatment should be aimed at reducing the proteinuria by at least 30% of the baseline. The ARB is the drug of choice.
5. *Dual therapy*: Dual therapy with an ACE inhibitor and ARB should be considered in patients with severe proteinuria and/or uncontrolled hypertension.

6. *Practical point*: Hyperkalaemia and/or acute renal failure can occur with the use of ACE inhibitors or ARBs in patients with renal impairment. The serum creatinine and potassium should be monitored closely in these patients, especially those on dual therapy. After initiation of therapy, an increase in the serum creatinine of up to 30% from the baseline is acceptable.[53]

At this point in time, we probably have more than sufficient evidence-based guidelines and recommendations. What is currently lacking is the ability to translate these recommendations into actual clinical practice and more efforts should be directed towards this area in order for us to reap the benefits.

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