

PREVENTING PROGRESSION

Evidence-Based Treatment of Diabetic Nephropathy

All patients with diabetic nephropathy and one-third of patients with Type 2 diabetes will have hypertension. This article will discuss the factors leading to this condition and multi-factoral treatment considerations.



By Ellen D. Burgess, MD, FACP, FRCPC

Twenty years ago, doctors were taught that patients with Type 2 diabetes would develop large vessel disease, but they would not develop small vessel disease or those types of complications seen commonly in Type 1 diabetic patients, such as nephropathy and retinopathy. However, diabetes is now the leading cause of kidney disease and of end-stage renal disease (ESRD) requiring renal replacement treatments, such as dialysis. In Canada, 30% of new dialysis patients have diabetes; in the U.S., 40% of new renal patients have dia-

betes. The vast majority of these diabetic patients have Type 2 diabetes.¹

Factors Increasing the Risk of ESRD

It is currently unclear whether the process of kidney damage is identical for patients with Type 1 and Type 2 diabetes. Most of the clinical research in the past was done with patients who have Type 1 diabetes, although most of the current research looks into Type 2 diabetes. It is believed that genetics is an important factor in predicting which patients will develop diabetic renal disease.² However, the control of blood sugar levels has been considered the most important modifiable risk factor for the prevention of initial renal damage and an important modifiable risk factor in the progression of diabetic renal disease to ESRD (Table 1). Control

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of high blood pressure (BP) is likely the most important modifiable risk factor which can slow the progression of diabetic renal disease to ESRD.

Other risk factors include:

- the presence of albumin or protein in the urine;
- smoking;
- male sex;
- First Nations people or people of African origin;
- high dietary intake of protein; and
- high blood lipid levels.

Functional Changes in Diabetic Nephropathy

The changes that occur in the diabetic kidney can be categorized as metabolic related, hemodynamic effects, and growth factor effects. These categories will be briefly reviewed.

a) Metabolic related: Uncontrolled or poorly controlled hyperglycemia may cause the glycosylation of proteins and other large molecules as well as stimulation of transforming growth factor-beta (TGF- β).

The glycosylation of proteins and other molecules leads to the formation of advanced glycosylation endproducts (AGEs). A close correlation exists between the formation of AGEs and the changes taking place in connective tissue, including increased tissue rigidity. The AGEs formed in the vascular matrix are thought to interfere with the action of nitric oxide (NO), an important vasorelaxant. This implicates AGEs with the elevated BPs often seen in diabetic patients. AGE-modified matrix proteins may also block the anti-proliferative effect of NO on vascular smooth muscle cells and renal mesangial cells. AGE-formation may also be a primary

Table 1

Factors Increasing the Risk of ESRD for Type 2 Diabetics

Proven Factors

Poorly controlled blood sugar levels
Elevated BP
Albumin or protein in the urine
Smoking
Male sex
First Nations people or people of African origin

Possible Factors

High dietary intake of protein
High blood lipid levels

BP = Blood pressure

ESRD = End-stage renal disease

mechanism responsible for the pathogenetic modification of low density lipoprotein (LDL) particles, which are felt to be so important in the development of atherosclerosis.

Specific AGE receptors have been shown to be present on a variety of cells in human and animal models, including endothelial, mesangial and neural cells, as well as macrophages, T-lymphocytes and fibroblasts. The function of these cells, in response to stimulation of the receptors, is varied, but includes up-regulation of growth factors including TGF- β , stimulation of cytokine production and increased proliferation.

Increases in blood glucose levels are also known to stimulate the formation of TGF- β directly. TGF- β is now known to play a significant role in renal fibrogenesis, both within the glomerulus and the interstitium. It is also associated with increased matrix accumulation and glomerulosclerosis in diabetic and non-diabetic renal disease.

♥ Practical Point

Definition of Microalbuminuria

- ♥ 30-300 mg per 24 hour urine collection
- ♥ 20-200 mcg per milliliter of urine
- ♥ 20-200 mcg per minute

Test results cannot be interpreted correctly in the presence of a fever, urinary tract infection, uncontrolled high blood sugar or blood pressure levels, or congestive heart failure.

b) Hemodynamic effects: The filtration of fluid across the glomerular basement membrane (GBM) is dependent upon the hydrostatic pressure within the glomerular capillary. The glomerulus is normally protected from systemic BP by the afferent arteriolar resistance (AAR). In diabetic patients and in patients who have lost some renal function, either acutely or chronically, the AAR decreases. This results in an increase in pressure and flow to the glomerulus (Figure 1). In addition, in patients with reduced renal function, the efferent arteriolar resistance (EAR) will rise in an attempt to increase the glomerular filtration rate (GFR) from each individual glomerulus and return total GFR to normal. This increase in pressure within the glomerulus is damaging in the long term and will result in glomerulosclerosis. Since the increase in EAR is secondary to angiotensin II, the use of angiotensin converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) has been shown to reduce the intraglomerular pressure, GFR and proteinuria (Figure 1).

c) Growth factor effects: As mentioned above, TGF- β is stimulated by hyperglycemia. It has also been shown to be stimulated by angiotensin II. The TGF- β family of mediators is unique and not related to other fibrosis-

related mediators, such as basic fibroblast growth factor (bFGF). It is signaled through the Smad family of proteins, not the tyrosine kinase signal pathway that many other growth factors use. At this time, there is no specific blocker for TGF- β , but evidence indicates enalapril or losartan, with or without a low-protein diet, can block 40% to 65% of the action of TGF- β .

Microalbuminuria

The first evidence of diabetic renal damage is the presence of very small amounts of albumin in the urine.¹ In the past few years, the definition of the normal amount of albumin or protein in the urine has changed. This is the result of better technology for the measurement of albumin or protein in the urine. Therefore, having a negative result on a “dipstick” urinalysis does not mean there is only a normal amount of albumin or protein in the urine. There may be a small, but abnormal amount of albumin in the urine (microalbuminuria).

The proper screening test for assessment of early damage to the kidney from diabetes is to look for microalbuminuria-urine specific testing. In the original research into microalbuminuria, patients were asked to collect urine either for 24 hours or for the hours that they were recumbent or sleeping in bed. However, this type of testing was not always possible, and now spot urine testing is done on urine samples that are not timed. Therefore, the results of these “un-timed” urine tests needed to be standardized. That is why the results for urine protein tests (either micro- or macroalbuminuria) are sometimes expressed as “mg of albumin per mmol of creatinine in the urine” (see Practical Point, p. 32).

All patients with Type 2 diabetes should be

screened for microalbuminuria on a yearly basis. Patients who are being treated for microalbuminuria should undergo urine testing every three months while drug therapy is being titrated and once a year while on stable therapy.³ Before patients are labeled as having microalbuminuria, it is important to obtain consistent results from two or three consecutive tests. Test results cannot be interpreted correctly if the patient has a fever, urinary tract infection, a recent viral infection, uncontrolled high blood sugar or blood pressure levels, or congestive heart failure.¹

The presence of microalbuminuria is a very good predictor of the development of non-reversible diabetic nephropathy and ESRD. However, microalbuminuria can be lowered, and possibly reversed, by intensive treatment of the blood sugar levels or treatment with either an ACEI or an ARB. In the Irbesartan Microalbuminuria (IRMA-2) study, the higher dose of irbesartan (300 mg) was shown to reduce microalbuminuria better than placebo and to normalize the microalbuminuria in 10% of patients.⁴ (The lower dose of 150 mg of irbesartan was shown to be no different than placebo in effect.) A different study showed that losartan could reduce microalbuminuria as well as an ACEI, previously considered the best treatment of microalbuminuria in patients with either Type 1 or Type 2 diabetes with microalbuminuria, regardless of whether they had normal or high BP.^{5,6,7}

Harmful Effect of Proteinuria

With recent research showing that proteinuria is harmful to the kidney, and not just a consequence of glomerular damage, medications and diets are being used specifically to reduce urinary protein excretion. The general recommendation is to reduce proteinuria to below

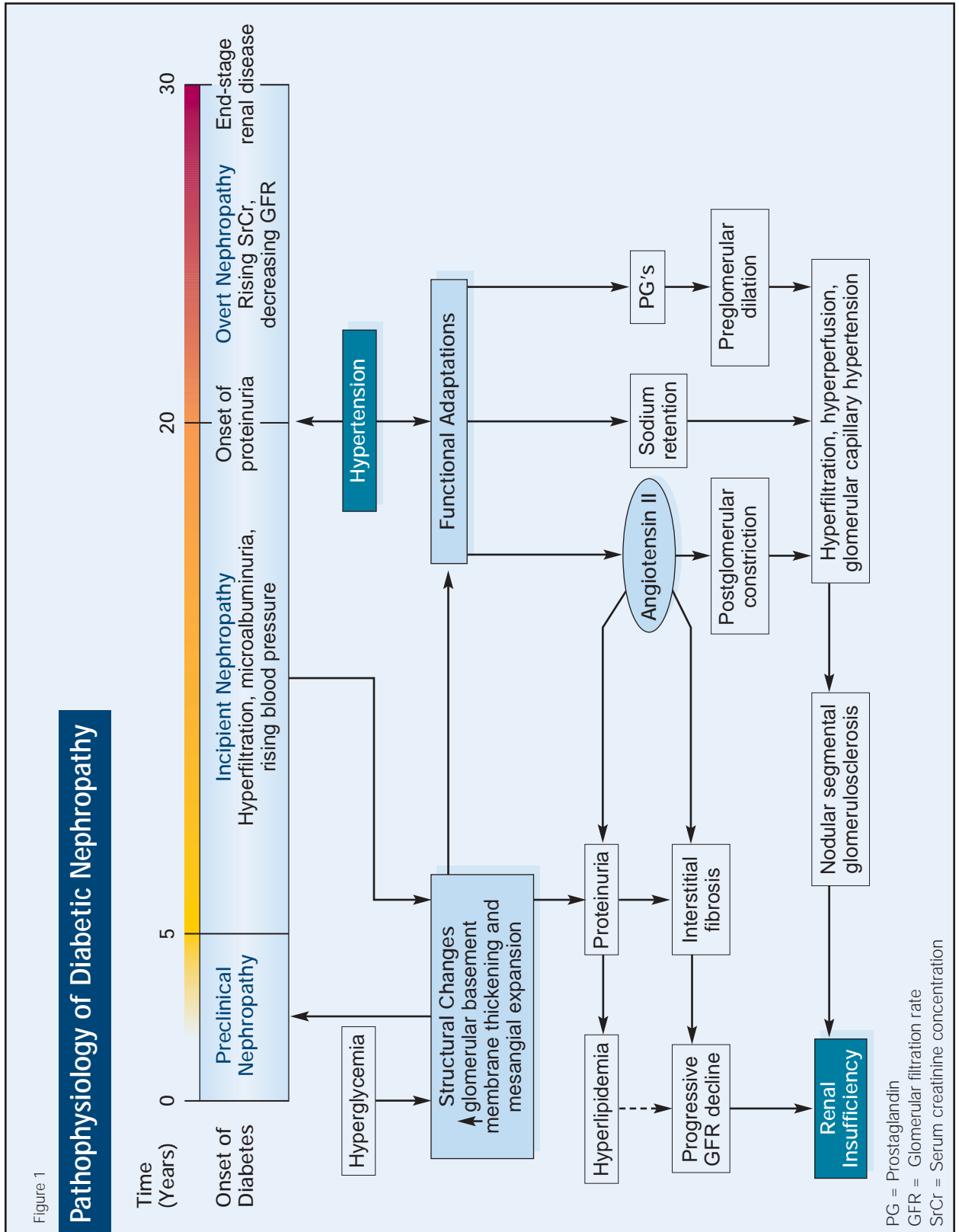
1 g per day,¹ although many physicians will titrate medications to reduce proteinuria even more. Studies with patients having non-diabetic kidney disease have shown that, if patients have at least a 50% reduction in proteinuria, their long-term prognosis is very good.¹

Lowering BP will usually allow for a reduction in proteinuria. However, the use of ACEIs or ARBs results in a greater reduction in proteinuria, despite similar BP reductions. This lowering of proteinuria can be augmented by a low-salt diet or the use of diuretics. The use of dihydropyridine calcium channel blockers (CCBs) may have the opposite effect, *i.e.*, increasing proteinuria, whereas the other CCBs may have a neutral effect.

Current research is looking into the use of higher-than-recommended doses of ACEIs or ARBs, or combinations of recommended doses of ACEIs and ARBs as ways to reduce proteinuria and protect the kidney better, even though there may be no further BP reduction.

Preventing Progression from Microalbuminuria to Macroalbuminuria to ESRD

The research on the progression of diabetic renal disease in patients with Type 1 diabetes described a three- to five-year time frame for the progression from microalbuminuria to macroproteinuria, or “gross proteinuria,” and then a three- to five-year progression from the development of nephrotic syndrome to ESRD. The time frame for this progression is not as clear for older patients with Type 2 diabetes. Although some researchers have suggested that the progression is slower, others have suggested it may be faster because the patients and their kidneys are older, with less active function, less reserve function and more age-related damage.



♥ Practical Point

Diabetic Nephropathy: Ways to Prevent Progression

- ♥ **Good blood sugar control**
- ♥ **Maintain blood pressure < 130/80 mmHg**
- ♥ **Reduce dietary protein intake to < 0.8 g/kg body weight**
- ♥ **Stop smoking**
- ♥ **Reduce urinary protein levels to < 1 g/day**

To slow the progression of renal damage, optimal control of the blood sugar and BP should be attempted (see Practical Point at right). This may require the use of two or three drugs for the control of each condition. Optimal BP for diabetic patients is believed to be less than 130/80 mmHg.⁸ Although the diastolic BP may be easily reached, the systolic target BP is more difficult to attain.^{9,10}

The recently published Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) study demonstrated that losartan, when compared to standard therapy including CCBs (but not including ACEIs), was able to lengthen the time it took for the serum creatinine level to double (an indication that the patient has lost half of their remaining kidney function) and lengthened the time it took the kidneys to fail (gave the patient more time living with their own kidneys).⁹ The Irbesartan Diabetic Nephropathy Trial (IDNT) demonstrated that irbesartan could lengthen the time to doubling of the serum creatinine level, but that amlodipine was no different from placebo (all groups received conventional anti-hypertensive treatment).¹⁰ Therefore, amlodipine, and probably all dihydropyridine CCBs, should not be used in patients with diabetic kidney disease unless they are also receiving losartan (or possibly irbesartan). No large studies have been done using ACEIs for patients with diabetic kidney disease.

Patients should stop smoking since tobacco use has recently been linked to the development of kidney disease and a faster deteriora-

tion in renal function, leading to dialysis. Limiting dietary protein intake to approximately 0.8 g of protein per kilogram of body weight should be attainable. Lowering it further is not possible without having to increase fat intake to maintain caloric intake. High-protein diets or supplements should be avoided by all diabetic patients.¹



Treatment of Hypertension in Diabetics

About one-third of patients recently diagnosed with Type 2 diabetes will have hypertension. Virtually all patients with diabetic nephropathy will have hypertension. The BP level at which treatment should be instituted is debatable, but it is suggested that if the target BP is less than 130/80 mmHg, then a patient with a BP higher than that level should be treated. If the patient does not yet have renal disease, then a low-salt diet with,

Table 2

Anti-hypertensive Therapy in Diabetic Nephropathy

Therapy 1

Low-salt diet

Therapy 2

ARB

Losartan has been shown to reduce the risk of developing end-stage renal disease, requiring dialysis or death; losartan and irbesartan have been shown to slow the rate of deterioration of diabetic renal disease.

Therapy 3

Diuretic appropriate to patient's level of renal function

Therapy 4

Other agents, such as CCBs or central alpha-adrenergic agonist

Since reducing urinary protein excretion is associated with a better long-term outcome, it may be preferable to use a non-dihydropyridine CCB, but this remains to be proven.

ARB = Angiotensin receptor blocker

CCB = Calcium channel blocker

or without, weight loss and exercise would be a reasonable beginning (Table 2).

The new guidelines from the American Diabetes Association suggest that patients with renal disease should be on losartan 100 mg or irbesartan 300 mg daily.³ It is not clear if the renoprotective effects of the different ARBs are similar and they should be considered a "class effect."

Class effect would be judged to be present if:

- a) drugs of similar pharmacologic mechanism of action generate relative risk reductions (RRRs) that are similar in direction and magnitude; or if
- b) head-to-head trials with drugs of the same class show similar clinical effects on important outcomes. This

would not include surrogate outcomes like proteinuria.

There are risks of assuming class effect. These include:

- a) a drug within a class may not share the same benefit on important clinical outcomes (*i.e.*, sotalol is a beta-blocker not lowering mortality risk post-myocardial infarction); or
- b) a drug having significantly greater toxicity than other drugs within the class, which may result in its withdrawal from the market.

As well, a drug within a class may have an effect that other members in the class do not share (*i.e.*, the uricosuric effect of losartan or the ability of captopril to cross-link cystine in the urine).¹¹

Due to the risk of hyperkalemia in diabetic patients receiving ACEIs or ARBs, patients should have serum potassium levels checked before these drugs are started and again within a week of starting them. If the baseline serum potassium level is

greater than the upper limit of normal, then it may be prudent to use an ARB and titrate the dose to maximum with frequent testing of the serum potassium level. A study of the excretion of potassium demonstrated that patients with reduced renal function were able to excrete potassium better when taking ARBs, as compared to an ACEI.

If the BP is greater than 130/80 mmHg, then addition of a diuretic is advisable (hydrochlorothiazide 12.5 to 25 mg daily, or furosemide 40 mg twice daily depending upon renal function). All these patients should have counseling about low-sodium diets (100 mmol/day), with frequent reinforcement, and periodic assessment of compliance with a 24-hour urine collection for sodium content. The “best” third-line drug is debatable and the subject of research, but usually a CCB is recommended.

The Heart Outcomes Prevention Evaluation (HOPE) study results were embraced since a very significant reduction in mortality was shown for diabetic patients treated with ramipril.¹² The Losartan Intervention For Endpoint reduction in hypertension (LIFE) study has shown similarly significant reductions in mortality for patients with diabetes and left ventricular hypertrophy.¹³ Therefore, there are data to support the use of either ACEIs or ARBs for cardiovascular benefits in these patients, although the data only support the use of ARBs for renoprotection.

Table 3

Common Problems in Patients with Diabetic Nephropathy

Macrovascular Complications

- Coronary artery disease
- Cerebrovascular disease
- Arterio-occlusive disease
- Ischemic nephropathy

Microvascular Complications

- Retinopathy
- Neuropathies
- Foot problems
- Impotence
- Autonomic neuropathy (with problems like gastroparesis and hypotension)

Resistant Hypertension

The most common causes of “resistant” hypertension include non-compliance with the medication or non-compliance with lifestyle modifications, such as low-sodium diets or alcohol restriction.

Patients who are not responding to ACEI or ARB therapy may require further counseling on a low-salt diet from a dietitian, and/or the addition of a diuretic.

Some patients with resistant hypertension may have renal artery stenosis. If the stenosis is hemodynamically significant, then the patient will have a significant increase (30%) in serum creatinine concentration within one to two weeks of starting an ACEI or ARB. Assessment of increases in serum creatinine levels that were found months or years after these drugs were started is more difficult. If there is a significant renal artery stenosis, however, then withdrawal of these anti-hypertensive agents should result in a significant reduction in the serum creatinine level (20% to 30%).

Patients with atherosclerotic renal artery stenosis are likely to have other evidence of atherosclerotic disease, such as a history of coronary artery disease with angina or infarction, peripheral arterial disease with claudication, bruits, or poorly palpable pulses.

♥ Practical Point

Common Causes of a Poor Response to an ACEI or ARB


- ♥ High salt intake (ideal intake < 110 mmol/day)
- ♥ Too low a dose of diuretic
- ♥ Giving short-acting loop diuretics only once daily

Developing Acute or Chronic Renal Failure

Diabetic patients have unusual risks for developing acute reductions in renal function. Due to the other diabetic complications that they often have (Table 3), these patients may need to undergo angiography. The contrast media injected intravascularly for angiography can be harmful to the kidneys as it flows through the tubules for excretion. Patients with proteinuria are at higher risk for acute renal failure particularly if they are volume depleted or if blood flow is reduced (Heart failure, recent MI, arrhythmia). These patients should be kept well-hydrated and not receive vasoconstrictive agents which may decrease renal blood flow further.

Angiotensin II is an important hormone that helps to maintain renal function during episodes of volume depletion or dehydration. Patients often continue their medications even when they are too ill to eat or drink, are febrile or have diarrhea, *etc.* ACEIs and ARBs will interfere with the normal response to keep the kidneys working and patients may develop acute renal failure, particularly if the volume depletion is significant. Patients should be counseled to stop taking their medication if they are unable to drink fluids.

The use of non-steroidal anti-inflammatory drugs (NSAIDs) or selective COX-2 inhibitors interfere with the production of

prostaglandins that maintain renal function during periods of reduced renal blood flow. These medications, used with ACEIs or ARBs, can cause renal failure. At any given time, approximately one-third of the elderly are taking these medications. Patients with renal disease should be cautioned against the use of these drugs without specific physician guidance. 

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