EARLY DETECTION OF DIABETIC MICROVASCULAR COMPLICATIONS: THE KEY TO IMPROVING OUTCOMES*

Andreas F. H. Pfeiffer, MD†

ABSTRACT

Perhaps the strongest argument for early detection of diabetic microvascular complications is the finding that 50% of all patients with type 2 diabetes mellitus already have signs of at least 1 diabetic microvascular or macrovascular complication at the time of diagnosis.

Prevention of diabetic nephropathy hinges on monitoring: screening for hypertension, poor glucose control, and microalbuminuria (3 treatable risk factors); and instituting or modifying therapy as necessary. Because patients with diabetic nephropathy are at an increased risk for cardiovascular disease, cardiovascular risk factors such as hyperlipidemia should also be monitored and controlled when nephropathy is identified.

The importance of glucose control can best be emphasized by findings that a 1% reduction in glycosylated hemoglobin can result in a 21% to 57% reduction in diabetic microvascular complications.

The role of the renin-angiotensin system in hypertension and diabetic nephropathy should also be acknowledged, particularly because agents that effectively block this system (the angiotensin-converting enzyme inhibitors and the angiotensin II receptor blockers) are available.

Every 10-mm Hg decrement in mean systolic blood pressure reduces the risk for all microvascular endpoints by 13%.

Several other pathways have been implicated in the pathogenesis of diabetic microvascular complications, raising the possibility that newer therapies directed at these pathways may improve outcome. Inhibition of the protein kinase C (PKC) pathway appears to be most promising; ruboxistaurin, an orally active PKC-β inhibitor, is currently being evaluated in clinical trials involving patients with diabetic nephropathy, diabetic peripheral neuropathy, diabetic retinopathy, and diabetic macular edema. Results from earlier animal studies and clinical studies with this agent have been encouraging, and results of the current trials are eagerly awaited.


*Based on a presentation given by Dr Pfeiffer at a symposium held on the occasion of the 40th Annual Meeting of the European Association for the Study of Diabetes.
†Professor of Internal Medicine and Chairman, Department of Endocrinology, Diabetes and Nutrition, Campus Benjamin Franklin-Charité University Medicine, Berlin, Germany; Director, Department of Clinical Nutrition, German Institute of Human Nutrition Potsdam, Nuthetal, Germany.

Address correspondence to: Andreas F. H. Pfeiffer, MD, Director, Department of Clinical Nutrition, German Institute of Human Nutrition Potsdam, Arthur-Scheunert Allee 114-116, D14558 Nuthetal, Germany. E-mail: afhp@mail.dife.de.

Study results have shown that 50% of all patients with type 2 diabetes mellitus have signs of a serious microvascular or macrovascular complication of diabetes at diagnosis. These results prove that earlier intervention is necessary and that early detection of these complications is the key to improving outcomes.

According to a report from the United Kingdom Prospective Diabetes Study (UKPDS), 21% of patients with type 2 diabetes mellitus have signs of retinopathy at diagnosis, 18% have abnormal electrocardiographic readings, 14% have 2 or more absent foot pulses and/or ischemic feet, 7% have impaired reflexes and/or decreased vibration sense, approxi-
approximately 2% to 3% have had a myocardial infarction or have angina and/or claudication, and approximately 1% have had a stroke or transient ischemic attack. Some patients have more than one of these complications at diagnosis.

Another report underscores the increasing prevalence of dialysis in industrialized countries over the past 2 decades. Most of the increase in renal insufficiency is a result of diabetes, plus more patients with diabetes and nephropathy are living long enough to progress to terminal renal insufficiency.

Ironically, the increase in longevity is attributed to better treatment of diabetes, which suggests that newer therapies are needed, in addition to early detection of diabetic microvascular complications, to prevent these complications from developing and progressing.

**EARLY DETECTION OF DIABETIC NEPHROPATHY**

Diabetic nephropathy develops in 35% to 45% of patients with type 1 diabetes mellitus and in 20% to 30% of patients with type 2 of the disease. However, some patients with diabetes never develop diabetic nephropathy. Although genetic factors may be involved, there is no evidence to support this hypothesis. Nevertheless, in the United States and in Europe, diabetic nephropathy is the single most common cause of end-stage renal disease (ESRD) requiring dialysis.

**RISK FACTORS**

There are several predictors of diabetic nephropathy, including advancing age, duration of diabetes, body weight, smoking, diabetic ketoacidosis, mild to moderate nonproliferative diabetic retinopathy, proliferative diabetic retinopathy (the most prevalent predictor), and proteinuria. There is some debate about disease management programs in Germany as to whether screening for proteinuria should be limited to patients with diabetic retinopathy because of the strong link between retinopathy and the risk of nephropathy. However, I think that early screening for nephropathy is important because it also helps focus management on the greatly increased cardiovascular risk conferred by the diagnosis of nephropathy.

There are other markers of increased risk for nephropathy that should not be overlooked. Ethnicity and family history affect the risk of diabetic nephropathy. Several studies have shown that diabetes and subsequent nephropathy are highly prevalent in Pima Indians in the American Southwest. Studies of white and Polynesian families with a history of diabetic nephropathy have shown that the risk of nephropathy runs in families with type 2 diabetes mellitus, independent of poor glycemic control, but may not be familial in type 1 diabetes. Apparently, there is some genetic protection against nephropathy that is not yet fully understood.

In sum, the predictors of diabetic nephropathy are microalbuminuria, hypertension, poor glucose control, duration of diabetes (particularly type 2 diabetes mellitus), and familial disposition.

**NATURAL HISTORY OF DIABETIC NEPHROPATHY**

In type 1 diabetes mellitus, the earliest sign of abnormal renal function is hyperfiltration, a consequence of hyperglycemia. Hyperfiltration leads to an increase in renal volume, which progresses to microalbuminuria and eventually (15–20 years) macroalbuminuria. Macroalbuminuria is a strong indicator of risk for renal failure, which develops within 4 to 5 years after macroalbuminuria first occurs. The development of azotemia ultimately progresses to ESRD.

In type 2 diabetes mellitus, the sequence of events in the natural history of nephropathy is somewhat different. Here, microalbuminuria is not only an indicator of kidney disease but also of cardiovascular disease.

**DIAGNOSTIC CRITERIA AND SCREENING**

The diagnostic criteria for microalbuminuria and clinical albuminuria are shown in Table 1. Although

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<table>
<thead>
<tr>
<th>Stage</th>
<th>24-Hour Collection (µg/mg creatinine)</th>
<th>Timed Collection (µg/mg creatinine)</th>
<th>Spot Collection (µg/mg creatinine)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&lt;30</td>
<td>&lt;20</td>
<td>&lt;30</td>
</tr>
<tr>
<td>Microalbuminuria</td>
<td>30–299</td>
<td>20–199</td>
<td>30–299</td>
</tr>
<tr>
<td>Clinical albuminuria</td>
<td>≥300</td>
<td>≥200</td>
<td>≥300</td>
</tr>
</tbody>
</table>

Reproduced with permission from Molitch et al. Diabetes Care 2004;27(suppl 1):S79-S83.
24-hour collection of urine is considered the most accurate means of determining albumin levels, it is impractical in outpatient clinics and day-to-day clinical practice. However, many studies have shown that spot collection of urine, particularly a morning spot collection, correlates well with 24-hour collection in determining albumin levels and estimating the risk of progression to nephropathy.

Because microalbuminuria is an early marker of renal disease, screening is helpful in identifying patients at risk for further complications and guiding treatment. Screening for albuminuria is outlined in the American Diabetes Association algorithm shown in Figure 1. The test used for routine urinalysis should be sensitive for microalbuminuria. If the initial test is positive for protein, conditions such as heavy exercise or infection should be ruled out before initiating treatment and/or retesting.

The importance of screening for an early marker of diabetic nephropathy and of instituting appropriate treatment is underscored by the findings of the Diabetes Control and Complications Trial (DCCT), which compared the effect of intensive treatment versus conventional treatment of diabetic complications. The DCCT found that in type 1 diabetes, even patients with relatively good glucose control were at risk for diabetic nephropathy, although the risk was directly and sharply proportional to glycosylated hemoglobin (HbA1c) values. However, even moderate dysregulation of glucose control can be dangerous.

**ROLE OF THE RENIN-ANGIOTENSIN SYSTEM**

One of the important mechanisms involved in diabetic and hypertensive nephropathy is the renin-angiotensin system. The availability of the angiotensin-converting enzyme (ACE) inhibitors, which are effective in interfering with the system at the level of the converting enzyme, and the angiotensin II receptor blockers (ARBs), which effectively block the type 1 receptors of angiotensin II, is an important advance in treating diabetic nephropathy and slowing its progression.

As demonstrated in the European Collaborative Study of Lisinopril in Diabetes (EUCLID) study, which involved normotensive patients with type 1 diabetes mellitus and normal albumin excretion or microalbuminuria, ACE inhibition decreases production of angiotensin II, decreases interglomerular pressure by dilating the efferent arteriole, prevents glomerular hypertrophy, reduces proteinuria and microalbuminuria, and slows the rate of decline in the glomerular filtration rate. The decrease in interglomerular pressure is a particularly important effect because hypertension within the glomerulus may be one of the processes that drive diabetic nephropathy.

Although the EUCLID study involved patients with type 1 diabetes mellitus, longer-term studies have shown that ACE inhibitors reduce proteinuria and microalbuminuria in patients with type 1 or type 2 diabetes mellitus.

Angiotensin II receptor blockers have also been shown to slow the progression of renal disease. Two large studies, the Reduction in Endpoints in NIDDM with the Angiotensin II Antagonist Losartan trial and the Irbesartan in Diabetic Nephropathy Trial, have demonstrated that the effects of ARBs in reducing the progression of renal disease are equivalent to those effects of the ACE inhibitors.

Angiotensin-converting enzyme inhibitors also affect other protein systems, such as the bradykinin system, that may have positive effects on renal disease. Researchers and clinicians question whether ARBs are more effective than ACE inhibitors. The results of a trial directly comparing the 2 classes of drugs were recently published but did not show important differences between these treatments.

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**Figure 1. Screening for Albuminuria**

Adapted with permission from Molitch et al. *Diabetes Care*. 2004;27(suppl 1):S79-S83.
The Role of Blood Glucose Control in Preventing Diabetic Nephropathy

The well-established steps for preventing renal disease are outlined in Table 2. The importance of glucose control cannot be over emphasized. Although achieving and maintaining normal glucose levels within the reference range through lifestyle modifications, oral agents, and/or insulin is often difficult, patients should be encouraged to achieve as close to normal glycemia as possible. Diabetes education is often a great motivator for patients.

An important observation regarding prevention of renal disease progression is the “holdover” benefit of periods of intensive glucose control even after glucose control worsens. As demonstrated in the Epidemiology of Diabetes Interventions and Complications (EDIC) study, a 4-year follow-up to the DCCT, HbA1c values, which were significantly lower in the group receiving intensive treatment than in the group receiving conventional treatment at DCCT closeout, were more or less the same in both groups at the end of the 4-year follow-up. However, when risk for further progression of renal disease was evaluated, patients who received intensive treatment and had lower HbA1c values during the DCCT had significantly less risk than those patients who received conventional treatment in the DCCT at the end of the EDIC follow-up (Table 3).

In sum, it is clear from all studies evaluating the impact of glucose control on the microvascular complications of diabetes that good control reduces the risk of complications. Table 4 shows the percentage reductions in the risk of diabetic retinopathy, microalbuminuria, proteinuria, and diabetic peripheral neuropathy resulting from a 1% reduction in HbA1c.

These results underscore the importance of glucose control and achieving, insofar as possible, the target goals established by the American Diabetes Association, the International Diabetes Federation, and the American College of Endocrinology (Table 5). Although the target levels established by all 3 groups are strict, patients should be encouraged to monitor their glucose levels regularly and attain levels as close to these target goals as possible.

The Role of Blood Pressure Control in Preventing Diabetic Nephropathy

In addition to the role of glycemic control, it is clear that blood pressure control is important in reducing the risk of microvascular complications. As demonstrated in UKPDS 36, there is a 13% reduction in risk for all microvascular endpoints, particularly diabetic nephropathy and diabetic peripheral neuropathy, for every 10-mm Hg decrement in mean systolic blood pressure.

<table>
<thead>
<tr>
<th>Outcome Measure</th>
<th>Worse</th>
<th>Odds Reduction*</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumin excretion rate 40 mg/24 hours</td>
<td>11%</td>
<td>53</td>
<td>&lt;.002</td>
</tr>
<tr>
<td>Albumin excretion rate 300 mg/24 hours</td>
<td>5%</td>
<td>86%</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>40 mg/24 hours in DCCT</td>
<td>2%</td>
<td>92%</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>40-300 mg/24 hours in DCCT</td>
<td>31%</td>
<td>80%</td>
<td>&lt;.006</td>
</tr>
</tbody>
</table>

*Adjusted for value at DCCT closeout.
C = conventional treatment; DCCT = Diabetes Control and Complications Trial; EDIC = Epidemiology of Diabetes Interventions and Complications; I = intensive treatment.
Adapted with permission from Vinik AI, Vinik E. Am J Manag Care. 2003;9(3 suppl):S63-S80.
Several studies have shown that many patients maintain good blood pressure control under study conditions. However, after study completion, those same patients experience a rise in blood pressure (often to levels that are well above what is considered optimal). Therefore, combination therapy with 2, 3, or even 4 antihypertensive agents may be necessary to lower blood pressure into the reference range. ACE inhibitors or ARBs are the primary choice of antihypertensive agents prescribed for patients with type 2 diabetes mellitus because these drugs lower blood pressure and have other beneficial effects on diabetes and renal disease.

Although limiting protein intake to 0.8 mg/kg or less per day is recommended by many clinicians to prevent renal disease, there is no evidence that this is helpful once diabetic nephropathy has developed. In practice, reducing protein intake to 0.8 mg/kg per day is difficult because even foods not considered as major sources of protein (eg, bread and potatoes) contain small amounts of protein that add up over the course of the day.

THE ROLE OF BLOOD LIPID CONTROL IN PREVENTING DIABETIC NEPHROPATHY

Lowering low-density lipoprotein cholesterol with a lipid-lowering agent and/or diet is recommended to reduce the greatly increased risk of cardiovascular disease among patients with diabetes and kidney disease. Risk for cardiovascular disease is particularly high in patients with established renal insufficiency, probably because they are unable to eliminate agents that damage the blood vessels. Although lipid-lowering drugs may provide additional benefits in patients with kidney disease, this has not yet been established.

NEW THERAPIES FOR DIABETIC NEPHROPATHY

The rationale for screening and early detection is supported by studies demonstrating that treatment works, at least to slow the progression of diabetic nephropathy. However, clinicians question whether promising new therapies, which also stress the importance of early detection of diabetic microvascular complications, could target early pathophysiologic events even before clinical signs and symptoms develop, and whether this will actually provide a novel means of preventing ESRD altogether.

Several pathways have been implicated in the pathogenesis of diabetic microvascular complications. A current hypothesis is that blocking any one of these pathways may minimize vascular damage and improve outcome. The pathways include decreased Na/K-ATPase,24 increased polyol flux, myoinositol depletion, increased eicosanoid production, formation of advanced glycosylation end products,25 increased oxidative stress,26 and protein kinase C (PKC)-β activation.27 Protein kinase C inhibition seems especially promising in this regard because it blocks PKC, an enzyme that when activated by hyperglycemia and diacylglycerol (DAG) plays a key role in capillary dysfunction, eventually leading to diabetic peripheral neuropathy, diabetic nephropathy, and diabetic retinopathy.

**Table 4. Impact of a 1% Reduction in HbA1c on Risk for Diabetic Microvascular Complications**

<table>
<thead>
<tr>
<th>Study</th>
<th>Retinopathy</th>
<th>Microalbuminuria</th>
<th>Proteinuria</th>
<th>Neuropathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>DCCT8</td>
<td>↓ 38%</td>
<td>↓ 22%</td>
<td>↓ 28%</td>
<td>↓ 28%</td>
</tr>
<tr>
<td>Kumamoto17</td>
<td>↓ 35%</td>
<td>↓ 36%</td>
<td>↓ 32%</td>
<td>↑ NCV</td>
</tr>
<tr>
<td>UKPDS18</td>
<td>↓ 21%</td>
<td>↓ 38%</td>
<td>↓ 34%</td>
<td>↓ 57%</td>
</tr>
</tbody>
</table>

HbA1c = glycosylated hemoglobin; NCV = nerve conduction velocity.

**Table 5. Targets of Glycemic Control**

<table>
<thead>
<tr>
<th>Outcome Measure</th>
<th>ADA</th>
<th>IDF</th>
<th>ACE</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c, % (Normal: 4%–6%)</td>
<td>&lt;7.0</td>
<td>≤6.5</td>
<td>≤6.5</td>
</tr>
<tr>
<td>Blood glucose (mg/dL)</td>
<td>80–20</td>
<td>&lt;100</td>
<td>&lt;110</td>
</tr>
<tr>
<td>Postprandial blood glucose (mg/dL)</td>
<td>—</td>
<td>&lt;135</td>
<td>&lt;140</td>
</tr>
</tbody>
</table>

ACE = American College of Endocrinology; ADA = American Diabetes Association; IDF = International Diabetes Federation.
As shown in Figure 2, activation of the PKC-β isoform, which is particularly involved in hyperglycemia-induced vascular injury, results in diabetic peripheral neuropathy by causing capillary dysfunction, which in turn leads to endoneurial hypoxia, decreased axonal transport, axonal atrophy, and decreased nerve conduction velocity. A similar sequence of events stemming from PKC-β–induced capillary dysfunction leads to nephropathy and retinopathy.

An important marker of PKC activation by hyperglycemia and DAG is its translocation from the cytosol to the plasma membrane. When healthy normoglycemic individuals are administered an intravenous infusion of glucose to mimic postprandial hyperglycemia in patients with diabetes, PKC is activated. The activation (indicated by translocation of the enzyme from the cytosol to the plasma membrane) of the α and β2 isoforms is increased considerably in platelets 2 hours after infusion.

The increase in activated PKC seen in normoglycemic individuals is more difficult to demonstrate in patients with diabetes because they have a higher level of activation. Nevertheless, there is no doubt that PKC is activated in diabetes and with each increase in blood glucose, which may be an important reason to keep postprandial glucose levels as low as possible and to minimize fluctuations in glucose levels.

Ruboxistaurin, an orally active PKC-β inhibitor, is currently being evaluated in clinical trials involving patients with diabetic peripheral neuropathy, diabetic nephropathy, diabetic retinopathy, and diabetic macular edema. Results from earlier studies involving animals and humans have been encouraging. Studies have shown that ruboxistaurin normalizes endoneurial blood flow in diabetic peripheral neuropathy and reduces vascular permeability to vascular endothelial growth factor in animals with experimentally induced retinopathy.

**CONCLUSIONS**

With 50% of all patients with type 2 diabetes already having signs of a serious complication of diabetes at diagnosis, it is clear that earlier detection and intervention are needed. The need is further compounded by the fact that the worldwide prevalence of diabetes is on the rise.

Early detection of nephropathy begins with recognition of the factors that are most strongly correlated with increased risk (eg, microalbuminuria, hypertension, poor glucose control, duration of diabetes, and familial disposition). Routine urinalysis to screen for albuminuria, attention to glucose and blood pressure control, and lowering cholesterol levels to reduce the risk for cardiovascular disease are essential.

The importance of glucose and blood pressure control cannot be emphasized strongly enough. The percentage reductions in risk for nephropathy, nephropathy, and retinopathy for every 1% reduction in HbA1c are considerable, as is the 13% reduction in risk for all microvascular endpoints for every 10-mm Hg decrement in mean systolic blood pressure.

Several pathways have been implicated in the pathogenesis of diabetic microvascular complications, and current thinking holds that blocking any one of the pathways would minimize vascular damages and improve outcome.

Inhibition of the PKC pathway appears to be most promising, as an orally active PKC-β inhibitor (ie, ruboxistaurin) is currently being evaluated in clinical trials in patients with diabetic peripheral neuropathy, diabetic peripheral nephropathy, diabetic retinopathy, and diabetic macular edema. Results from earlier studies in animals and humans have been encouraging, and results from the current trials are awaited with great interest.
Q & A HIGHLIGHTS

Member of the audience: Why do you think the use of ACE inhibitors and ARBs together is essential in the treatment of diabetic renal disease? Wouldn’t well-controlled blood pressure be enough? Also, is it wise to use ACE inhibitors or ARBs or both in patients with diabetes with blood pressure in the reference range?

Dr. Pfeiffer: You are alluding to the cardiovascular disease trials that showed that complete blockade of the renin-angiotensin system is more effective than the use of either one alone. Several large and well-designed studies support that notion. However, it is not known if blockade with both drugs provides more protection against kidney disease in patients with type 2 diabetes. I think it is possible, but a study should be conducted to demonstrate this.

As for using ACE inhibitors or ARBs in normotensive patients with diabetes, several studies have found that ACE inhibitors are helpful in these patients by decreasing microalbuminuria and probably preventing the progression of renal disease.

Dr. Saudek: You mentioned that the combination of an ACE inhibitor and an ARB has not been tested. Would you expect such a study to be worthwhile and the results to be positive?

Dr. Pfeiffer: I was amazed by the strong and positive cardiovascular data from one of the studies. A more complete inhibition of the renin-angiotensin system may be beneficial, but it needs to be tested.

REFERENCES


**Panel Discussion**

*View Panel Discussion Online*

The symposium concluded with a panel discussion that reprised major points and addressed audience member questions. Christopher D. Saudek, MD, Program Director, served as moderator.

*Highlights of the discussion are available at:*

www.JHASIM.com

Click on “CME Programs”, then “Endocrinology/Diabetes”, then “Volume 5, (3A)”