

Diabetic Nephropathy

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BY MOHAMED G. ATTA, MD

STATEMENT OF NEED

Diabetes is responsible for 50% of the patients on dialysis in the United States (Figure 1). This trend is likely to continue, as the World Health Organization (WHO) projects a 46% increase in the number of people with diabetes worldwide by 2010.

Microalbuminuria may be a marker for early generalized endothelial damage as well as diabetic nephropathy (DN), and its early detection has important practical implications. The management of DN should target all risk factors, not just specific organs. Optimal blood pressure control is a key to managing the diabetic patient at risk for kidney disease, as is treatment targeting hyperglycemia, dyslipidemia and antismoking efforts.

TARGET AUDIENCE

This activity is designed for primary care physicians, endocrinologists, cardiologists and nephrologists.

LEARNING OBJECTIVES

After successful completion of this program, the participant should be able to:

- discuss the implications of DN and end stage renal disease (ESRD);
- describe the concept of microalbuminuria and how it develops;
- list the criteria for diagnosing microalbuminuria and the recommendations for screening; and

Microalbuminuria may be a marker for early generalized endothelial damage and DN.

- review the clinical trials that form the basis for treatment of patients with microalbuminuria.

METHOD OF INSTRUCTION

Participants should read the learning objectives and CME program in their entirety. After reviewing the material, they must complete the self-assessment test, which consists of a series of multiple-choice questions.

Upon completing this activity as designed and achieving a passing score of 70% or higher on the self-assessment test, participants will receive a CME credit letter awarding AMA/PRA category 1 credit and the test's answer key 4 weeks after the registration and evaluation materials are received.

The estimated time to complete this activity as designed is 1 hour.

ACCREDITATION

This activity has been planned and implemented in accordance with the essentials and standards of the ACCME through the joint sponsorship of The Dulaney Foundation and *Diabetic Microvascular Complications Today*.

TABLE 1. NATURAL HISTORY OF DIABETIC NEPHROPATHY IN TYPE 1 DIABETIC PATIENTS

Duration after diagnosis	Symptom
<5 years	Functional increase in glomerular filtration that is associated with microalbuminuria
10 to 15 years	Overt proteinuria
15 to 20 years	Azotemia
20 to 25 years	ESRD

DISCLOSURE

In accordance with the disclosure policies of The Dulaney Foundation and to conform with ACCME and FDA guidelines, all program faculty are required to disclose to the activity participants: 1) the existence of any financial interest or other relationships with the manufacturers of any commercial products/devices, or providers of commercial services, that relate to the content of their presentation/material or the commercial contributors of this activity, and 2) identification of a commercial product/device that is unlabeled for use or an investigational use of a product/device not yet approved.

FACULTY DISCLOSURE DECLARATIONS

The physician faculty whose material appears in this program has a financial interest, relationship or affiliation in the following forms:

Dr. Atta has had consultant relationships with the following companies: Pfizer (New York), Orthobiotech (Bridgewater, NJ), Amgen (Thousand Oaks, Calif) and Scios (Fremont, Calif).

FACULTY CREDENTIALS



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INTRODUCTION

According to the United States Renal Data System, there is a progressive increase in the incidence of ESRD among patients with diabetes mellitus (DM).¹ The majority of these patients have type 2 DM because of factors that include the aging population, increased survival of diabetic patients, and the obesity epidemic.

Currently, DM is responsible for 50% of the patients on dialysis in the United States. This trend is likely to continue as WHO projects a 46% increase in the number of people with diabetes worldwide by 2010. It is estimated that 30% to 40% of patients with type 1 diabetes develop DN. Its prevalence varies among patients with type 2 diabetes depending on ethnic group.

CLINICAL COURSE

The natural history of DN (Table 1) is predictable in type 1 diabetes. Classically, there is a functional increase in glomerular filtration rate in the first 5 years after diagnosis that can be associated with microalbuminuria. Overt proteinuria follows in 10 to 15 years, followed by azotemia in 15 to 20 years, and ultimately ESRD in 20 to 25 years. This pattern supports microalbuminuria being the first clinical sign of DN.

A group from Spain, however, presented findings suggesting that changes in the circadian pattern of blood pressure (BP) in type 1 diabetic patients may predict development of albuminuria.² The authors showed that a relative increase in nocturnal BP precedes the subsequent development of microalbuminuria. They prospectively followed a cohort of 75 patients with type 1 diabetes who had normal BP measured by ambulatory BP monitoring and normal urinary albumin excretion (UAE) at enrollment. Over time, microalbuminuria developed in 14 patients and those without a nocturnal dip in BP were more likely to develop microalbuminuria.

EARLIEST SIGN OF DN

The results suggest that nocturnal hypertension may in fact be the earliest sign of DN. Currently, Medicare covers the cost of ambulatory BP monitoring to only rule out white coat hypertension. Microalbuminuria, therefore, remains for now the predictive tool used to identify patients with early DN.

MICROALBUMINURIA MARKER

The concept of microalbuminuria was introduced more than 30 years ago when it became possible to measure urinary albumin below the level of detection by a urinary dipstick. Microalbuminuria, defined as a UAE of >300 mg in a 24-hour urinary collection, was subsequently shown to be an early marker of DN. This was first described in patients with type 1 diabetes. As the studies expanded to those patients with type 2 DM, microalbuminuria was found, quite remarkably, to be a stronger predictor of cardiovascular mortality than of renal events. In fact, depending upon the degree of albuminuria, the death rate from cardiac events increased from 100% to 150%.³ In the Heart Outcomes Prevention Evaluation (HOPE) Study, microalbuminuria was the strongest predictor of cardiovascular events in a high-risk population with underlying atherosclerosis, stronger than other risk factors such as coronary artery disease or diabetes.⁴

MICROALBUMINURIA AS A PREDICTOR

It is important to appreciate that microalbuminuria not only predicts cardiovascular events but also other atherosclerotic vascular events. Miettinen et al. followed over 2,000 diabetic and nondiabetic patients for 7 years, looking at the association of the different degrees of proteinuria and atherosclerotic vascular events.⁵ In both groups, microalbuminuria was associated with increased incidence of cardiovascular events, stroke and aggregate vascular events. Clinical proteinuria increased the incidence of amputation.

TRADITIONAL RISK FACTORS

Compared to traditional risk factors, microalbuminuria has been shown to be a strong predictor of cardiovascular death in healthy populations.⁶ In a cohort of healthy individuals, Borch-Johnsen et al. prospectively followed more than 2,000 patients for 10 years. The participants had no ischemic heart disease or diabetes. In this study, microalbuminuria increased the relative risk of cardiovascular death by 2.3-fold, independent of other risk factors. These data strongly suggest that microalbuminuria is not only a predictor of renal events in diabetic patients, but is also a much stronger predictor of macrovascular or cardiac events: the most common causes of death in this population.

Microalbuminuria is a strong predictor of cardiovascular and other atherosclerotic vascular events.

It is conceivable that extravasation of microalbuminuria across the capillary wall marks the leak of albumin and other macromolecules such as oxidized low-density lipoproteins at other vascular beds that promote further vascular injury. By this logic, microalbuminuria, easily measurable in urine, is a likely marker of generalized endothelial dysfunction in the circulation at large. The good news is that the onset of microalbuminuria in diabetic patients does not seal the fate of the patients

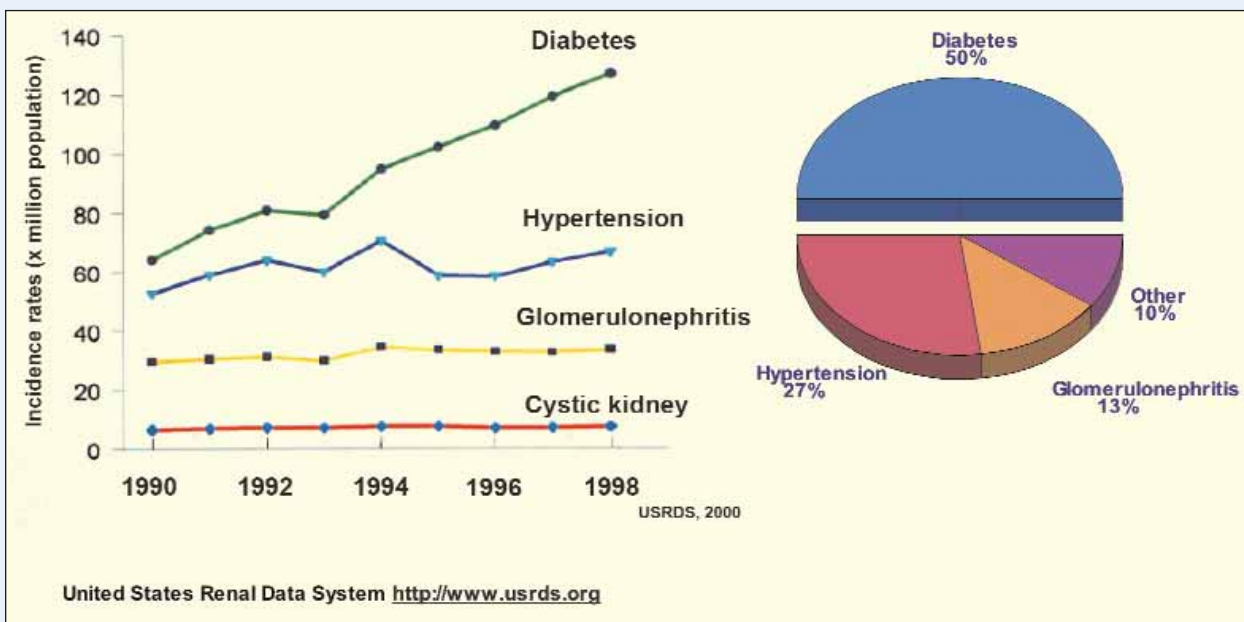


Figure 1. Primary diagnoses for patients who start dialysis.

TABLE 2. STUDIES THAT FOUND MICROALBUMINURIA TO BE A STRONG PREDICTOR

- **The Heart Outcomes Prevention Evaluation (HOPE) Study**

This study enrolled 9,541 patients who were aged >55. Patients had a high risk of cardiovascular events because of their history with diabetes, ischaemic heart disease, peripheral vascular disease or stroke.

The study investigated the effects of ramipril and/or vitamin E on vascular endpoints. Researchers found that the therapy caused reduced myocardial infarction, cardiovascular death and stroke rates. They also wrote that microalbuminuria was the strongest predictor of cardiovascular events in high-risk populations.

- **Miettinen et al.**

This 7-year study enrolled 2,431 patients to investigate the relationship between baseline degrees of proteinuria and the incidence of stroke and other atherosclerotic vascular disease events. A total of 1,056 patients had diabetes.

Researchers concluded that all patients in the study experienced an association between clinical proteinuria and the incidence of stroke, and that the presence of proteinuria was a significant predictor of stroke and other atherosclerotic vascular diseases. This was independent of additional cardiovascular risk factors.

- **Borch-Johnsen et al.**

This study enrolled 2,085 patients, all of whom had no signs of diabetes, ischemic heart disease, renal disease or urinary tract infection at baseline. Researchers set out to test the notion that the urinary albumin-to-creatinine ratio predicted ischemic heart disease.

Researchers determined that the potential to develop ischemic heart disease more than doubled with the presence of microalbuminuria. They found that microalbuminuria is an independent ischemic heart disease predictor.

- **Perkins BA, Ficociello LH, Sliva KH, et al.**

Researchers from this 6-year study enrolled 386 type 1 diabetic patients with persistent microalbuminuria, and studied the reductions of urinary albumin excretion. They also determined what factors affected these reductions.

Results indicated that microalbuminuria regression occurred frequently, and using an angiotension-converting enzyme inhibitor did not have an association with regression. Researchers noted that regressed microalbuminuria implied early DN.

as previously proposed. In fact, Perkins observed regression of microalbuminuria (defined as 50% reduction in urinary albumin excretion) between successive 2-year periods.⁷ At the end of 6 years, the cumulative incidence of regression was 58%. Regression was seen in patients of young age, with short duration of microalbuminuria, low HbA1c, low systolic BP (SBP), and either low cholesterol or triglycerides. As one would expect, patients with low HbA1c, low SBP, and either low cholesterol or triglycerides had a hazard ratio for regression of 3 versus those patients with none of these factors.

RECOMMENDATIONS FOR SCREENING

It is recommended that clinicians obtain standard urinalysis on a yearly basis 5 years after the onset of diagnosis in type 1 diabetic patients and at the time of diagnosis in those with type 2 diabetes. If urinalysis is positive for protein by dipstick reaction, quantification of proteinuria with 24-hour urine collection or protein-to-creatinine ratio should follow. If standard urinalysis is negative, a nontimed screening for microalbuminuria

is advised. There is no need for microalbuminuria testing if the standard urinalysis test for protein is positive (Figure 2).

TREATMENT STRATEGIES

The benefit of inhibiting the renin-angiotensin system was first determined by Ed Lewis, MD in his landmark study in 1993.⁸ In this study, 409 patients with type 1 diabetes were randomized in a double-blind fashion to placebo or captopril. Patients assigned to captopril had a risk reduction of doubling serum creatinine by 48%.

This benefit of inhibiting the renin-angiotensin system was subsequently extended to patients with type 2 diabetes. The Reduction of Endpoints in NIDDM with the All Antagonist Losartan (RENAAL) study was one of three studies published in the same issue of the *New England Journal of Medicine* in 2001.⁹ All three studies evaluated angiotensin receptor blockers (ARBs) on the progression of DN. In RENAAL, the use of losartan resulted in a 28% reduction in risk development of ESRD.

The advantage of beta-blockers was revealed in the

longest running study on type 2 diabetic patients ever performed. The United Kingdom Prospective Diabetes Study (UKPDS) showed no difference in the use of the beta-blocker tenormin, or the angiotension-converting enzyme (ACE) inhibitor captopril, on either fatal or nonfatal clinical endpoints or death related to diabetes.¹⁰ Renal outcome measures were not significantly different in both groups.

Approximately 11 million Americans have both diabetes and hypertension, increasing the risk for both micro- and macrovascular complications.

NEW TREATMENT PARADIGM

Our management strategies of DN, however, should shift to a new treatment paradigm that targets all risk factors rather than specific organs in isolation. This multifactorial approach has been proven to be successful. The Steno study from Denmark compared intensive treatment targeting hyperglycemia, dyslipidemia, smoking and hypertension to conventional therapy.¹¹ Aspirin was also administered to the intensive group for secondary prevention. Despite the good intentions, only cholesterol and SBP were significantly improved in the intensive group. Even with this limited success, however, cardiovascular events were reduced by 50%, and there was >50% reduction in several microvascular complications including autonomic neuropathy, retinopathy and nephropathy.

Optimal BP control is clearly one of the most important issues that should be addressed by all primary care physicians, endocrinologists, cardiologists and nephrologists. Approximately 11 million Americans have both DM and hypertension, which increases the risk of

macro- and microvascular complications including stroke, coronary artery disease, peripheral vascular disease, retinopathy and nephropathy.^{12,13} The National Kidney Foundation recommends a target blood pressure of <125/75 mm Hg, which is slightly less than the recommendation by the American Diabetic Association of <130/80 mm Hg.

SUMMARY

In conclusion, microalbuminuria may be a marker for early generalized endothelial damage as well as DN, and its early detection has important practical implications. Once overt nephropathy is detected, treatment should focus on reducing the risk of disease progression. Treatment strategies should focus on a multifactorial approach to simultaneously target hyperglycemia, dyslipidemia and hypertension, in addition to lifestyle modification and inhibition of the renin-angiotensin system. ■

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13. Molitch ME, DeFronzo RA, Franz MJ, et al. Diabetic nephropathy. *Diabetes Care*. 2003; 26 (suppl 1): S94-98.

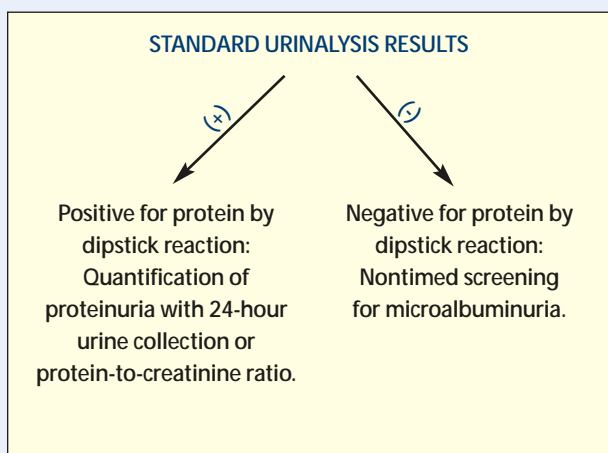


Figure 2. Screening for Standard Urinalysis.

CME QUESTIONS

Circle the most appropriate answer in the "ANSWER SECTION" on the following page.

1. The first clinical sign of diabetic nephropathy in type 1 diabetic patients is:
 - a. Changes in the circadian pattern of blood pressure
 - b. Glycosylated hemoglobin >8%
 - c. History of diabetes >20 years
 - d. Microalbuminuria
2. In type 2 diabetic patients the finding of microalbuminuria is a stronger predictor of which of the following:
 - a. Renal events
 - b. The development of hypertension
 - c. The progression to ESRD
 - d. Cardiovascular events
3. Microalbuminuria in diabetic patients is a risk factor for:
 - a. Endothelial dysfunction
 - b. Stroke
 - c. Amputation
 - d. Both a and b
4. Hypertension in diabetic patients is a risk factor for:
 - a. Microvascular complications
 - b. Macrovascular complications
 - c. Both microvascular and macrovascular complications
 - d. Coronary artery disease and microvascular complications
5. Regression of microalbuminuria is associated with:
 - a. The use of ACE inhibitors
 - b. Low triglycerides
 - c. Low diastolic blood pressure
 - d. The duration of microalbuminuria
6. If the urinary dipstick is 1+ positive in a diabetic patient, the next step is:
 - a. A nontimed screening for microalbuminuria in the urine by radioimmunoassay
 - b. Start the patient on an ACE inhibitor or ARB
 - c. Quantify proteinuria by 24-hour urine collection or urine protein-to-creatinine ratio
 - d. Check the patient's lipid profile
7. Patients with established diabetic nephropathy would benefit from which of the following:
 - a. ACE inhibitors or ARBs
 - b. Alpha-blockers
 - c. Beta-blockers
 - d. Both a and c
8. The target blood pressure in diabetic nephropathy as recommended by the National Kidney Foundation is:
 - a. 130/80 mm Hg
 - b. 120/80 mm Hg
 - c. 120/75 mm Hg
 - d. 125/75 mm Hg
9. Which of the following factors has not been proven to be of benefit in diabetic nephropathy:
 - a. Systolic blood pressure control
 - b. Glycosylated hemoglobin <7%
 - c. Control of hypertriglyceridemia
 - d. Control of diastolic blood pressure
10. The multifactorial approach to target all risk factors in diabetic patients was shown to be beneficial in which of the following studies:
 - a. RENAAL
 - b. UKPDS
 - c. STENO
 - d. VMAC

REGISTRATION/EVALUATION FORM

To obtain AMA/PRA category 1 credit, you must:

- Read the learning objectives and the CME article and complete the self-assessment test.
- Photocopy and complete this registration/evaluation form and record your test answers in the Answer Section below.
- Send the Registration/Evaluation form to **The Dulaney Foundation, Post Office Box 25271, Tampa, FL 33622-5271, or fax to 813-258-8002.**
- Retain a copy of your test answers. Your answer sheet will be graded, and if you achieve a passing score of 70% or better, you will receive a CME credit letter awarding AMA/PRA category 1 credit as well as the test answer key by mail within 4 weeks. If you do not achieve a passing score, you will be notified and offered the opportunity to complete the activity again.

ANSWER SECTION

Circle the best answer for each question on page 41.

1. A B C D 2. A B C D 3. A B C D 4. A B C D 5. A B C D
6. A B C D 7. A B C D 8. A B C D 9. A B C D 10. A B C D

REGISTRATION FORM

First name _____ Last name _____ Degree (MD, PhD) _____

Specialty _____

Institution or practice name _____

Address _____

City _____ State _____ Zip Code _____ Country _____

Telephone _____ Fax _____ E-mail address _____

The processing fee has been underwritten by an unrestricted educational grant from Eli Lilly and Company.

I attest that I have completed this activity as designed and I am claiming ____ (up to 1 credit) AMA/PRA category 1 credit.

Signature _____ Date _____

Credit for this activity is available until December 31, 2005.

The planning and execution of useful and educationally sound continuing education activities are guided in large part by input from participants. Please assist us in evaluating the effectiveness of this activity and make recommendations for future educational offerings by completing this evaluation form. Your response will help ensure that future programs are informative and meet the educational needs of all participants. Please note: CME credit letters and long-term credit retention information will only be issued upon receipt of this completed evaluation. Thank you for your cooperation.

OBJECTIVES

After successful completion of this program, you should be able to:

- | | | | | | |
|---|---|---|---|---|---|
| • Discuss the implications of DN and ESRD. | 5 | 4 | 3 | 2 | 1 |
| • Describe the concept of microalbuminuria and how it develops. | 5 | 4 | 3 | 2 | 1 |
| • List the criteria for diagnosing microalbuminuria and the recommendations for screening. | 5 | 4 | 3 | 2 | 1 |
| • Review the clinical trials that form the basis for treatment of patients with microalbuminuria. | 5 | 4 | 3 | 2 | 1 |

(Please circle the number that is most accurate; 5 represents strongly agree and 1 represents strongly disagree.)

OVERALL EVALUATION

- | | | | | | |
|--|---|---|---|---|---|
| • The information presented increased my awareness/understanding of the subject. | 5 | 4 | 3 | 2 | 1 |
| • The information presented will influence how I practice. | 5 | 4 | 3 | 2 | 1 |
| • The information presented will help me improve patient care. | 5 | 4 | 3 | 2 | 1 |
| • The faculty demonstrated current knowledge of the subject. | 5 | 4 | 3 | 2 | 1 |
| • The program was educationally sound and scientifically balanced. | 5 | 4 | 3 | 2 | 1 |
| • The program avoided commercial bias or influence. | 5 | 4 | 3 | 2 | 1 |
| • Overall, the program met my expectations. | 5 | 4 | 3 | 2 | 1 |
| • I would recommend this program to my colleagues. | 5 | 4 | 3 | 2 | 1 |

(Please circle the number that is most accurate; 5 represents strongly agree and 1 represents strongly disagree.)

• If you anticipate changing one or more aspects of your practice as a result of your participation in this activity, please provide a brief description of how you plan to do so: _____

• Please provide any additional comments pertaining to this activity (positive and negative) and suggestions for improvements: _____

• Please list any topics you would like to see addressed in future educational activities: _____