

Detection of Peripheral Neuropathy: Screening and Diagnosis Strategies

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DIABETIC MICROVASCULAR COMPLICATIONS TODAY.

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STATEMENT OF NEED

Diabetes is an epidemic disease associated with many complications that affect every part of the body. In the eyes, diabetic retinopathy is the leading cause of blindness in working age adults. In the kidneys, diabetic nephropathy is the leading cause of end-stage renal disease. In the legs, diabetic neuropathy is the leading cause of nontraumatic lower-extremity amputations. Diabetes also has ties to other diseases and dysfunctions, as it infers a two- to fourfold increase in cardiovascular mortality and stroke.

TARGET AUDIENCE

This activity is designed for podiatrists, neurologists, primary care physicians and other practitioners treating patients with diabetes and diabetic neuropathy.

LEARNING OBJECTIVES

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

- identify the protein kinase-C (PKC) isoform that plays a critical role in the pathway of diabetic microvascular complications and how it affects vascular function;
- identify the most common reason for hospital admission in reference to diabetes;
- identify the incidences of hospitalization, amputation and mortality rates among patients with diabetes; and
- identify the key ingredient for the development of diabetic foot wounds.

METHOD OF INSTRUCTION

Participants should read the learning objectives and continuing medical education (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.

Participants have a choice of completing this activity online by visiting www.DiabeticMCToday.com; getting real-time results at www.CMEToday.net; or by using the print forms following this activity.

Upon completing the activity and achieving a passing score of $\geq 70\%$ on the self-assessment test, participants will receive a CME credit letter awarding *AMA/PRA Category 1 Credit* 4 weeks after the registration and evaluation materials are received. The estimated time to complete this activity is 1 hour.

ACCREDITATION

This activity has been planned and implemented in accordance with the Essentials and Standards of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of The Dulaney Foundation and *DIABETIC MICROVASCULAR COMPLICATIONS TODAY.*

The Dulaney Foundation designates this educational activity for a maximum of *1 AMA/PRA Category 1 Credit*. Physicians should only claim credit commensurate with the extent of their participation in the activity.

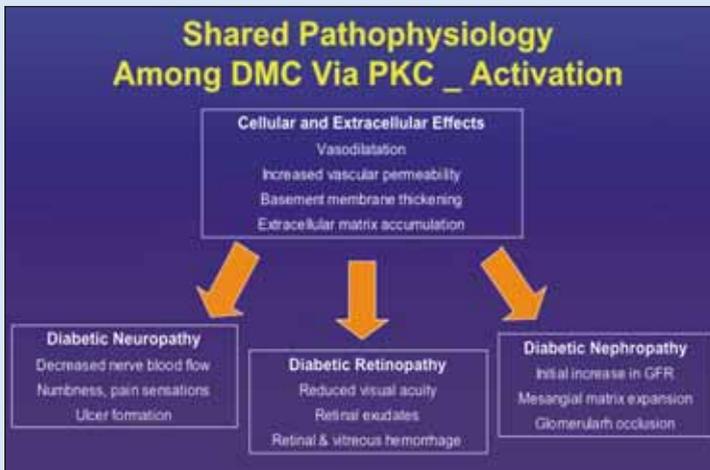


Figure 1. Diabetic neuropathy, retinopathy and nephropathy have a shared pathophysiology.



Figure 2. Hospitalization for infected wounds is common among patients with diabetes.

DISCLOSURE

In accordance with the disclosure policies of The Dulaney Foundation and to conform with ACCME and Food and Drug Administration (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

None.

FACULTY CREDENTIALS

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INTRODUCTION

Several metabolic pathways are responsible for diabetic microvascular complications (Figure 1). One of the shared areas in the pathophysiology of diabetic microvascular complications is that of PKC-beta activation. The cellular and extracellular effects enhance vasodilation, which leads to increased vascular permeability, basement membrane thickening and extracellular matrix accumulation.

This cascade of effects, in turn, leads to diabetic neuropathy, retinopathy and nephropathy. In diabetic neuropathy there is decreased nerve blood flow causing numbness and pain, which ultimately leads to ulcer formation. In diabetic retinopathy, patients experience reduced visual acuity, retina exudates and retinal and vitreous hemorrhage. In the setting of diabetic nephropathy, patients experience initial increases in glomerular filtration rate, an expansion of the mesangial matrix and glomerular occlusion.

PKC plays a critical role in the pathway to diabetic microvascular complications. There is much preclinical data to suggest that the PKC-beta isoform has a large role in this process. For example, in animal models of diabetes, specific inhibition of PKC-beta normalizes many diabetes-related changes in vascular function, such as retinal blood flow, endoneurial blood flow and sensory and motor nerve conduction velocity.

Where do diabetic microvascular complications rank? Infected wounds are the most common reason for hospital admission. The infection to ulcer ratio is 0.56, with 1 in 5 infections leading to a lower-extremity amputation (Figure 2).

FOCUS ON THE FOOT

More inpatient days are spent treating pedal wounds than any other diabetic complication. Of diabetes-related hospital admissions, 20% to 25% are infected pedal wounds, and <14% are evaluated with minimum competency (Figure 3).

Following the first lower-extremity amputation, a patient has a 68% incidence of a contralateral amputation

TABLE 1. CUMULATIVE RISK FOR ULCERATION BY FOOT RISK CATEGORY

Risk category for ulceration	Odds Ratio (95% CI)
Foot risk category 0	NA
Foot risk category 1	1.7 (0.7 to 4.3)
Foot risk category 2	12.1* (5.2 to 28.3)
Foot risk category 3	36.4* (16.1 to 82.3)

* $P < .05$

within 5 years. Within 3 years, the patient has a 50% mortality rate and a 25% chance of institutionalization.

Ulcerations are pivotal when it comes to the loss of a limb. Ulcerations provide a portal for infection. When necrosis exists in the presence of critical ischemia, the situation becomes dire.

Neuropathy – the loss of protective sensation – is the key ingredient for the development of diabetic foot wounds. Data from Aventis Pharmaceutical's (Bridgewater, NJ) GOAL A1c study showed that 37% had neuropathy. The first 7,378 of 14,000 patients were enrolled. This crucial diagnosis was missed in 63% of patients by both generalists and specialists.

Patients with a loss of protective sensation were more than 15 times more likely to present with an ulceration, which is consistent with other case-controlled studies. This reveals the importance of a neurological evaluation in these patients. This strong risk factor is easily identified by tests such as the biothesiometer or the 10-g Semmes-Weinstein monofilament.

Identifying patients who are at high risk is critical in order to prevent limb loss, schedule patient visits and allocate the appropriate resources. When studying the extent of this problem, previous reports have met with limitations based on univariate models, associations versus cause and effect, as well as confounding variables.

The Infected Diabetic Pedal Wound

- More inpatient days spent treating pedal wounds than any other diabetic complication
- 20-25% of all diabetes-related hospital admissions
- <14% evaluated with minimum competency

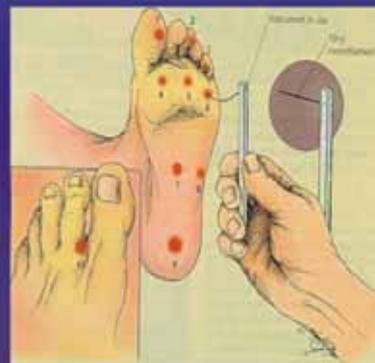


Elshoff GW, et al. Arch Intern Med 1994;154:2273-2279.

Figure 3. Infected diabetic pedal wounds are the cause of 20% to 25% of all diabetes-related hospital admissions.

10-gram Semmes-Weinstein Monofilament

- 10 sites
- "Yes-no" method of administration
- 4 or more imperceptible = LOPS



Semmes DG, Leary LA. J Am Podiatr Assoc 1984;57:1125-1132, 1132-1138.

Figure 4. The 10 sites of the 10-g Semmes-Weinstein monofilament are pictured.



Figure 5. The Xilas vibration detection threshold meter, pictured on the right.

We thought it was time for practical criteria for screening patients at risk for diabetic foot ulceration. So along with my colleague Lawrency A. Lavery, DPM, PhD, and others, we sought to identify the factors that are significantly associated with the presence of foot ulceration. They include:

- duration of diabetes >10 years;
- being male;
- poor diabetes control;
- neuropathy;
- foot deformity, limited joint mobility, high plantar pressures; and
- history of amputation.

We also wanted to determine if the risk factors were cumulative (Table 1).

Several associations were found to be conspicuously absent as key risk factors for ulceration in this analysis. They included:

- vascular disease;
- level of formal education;
- nephropathy;
- retinopathy;
- impaired vision;
- ethanol or tobacco use; and
- obesity.

While these are critical factors to assess (particularly vascular disease), they are probably not primary risk factors for developing a foot wound, but rather for not healing a wound, and thus are important in amputation.

We came up with three questions to determine how can we screen for ulcer risk:

1. **Is there a loss of protective sensation?** How do we define protective sensation? First we have to choose a practical screening instrument to identify patients at

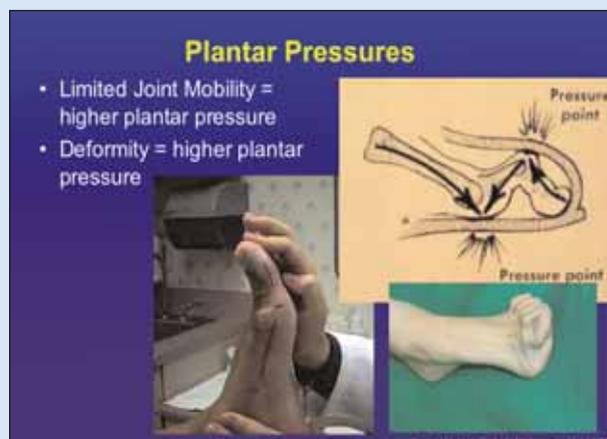


Figure 6. Higher plantar pressure is associated with limited joint mobility and deformity.

risk for diabetic foot ulceration.

The 10-g Semmes-Weinstein monofilament is a practical and simple option. It offers a yes-or-no method of administration. It is administered at 10 sites on each foot. If there are four or more imperceptible sites, then that equals a loss of protective sensation (Figure 4). This device, however, has the downside of being highly subjective and there may be significant differences between manufacturers' quality control. Additionally, if the device is used on numerous patients, by the end of the day the device may become more viscoelastically supple, thus imparting less force on the foot and leading to potential false positives.

Vibration detection threshold provides a quantitative measure. There are numerous commercially available handheld vibration measuring devices (Figure 5). The one in widest use is the biothesiometer (Xilas Medical, San Antonio). While still subjective, it provides a potentially far more quantitative measure of loss of protective sensation than does the 10-g Semmes-Weinstein monofilament.

2. **Is there a deformity causing a focus of high pressure?** The mechanisms of injury for foot ulceration can be caused by low, moderate or high pressure. Low pressure is constant exposure, moderate pressure results in repetitive exposure and high pressure is a single exposure.

Limited joint mobility (for instance <50° of static dorsiflexion of the hallux) also leads to higher plantar pressure, so it can be equated as a deformity as well (Figure 6).

3. **Is there a previous history of ulceration or amputation?** If so, then all the requisite ingredients are in place for another ulcer. A previous incidence is associated with a 10 times greater risk for ulceration. ■

CME QUESTIONS

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

1. Which statement is FALSE:
 - a. PKC activation is a critical step in the pathway to diabetic microvascular complications.
 - b. Preclinical data suggest that the PKC-beta isoform plays a major role in this process.
 - c. Animal models have not successfully shown that specific inhibition of PKC-beta normalized any diabetes-related changes in vascular function.
 - d. There are shared pathophysiology among diabetic microvascular complications and PKC-beta activation.

2. Which statements is TRUE.
 - a. Infected diabetic foot wounds are the most common reason for hospital admission.
 - b. Diabetic retinopathy is the most common reason for hospital admission.
 - c. Diabetic neuropathy is the most common reason for hospital admission.
 - d. Uncontrolled HbA1c is the most common reason for hospital admission.

3. Which statement is FALSE about the infected pedal wound:
 - a. Infected pedal wounds account for more inpatient days spent than any other diabetic complication.
 - b. Infected pedal wounds account for 20% to 25% of all diabetes-related hospital admissions.
 - c. Infected pedal wounds rarely cause lower limb amputation.
 - d. Infected pedal wounds can lead to mortality.

4. Why are ulcerations critical to limb loss?
 - a. they provide a portal for infections
 - b. they offer necrosis in the presence of critical ischemia
 - c. infections lead to amputations
 - d. there is no cure for an ulcer

5. What is NOT an important aspect of protective sensation in the diabetic foot?
 - a. loss of protective sensation carries more than a 15 times higher rate of ulceration
 - b. it can be easily diagnosed
 - c. loss of protective sensation in the foot signals kidney problems
 - d. identifying it can prevent limb loss

6. Which is not a factor significantly associated with the presence of foot ulceration:
 - a. duration of diabetes >10 years
 - b. poor diabetes control
 - c. foot deformity
 - d. unusually small feet for men

7. Which is an accepted screening test for protective sensation
 - a. Semmes Weinstein monofilament
 - b. vibration detection threshold
 - c. reflex hammer
 - d. visual exam
 - e. nerve conduction study
 - f. all of the above

8. Does foot deformity affect ulceration chances?
 - a. yes
 - b. no

9. Should the physician find out if the patient has had previous ulceration of amputation?
 - a. yes
 - b. no

10. Should all diabetic patients have their feet examined at every visit?
 - a. yes
 - b. no

REGISTRATION/EVALUATION FORM: DETECTION OF PERIPHERAL NEUROPATHY

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, PO Box 44408, Phoenix, AZ 85064, or fax to 602-508-4893.**
- 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 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 E F 8. A B 9. A B 10. A B

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 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 March 31, 2007.

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:

- | | | | | | |
|---|---|---|---|---|---|
| • identify the PKC isoform that plays a critical role in the pathway of diabetic microvascular complications and how it affects vascular function | 5 | 4 | 3 | 2 | 1 |
| • identify the most common reason for hospital admission in reference to diabetes | 5 | 4 | 3 | 2 | 1 |
| • identify the incidences of hospitalization, amputation and mortality rates among patients with diabetes | 5 | 4 | 3 | 2 | 1 |
| • identify the key ingredient for the development of diabetic foot wounds | 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: _____