Diabetes-Related Microvascular Complications – A Practical Approach

Basem M. Mishriky, MD[a,*], Doyle M. Cummings, PharmD, FCP, FCCP[b], James R. Powell, MD[a]

KEYWORDS

• Microvascular complications • Diabetic symmetric polyneuropathy
• Diabetic kidney disease • Diabetic retinopathy • Practical approach

KEY POINTS

- Screen for microvascular complications at the time of diagnosis of type 2 diabetes.
- Inspection of the feet is encouraged at every visit.
- Renal evaluation should be performed at least annually to screen for diabetic kidney disease.
- Retinal evaluation by an expert should be performed regularly.

DIABETIC SYMMETRIC POLYNEUROPATHY

What is Diabetic Symmetric Polyneuropathy?

Diabetic neuropathy is classified into diffuse neuropathy, mononeuropathy, and radiculopathy/polyradiculopathy.[1] Diabetic symmetric polyneuropathy (DSPN) is the most common form of diffuse neuropathy, which is the most common form of diabetic neuropathy.[1] DSPN affects 50% of individuals with type 2 diabetes (T2DM) after 10 years of disease duration and at least 20% of individuals with type 1 diabetes (T1DM) after 20 years of diagnosis.[1] DSPN can be referred to as distal symmetric polyneuropathy or even, although less accurate, as diabetic neuropathy.[2]

The American Academy of Neurology, the American Association of Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation define distal symmetric polyneuropathy (including DSPN) as polyneuropathy that must begin in the feet and include symptoms and signs that are the same on both sides of the body.[3,4] The symptoms may be primarily sensory, primarily motor, or combined. The

[a] Department of Internal Medicine, East Carolina University, 521 Moye Boulevard, 2nd Floor, Greenville, NC 27834, USA; [b] Department of Family Medicine, East Carolina University, 101 Heart Drive, Greenville, NC 27834, USA
* Corresponding author.
E-mail address: mishrikyb@ecu.edu

Prim Care Clin Office Pract 49 (2022) 239–254
https://doi.org/10.1016/j.pop.2021.11.008
primarycare.theclinics.com

signs may include pain, impairment to touch, impairment to proprioception, weakness and atrophy of muscles, depressed/absent ankle reflexes, or autonomic system.[3,4] Signs are better predictors of polyneuropathy compared with symptoms and multiple concurrent abnormalities provide greater sensitivity in predicting polyneuropathy.

In the position statement by the American Diabetes Association (ADA), DSPN is defined as the presence of symptoms or signs of peripheral nerve dysfunctions after excluding other causes.[1]

Can Patients without Numbness, Tingling, or Pain in the Feet have Diabetic Symmetric Polyneuropathy, and Why is this Important?

Around 50% of individuals with DSPN are asymptomatic; therefore, the absence of symptoms cannot rule out DSPN.[1] As DSPN with or without deformity increases the risk of amputation,[5] diabetic foot examinations are extremely important to allow the early identification of DSPN to prevent progression to ulcerations and amputations.

How do Individuals with Diabetic Symmetric Polyneuropathy Present?

The clinical presentation can be classified according to the type of nerve affected (motor, sensory, or autonomic) or according to the size of nerve fiber involvement (either small-fiber or large-fiber involvement) (Fig. 1).

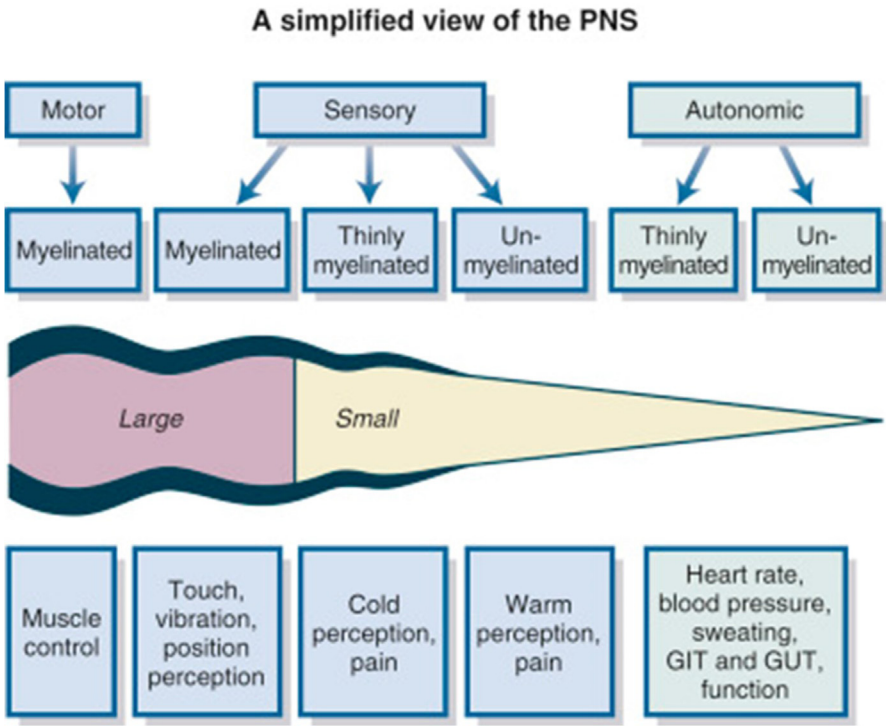

Fig. 1. A simplified view of the peripheral nervous system. (*From* Brownlee M, Aiello LP, Cooper ME, Vinik AI, Plutzky J, and Boulton AJM. Chapter 33: Complications of diabetes mellitus. In: Kronenberg HM, Larsen PR, Melmed S, and Polonsky KS, eds. Williams Textbook of Endocrinology. 13th ed. Elsevier: 2016: 1484-1581; with permission.)

Small-fiber involvement

Small-fibers usually involve sensory and autonomic nerves. The most common and early symptom is neuropathic pain which is characterized by burning, lancinating, and shooting pain that worsens at night. It may be associated with an unpleasant sensation of burning (dysesthesias), an exaggerated response to painful stimuli (hyperalgesia), and/or an exaggerated pain evoked by contact with socks, shoes, or bedclothes (allodynia).[1,5] Defects in the autonomic function of the nerves may result in decreased sweating, dry skin, impaired vasomotor function, and cold feet.[5,6]

Large-fiber involvement

Large-fibers usually involve sensory and/or motor nerves. Following the small-fiber involvement, the normal progression of symptoms is to develop numbness, tingling, and loss of protective sensations.[1,5,6] This is accompanied by loss of position sense and loss of reflexes. Later, muscle wasting with subsequent foot deformities develops.[5]

While the onset of symptoms is usually insidious, some patients may have an acute onset of symptoms.[5] DSPN typically affects the lower extremities in a stocking-like distribution. In more severe cases and by the time the symptoms reach the knees, the hands may be involved. While initially it may be reversible, the disappearance of pain in later stages should be interpreted as nerve death and is a worrisome sign.[6]

Is Ongoing Foot Pain and Numbness in Individuals with Diabetes Always Diabetic Symmetric Polyneuropathy?

While DSPN is principally a clinical diagnosis, health care providers (HCP) need to ensure that other causes of neuropathy are ruled out. A reasonable initial workup may include[1]:

- Complete blood count
- Basic metabolic panel
- Thyroid-stimulating hormone
- Serum vitamin B12 and folic acid levels
- HIV, if the patient is at high risk
- Serum protein electrophoresis to evaluate multiple myeloma if clinically suspected

While the confirmation of pathologic diagnosis may require nerve conduction studies and a biopsy, they are rarely needed in clinical practice.

What are the Criteria for Requesting a Nerve Conduction Study (Possible Reasons for Specialist Referral)?

- Patients with asymmetric symptoms[6]
- Rapid development or progression[6]
- Progression of symptoms despite adequate glycemic control[6]
- Symptoms more common in the hands[6]

It should be noted that if suspicion is high, but the nerve conduction studies are negative, a skin biopsy may still be needed to evaluate for small-fiber disease.[3]

What are the Minimum Criteria Required to Diagnose Diabetic Symmetric Polyneuropathy?

The Toronto Consensus has defined the minimal criteria for the diagnosis of DSPN[5]:

- Possible DSPN: The presence of a symptom or sign of DSPN.
- Probable DSPN: The presence of a combination of symptoms and signs.

- Confirmed DSPN: The presence of a symptom or sign confirmed with an abnormal nerve conduction study.

When Should the Health Care Providers Screen for Diabetic Symmetric Polyneuropathy?

While individuals with T1DM should be screened after 5 years from diagnosis, individuals with T2DM should be screened at the time of diagnosis as T2DM duration before diagnosis may not be known. While guidelines recommend screening for DSPN by examining the feet at least once yearly, it is our practice to examine/inspect the patient's feet at every visit. This practice of examining the feet at every visit reinforces the importance of the patient checking their own feet daily.

How Should the Health Care Providers Screen for Diabetic Symmetric Polyneuropathy?

History

The patient should be asked about symptoms of DSPN (including burning/shooting pain, numbness, tingling, coldness of the feet) at every visit. The history should also include symptoms of claudication, rest pain, and/or nonhealing ulcer. Past history should address any prior ulceration, amputation, Charcot joint, or vascular surgery. Finally, smoking history should be obtained.

Examination

A careful inspection of the feet in a well-lit room should always be carried out after the patient has removed their shoes and socks.

The foot examination should include[7]:

Inspection for:

- Dryness or cracking, infection, and calluses/corns of the skin.
- Evidence of deformities (eg, claw toes, hammer toes, overlapping toes, bunion).
- Evidence of muscle wasting.

Neurologic assessment:

This requires testing for sensation: usually, a monofilament test combined with one or more tests for both large-fiber involvement (such as vibration sense, reflexes, proprioception) and small-fiber involvement (such as pinprick sensation and thermal discrimination).

- Testing for protective sensations (large-nerve fiber): It is recommended to use at least a 5.07 (10-g) monofilament to screen for loss of protective sensations. While screening for the loss of protective sensations using the 5.07 (10-g) monofilament may be convenient during a busy clinical practice,[8] it is advised to follow clinical progression by using a graded monofilament kit with different target forces.[9–11] Individuals with diabetes but no DSPN should be able to sense the 4.31 (2-g) and the 3.61 (0.4-g) monofilaments.[9–11] It is reasonable to start with the 3.61 (0.4-g) monofilament and proceed in order of increasing stiffness.[9]

Steps to perform the monofilament testing:

- Explain the test to the patient before starting.
- The sensation of pressure with the monofilament should first be demonstrated to the patient on a proximal site, usually the hands. The patient should be instructed to report if a touch is felt, then specify the site they felt the touch.
- The patient should close their eyes while being tested.
- Areas of callus, abrasion, or scarring should be avoided.
- The monofilament is pressed perpendicular to the skin for approximately 1 second while it is buckling to ensure that the target force is delivered to the tested site.

- At least 4 sites should be tested on each foot (plantar surface of the big toe, 1st, 3rd, and 5th metatarsal heads). If using ≤4.08 (1-g) monofilament, the stimulus can be applied up to 3 times to elicit a response. If using greater than 4.08 (1-g) monofilament, the stimulus should be applied only once.
- If a graded monofilament kit is available, the examiner may begin with a 3.61 (0.4-g) monofilament. If the patient does not respond to the stimulus, choose the next largest monofilament. If a graded monofilament kit is not available, screening with a 5.07 (10-g) monofilament should be used.
- A test is considered abnormal if sensation is lost at one or more of the tested sites.[7]

If a 5.07 (10-g) monofilament is not available, an Ipswich touch test may be used instead.[12] This is a simple, cheap, and equally sensitive and specific test when compared with monofilament testing.[12] The patient should close their eyes and the examiner should rest an index finger (like a feather touching the skin) on the tip of the 1st, 3rd, and 5th toes of both feet. This should last for one to 2 seconds. The patients should indicate if they feel the touch. A test is considered abnormal if the patient cannot feel any 2 examined sites.

- Testing for vibratory sensations (large-nerve fiber): This should be done using a 128-Hz tuning fork.

Steps to perform the tuning fork testing:

- Explain the test to the patient before starting.
- The vibration sense should first be demonstrated to the patient usually over the thumb. The patient should be made aware that it is the sensation of vibration, not the pressure, that is being tested.
- The vibrating tuning fork should be placed over the tip of the big toe or at the base of the great toenail (or at the medial malleolus if there is toe amputation[13]) bilaterally for at least 8 to 10 seconds.[14]
- The examiner may report the test as present or absent.[11] In addition, the time (in seconds) the patient is feeling the vibration may be reported.[13,14] Finally, the examiner may compare the vibration sense of the patient compared with themselves.

- Testing for reflexes (large-nerve fiber) should be done using a reflex hammer.

Steps to perform reflex testing:

- The patient should be instructed to relax.
- The examiner should tap the Achilles tendon while the foot is dorsiflexed.
- If the reflex is absent or difficult to elicit, the examiner may ask the patient to perform reinforcement procedures (eg, asking the patient to clench teeth or hook their fingers together and pull apart)[7]
- If the ankle reflex remains absent, examining the knee reflex is encouraged.

Vascular assessment:

- The dorsalis pedis and posterior tibial pulses should be examined.
- Peripheral arterial disease may occur even if the pedal pulses are present. If there is a high index of suspicion, ankle-brachial index testing should be performed.

A Monofilament Test is Insensate to 5.07 but Intact to 6.65. Tuning Fork Vibrations Sense was Lost after Five Seconds. The Ankle Reflex and Pinprick Sensation were Intact Bilaterally. What is the Significance of that Foot Examination?

The importance of performing the foot examination is to identify high-risk patients and to prevent ulceration and amputation. Individuals who are insensate to the 5.07 (10-g) monofilament have a tenfold increased risk of ulceration.[15] The presence of

abnormalities in the foot examination may also point to a need to increase the frequency of foot examinations. While the general recommendation for HCP is to examine the healthy feet once yearly, individuals with loss of protective sensation should have a foot examination at least every 3 to 6 months.[7] Individuals with insensate feet may not be able to recognize wounds given the loss of protective sensations; therefore, it is important for patients to examine their feet daily and for HCP to examine the feet at every visit.

What Measures can Health Care Providers do to Prevent Diabetic Symmetric Polyneuropathy and Ulcerations?

Foot care education

Diabetic foot care should be provided to the patient at least at the initial visit and as indicated thereafter and should include the following recommendations[16]:

- Feet should be checked daily. Individuals should look for cuts, redness, swelling, sores, blisters, corns, calluses, or any changes. If the patient cannot see the bottom (plantar aspect) of the foot, a mirror can be used, or a family member can inspect the foot. If none are available, the patient may use their hand as a method to inspect the bottom of the foot.
- Feet should be washed every day in warm, not hot, water. After washing the feet, they should be completely dried particularly between the toes.
- Avoid barefoot walking. Individuals with diabetes should be encouraged to wear socks and shoes outdoors and slippers indoors.
- Shoes should fit well. Patients should be encouraged to always check the inside of the shoes.
- Avoid cutting corns/calluses.
- Toenails should be trimmed straight across.
- Protect the feet from hot and cold. In individuals with insensate feet, it is important to check shower or bath water with the elbow to test the warmth of the water. Patients should be cautious at the beach as sun and sand exposure may result in skin burns.
- Smoking cessation should be encouraged.
- The HCP can guide patients to access publicly available materials: https://www.niddk.nih.gov/health-information/diabetes/overview/preventing-problems/foot-problems and https://www.cdc.gov/diabetes/library/features/healthy-feet.html

Proper footwear

In individuals with increased risk of ulceration, custom-made shoes with inserts are encouraged.[16] If a custom-made shoe is not available or not affordable, cushioned socks are inexpensive and may decrease pressure points.[11]

Glycemic control

Improvement of glycemic control in T1DM has been shown to prevent and delay DSPN. Although the evidence is not as strong in T2DM, improvement in glycemic control may slow the progression of DSPN and is recommended in published guidelines.[17]

Management of Symptomatic Diabetic Symmetric Polyneuropathy

Patients should be offered therapies in a stepwise fashion.[17] Before the initiation of medications, the patient's medication list should be reviewed, and clear goals and expectations should be discussed. In individuals with symptoms impacting the quality of life, pregabalin or duloxetine can be initiated (both have received FDA approval to treat neuropathic pain). If symptoms remain uncontrolled despite adequate titration of one

agent, switching to the other agent is recommended.[1,17] If no clinically meaningful effect is observed despite switching to the other agent, combining both pregabalin and duloxetine is recommended.[1] If pregabalin is not affordable, gabapentin may be an acceptable alternative.[17] Pregabalin and gabapentin should be used with caution in older adults and should not be combined. In individuals having neuropathic pain and depression, duloxetine (preferably) or venlafaxine may be favored. In individuals with contraindication(s) to the above medications or unwilling to take oral medications, topical capsaicin, topical lidocaine, or alpha-lipoic acid may be tried.[11] While tapentadol received FDA approval for neuropathic pain, its use should be avoided due to high risk for addiction and limited evidence of benefit.[17]

DIABETIC KIDNEY DISEASE

What is Diabetic Kidney Disease?

The ADA defined diabetic kidney disease (DKD) as chronic kidney disease (CKD) attributed to diabetes, and CKD as the persistent presence of elevated urinary albumin excretion, low estimated glomerular filtration rate (GFR), or other manifestations of kidney damage.[17]

The Kidney Disease: Improving Global Outcomes (KDIGO) guidelines defined CKD as abnormalities of the kidney structure or function present for $\geq$3 months.[18] In 2007, the KDIGO guidelines recommended using the term "DKD" instead of "diabetic nephropathy" as there is no consensus definition of diabetic nephropathy.[19] In 2020, the KDIGO guidelines used the term "Diabetes and CKD" over "DKD" although DKD was still considered appropriate, to ensure that other causes of CKD are considered and avoid the assumption that all cases of CKD are caused by traditional diabetes pathophysiology.[18]

The Johns Hopkins Diabetes Guide defined DKD as a disease initially characterized by moderately increased urine albumin-to-creatinine ratio (UACR), then severely increased UACR, followed by renal insufficiency, and finally end-stage renal disease (ESRD).[20]

How Common is Diabetic Kidney Disease?

DKD occurs in 20% to 40% of individuals with diabetes.[17] While DKD may be present at the time of diagnosis of T2DM, it usually develops 10 years after the diagnosis of T1DM.[17] DKD remains the leading cause of ESRD in the United States,[17] as more than 50% of individuals on renal replacement therapy have diabetes as the major cause of renal failure.[5]

When should Health Care Providers Initiate Screening for Diabetic Kidney Disease? How Often Should the Screening be Done?

Similar to DSPN, screening for DKD should begin after 5 years from the time of diagnosis of T1DM but at the time of diagnosis of T2DM.[17] In individuals without DKD, annual screening with UACR and creatinine/GFR is recommended. In individuals with DKD, more frequent monitoring is recommended (**Fig. 2**).[17]

How Should the Health Care Providers Interpret the Urine Albumin-to-creatinine Ratio?

- Normal UACR: less than 30 mg/g.
- Moderately increased albuminuria: $\geq$30 mg/g and $\leq$300 mg/g.
- Severely increased albuminuria: greater than 300 mg/g.

Given the high biological variability of greater than 20% between measurements, an abnormal UACR requires 2 to 3 abnormal specimens within a 3 to 6 month period. It

CKD is classified based on: • Cause (C) • GFR (G) • Albuminuria (A)				Albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30–299 mg/g 3–29 mg/mmol	≥300 mg/g ≥30 mg/mmol
GFR categories (mL/min/1.73m²) Description and range	G1	Normal to high	≥90	1 If CKD	Treat 1	Refer* 2
	G2	Mildly decreased	60–89	1 If CKD	Treat 1	Refer* 2
	G3a	Mildly to moderately decreased	45–59	Treat 1	Treat 2	Refer 3
	G3b	Moderately to severely decreased	30–44	Treat 2	Treat 3	Refer 3
	G4	Severely decreased	15–29	Refer* 3	Refer* 3	Refer 4+
	G5	Kidney failure	<15	Refer 4+	Refer 4+	Refer 4+

Fig. 2. Frequency of monitoring renal functions in DKD. The numbers in the boxes are a guide to the frequency of visits (number of times/year). (*From* Chapter 2: Definition, identification, and prediction of CKD progression. *Kidney Int Suppl (2011)*. 2013; 3(1): 63-72; with permission.)

should be noted that the UACR result is also influenced by exercise, infection, fever, congestive heart failure, marked hyperglycemia, marked hypertension, and menstruation.[17]

What is the Likelihood of Diabetic Kidney Disease in Individuals with Moderate/Severe Albuminuria?

Individuals with severely increased albuminuria are likely to have DKD regardless of the GFR.[19] DKD is a possibility in individuals that have CKD3 and moderately increased albuminuria. Individuals with CKD4-5 with moderately increased albuminuria or CKD3-5 with normal albuminuria are unlikely to have DKD, and other etiologies of kidney disease should be explored.[19]

When to Refer to Nephrology?

Referral is recommended for a patient with GFR less than 30 mL/min/1.73 m^2, rapid worsening of UACR or creatinine/GFR, or an uncertain etiology.[17]

How Should the Health Care Providers Monitor Glycemic Control in Individuals with Diabetic Kidney Disease?

Measurement of blood or interstitial glucose via finger stick blood glucose (FSBG) or continuous glucose monitor (CGM) is likely to be accurate in CKD, dialysis, and kidney transplant.[18] While monitoring of hemoglobin A1c continues to be encouraged in DKD, its reliability is low, particularly in advanced DKD (GFR <30 mL/min/1.73 m^2), given the shortened survival of erythrocytes from anemia, transfusions, and use of erythropoiesis-stimulating agents or iron-replacement therapies.[18] The more advanced the kidney disease, the weaker the correlation between FSBG and hemoglobin A1c.[18] Although

monitoring glycemic control via hemoglobin A1c remains the currently recommended approach, CGM is expected to limit/eliminate the use of hemoglobin A1c in the future. Taken altogether, if there is a clinical concern that hemoglobin A1c is inaccurate based on discordance with FSBG levels, it is reasonable to either use FSBG or CGM.

What Measures can Reduce the Risk of Developing Diabetic Kidney Disease?

Nutrition

While lower dietary protein intake may slow the progression of CKD, it may be challenging in individuals with diabetes who are encouraged to limit carbohydrates. In addition, protein intake may help individuals on insulin avoid hypoglycemia.[18] Therefore, individuals with DKD not treated with dialysis should maintain a protein intake of 0.8 g/kg/day similar to that of healthy individuals.[18]

Lipid management

Individuals with DKD are at high risk for cardiovascular disease. Statin therapy has been shown to reduce the risk of cardiovascular and kidney disease.[18]

Blood pressure

It is encouraged to target a blood pressure (BP) <130/80 mmHg, particularly in high-risk individuals with albuminuria, if it can be achieved without complications. In those who cannot achieve a BP <130/80 mmHg, a less strict goal of less than 140/90 mmHg can be recommended.[17]

Glycemic control

Adequate glycemic control may be key to preventing microvascular complications, including DKD; however, targets should be individualized. While a lower hemoglobin A1c target of less than 7.0% may be key in preventing complications, a higher hemoglobin A1c target (<8.0%) might be preferred in individuals with established comorbidities or if they are at increased risk of hypoglycemia.[17,18]

Smoking

Counseling for smoking cessation should be provided.

A 55-year-old Individual with T2DM Treated with Metformin. His Last Creatinine was 1.7 mg/dL, GFR 51 mL/min/1.73 m^2, and UACR 389 mg/g. Should Metformin be Discontinued?

The ADA standards of management recommend the initiation and titration of metformin if GFR is $\geq$45 mL/min/1.73 m^2, to continue use if GFR falls to less than 45 mL/min/1.73 m^2 after reassessing benefits and risk, and to discontinue metformin if GFR is <30 mL/min/1.73 m^2. While the KDIGO guidelines similarly recommend metformin without restrictions when GFR is $\geq$45 mL/min/1.73 m^2, it recommends halving the dose (if already on metformin) or initiating metformin at half the dose and titrating upwards to half of the maximum dose (if not previously on metformin) if the GFR is between 30 to 45 mL/min/1.73 m^2.[18] In individuals with renal transplant, metformin can be used as long as the GFR is $\geq$30 mL/min/1.73 m^2.[18]

How can Health Care Providers Delay Progression of Diabetic Kidney Disease?

Renin–angiotensin system blockade

The use of a renin–angiotensin system (RAS) blocking agent is recommended as the initial drug of choice in DKD. In individuals with diabetes, hypertension, and albuminuria, RAS blockade, resulting from agents such as angiotensin-converting enzyme inhibitors (ACEi) or angiotensin II receptor blockers (ARBs), should be initiated and titrated to the highest approved dose that is tolerated.[18] In individuals with diabetes

and albuminuria but without hypertension, treatment with an ACEi or ARB may be considered.[18] It is recommended to follow-up with a repeat serum potassium and serum creatinine measurements in 2 to 4 weeks after the initiation of ACEi or ARB and to continue use unless the creatinine rise is greater than 30%. If hyperkalemia is noted, the dose of ACEi or ARB may need to be reduced.[18] The combination of ACEi and ARB should be avoided as side effects may be more pronounced.

Sodium–glucose co-transporter-2 inhibitors

In the renal outcome trials, dapagliflozin (DAPA-CKD)[21] and canagliflozin (CREDENCE)[22] showed a significantly lower risk of renal disease worsening. In individuals with DKD, sodium–glucose co-transporter-2 inhibitors (SGLT-2i) should be considered to reduce cardiovascular risk and to delay progression to ESRD provided that GFR is $\geq$25 to 30 mL/min/1.73 m^2 (although continuation with lower GFR is recommended and initiation at lower GFR may be evaluated in the future).[17] While SGLT-2i should be encouraged in DKD, it remains debatable in T1DM given the increased risk for diabetic ketoacidosis. Patients should be educated to withhold SGLT-2is if they cannot maintain adequate hydration (such as before surgery or if sick). In individuals on other diuretics who are at risk for hypovolemia, reducing the dose of diuretic may be reasonable, and close follow-up is encouraged.

What Anti-diabetic Medications Should be Added if Glycemic Control is not Achieved by Metformin and Sodium–glucose Co-transporter-2 Inhibitors?

Glucagon-like peptide-1 receptor agonists (GLP-1RA) may be a preferred agent given the known cardiovascular benefit and possible kidney benefit.[18] If GLP-1RA cannot be used, pioglitazone may be considered, as it delays cardio-renal disease progression. However, pioglitazone should be used with caution as it can cause fluid overload and unmask heart failure.[23,24]

Novel Therapy in Diabetic Kidney Disease

Mineralocorticoid receptor antagonists: In FIDELIO-DKD,[25] patients treated with finerenone had a significant reduction in CKD progression and cardiovascular events. Hyperkalemia remains a concern, particularly when added to RAS blockade. Nevertheless, this may be an option for add-on therapy in the future. This may be specifically beneficial in individuals with DKD and hypertension.[17,18]

DIABETIC RETINOPATHY

What is Diabetic Retinopathy?

The most common diabetes-related eye disease is diabetic retinopathy (DR). DR is characterized by a gradually progressive alteration in the retinal microvasculature resulting in areas of retinal nonperfusion with a resultant increase in vascular endothelial growth factor-A (VEGF). Elevated levels of VEGF can result in abnormal development of new blood vessels (neovascularization). Those new vessels can be friable and bleed into the vitreous cavity, causing vitreous hemorrhage. Vision-threatening DR develops in about 10% of people with diabetes and remains the leading cause of new cases of legal blindness.[26]

When Should Screening Begin and How Frequently Should Testing be Done?

Screening should be performed by an ophthalmologist or optometrist within 5 years from diagnosis of T1DM but at the time of diagnosis of T2DM.[17,27] The eye examination is needed annually for the first 2 years, then every 2 years if no retinopathy is noted and adequate glycemic control has been achieved.[17] Individuals with diagnosed DR

may be followed more frequently.[27] If there is limited access to ophthalmologists or optometrists (eg, in rural communities), digital retinal photography with remote reading may be an option to improve access to ophthalmologic evaluation.[27–29]

Are Pregnant Women Screened Similarly?

Pregnancy can exacerbate DR. Ideally, women planning to become pregnant should have a comprehensive eye examination within 1 year before conception and then again in each trimester.[5,17]

How Should the Health Care Providers Classify Diabetic Retinopathy?

- No apparent DR[30]
- Nonproliferative DR (NPDR): Can be further classified into mild (microaneurysms only), moderate (microaneurysms, blot hemorrhages, hard exudates, cotton wool spots but less than severe), and severe (intraretinal hemorrhages, venous beading) (**Fig. 3**).[30]
- Proliferative DR (PDR): Presence of neovascularization or vitreous/preretinal hemorrhage (**Fig. 4**).[30]

Diabetic macular edema (DME) can develop at any stage of DR. This disease is classified into no DME (no retinal thickening in the macula), noncenter involving DME (retinal thickening in the macula that does not involve the central zone), and center-involving DME (retinal thickening in the macular that involves the central zone that is 1 mm in diameter).

What is the Role of the Health Care Providers in Preventing/Treating Diabetic Retinopathy?

Ensure regular eye examination

Many individuals with DME are not aware that diabetes has affected their eyes, and many with PDR have not been examined by an ophthalmologist within the last 2 years.[5]

Hyperglycemia

The longer the duration of hyperglycemia and the worse the glycemic control, the greater the risk for developing DR.[27] Lowering hemoglobin A1c has been shown to prevent and delay the progression of DR. A target hemoglobin A1c <7.0% is considered ideal; however, any reduction in hemoglobin A1c can be beneficial.[27] It should be noted that the rapid correction of long-standing hyperglycemia may be associated with transient worsening of retinopathy. While any antidiabetic medication can be used, pioglitazone and semaglutide should be used with caution as DME was reported in individuals on pioglitazone and worsening retinopathy may be associated with semaglutide, although more research is needed.

Blood pressure control

Achieving a systolic blood pressure of less than 130 mmHg has been shown to slow the progression of DR. While controlling the blood pressure reduces retinopathy, the use of RAS inhibitors specifically has been shown to reduce the incidence and risk of progression of DR.[31]

Lipid control

Treatment with the peroxisome proliferative-activated receptor gamma (PPAR-α) agonist, fenofibrate, reduced the risk of progression by up to 40% among patients with NPDR.[31]

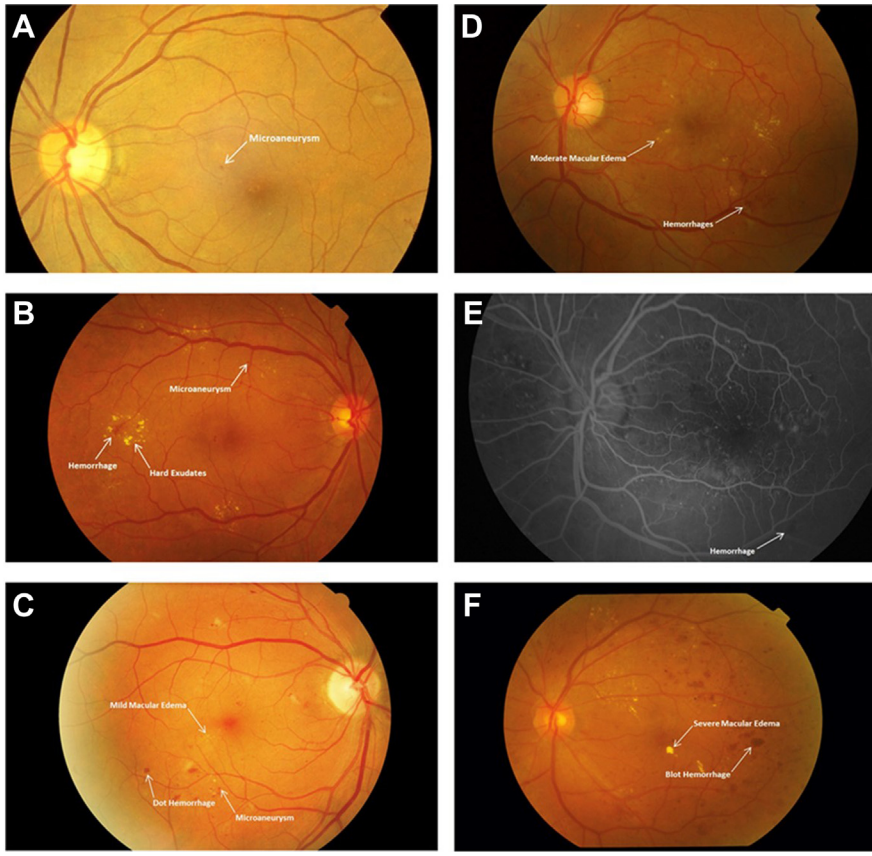

Fig. 3. Features of mild and moderate to severe stages of NPDR. (*A*) Fundus photograph showing mild NPDR with microaneurysms. (*B*) Fundus photograph showing moderate NPDR with hemorrhages, hard exudates, and microaneurysms. (*C*) Fundus photograph showing moderate NPDR with mild DME. (*D*) Fundus photograph showing moderate macular edema. (*E*) Fluorescein angiogram showing moderate NPDR with non–center-involving DME. (*F*) Fundus photograph showing severe NPDR with center-involving DME. (*From* Wong TY, Sun J, Kawasaki R, Ruamviboonsuk P, Gupta N, Lansingh VC, Maia M, Mathenge W, Moreker S, Muqit MMK, Resnikoff S, Verdaguer J, Zhao P, Ferris F, Aiello LP, Taylor HR. Guidelines on Diabetic Eye Care: The International Council of Ophthalmology Recommendations for Screening, Follow-up, Referral, and Treatment Based on Resource Settings. Ophthalmology. 2018 Oct; 125(10): 1608-1622; with permission.)

Lifestyle modifications

Regular exercise is encouraged in individuals with or without retinopathy, as it may prevent and/or delay the progression of retinopathy. In individuals with PDR, activities resulting in a Valsalva maneuver should be avoided as they may result in vitreous hemorrhage. Smoking cessation should be encouraged in individuals who smoke.

What are the Treatment Options for Diabetic Retinopathy?

If the measures above fail to prevent or control DR, laser photocoagulation and anti-VEGF therapy may be used for treatment. Pan-retinal laser photocoagulation is used to treat high-risk PDR and occasionally for severe NPDR.[30] While pan-retinal laser photocoagulation is still commonly used to manage PDR, the use of anti-VEGF

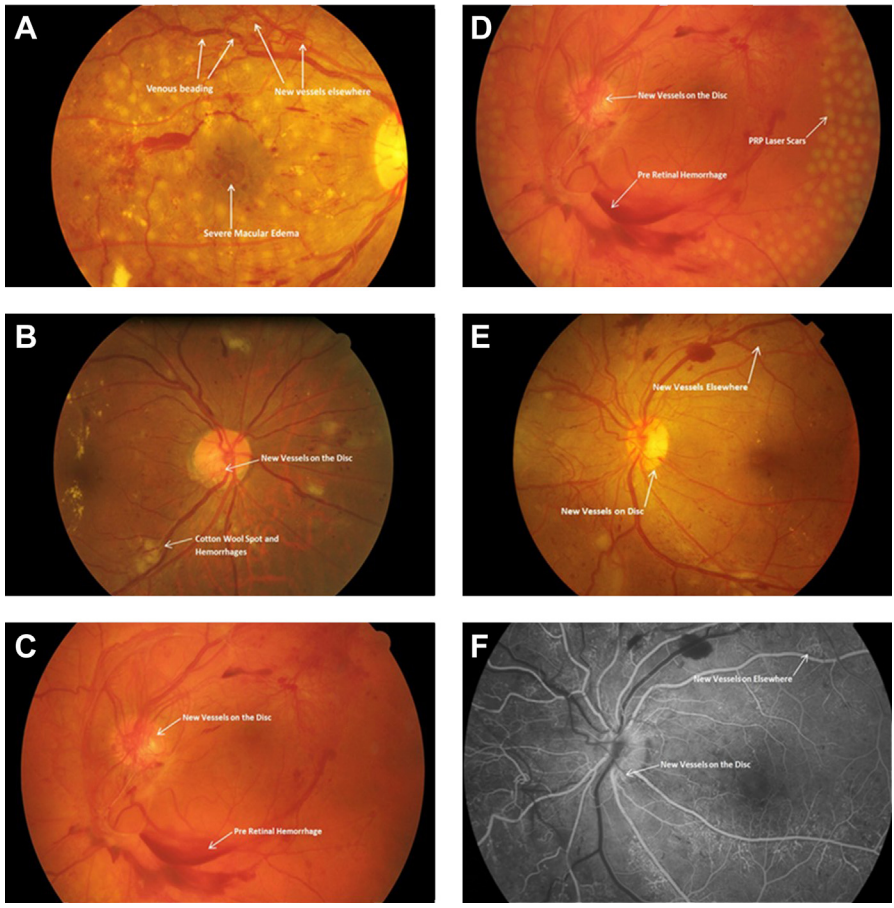

Fig. 4. Features of severe stages of PDR and DME. (*A*) Fundus photograph showing PDR with venous beading, new vessels elsewhere, and severe DME. (*B*) Fundus photograph showing high-risk PDR with new vessels at the disc. (*C*) Fundus photograph showing high-risk PDR with preretinal hemorrhage and new vessels on the disc. (*D*) Fundus photograph showing high-risk PDR with new panretinal photocoagulation (PRP) scars. (*E*) Fundus photograph showing PDR. New vessels seem on the disc and elsewhere. (*F*) Fluorescein angiogram showing PDR. New vessels seem on the disc and elsewhere. (*From* Wong TY, Sun J, Kawasaki R, Ruamviboonsuk P, Gupta N, Lansingh VC, Maia M, Mathenge W, Moreker S, Muqit MMK, Resnikoff S, Verdaguer J, Zhao P, Ferris F, Aiello LP, Taylor HR. Guidelines on Diabetic Eye Care: The International Council of Ophthalmology Recommendations for Screening, Follow-up, Referral, and Treatment Based on Resource Settings. Ophthalmology. 2018 Oct; 125(10): 1608-1622; with permission.)

therapy was associated with a rapid regression of retinal neovascularization.[27,30] Anti-VEGF agents are the current standard of care for central-involved DME.[27]

SUMMARY

In summary, microvascular complications including DSPN, DKD, and DR are common in patients with long-standing type 1 diabetes and new or existing type 2 diabetes and require active screening. Complications can be prevented or delayed by careful

attention to risk factors, careful education and monitoring by the patient, and prompt evaluation and treatment by consultants when indicated. This evaluation, monitoring, prevention, and treatment can help improve patients' quality of life and can be associated with reductions or delays in treatments such as dialysis with reduced cost.

CLINICS CARE POINTS

- Screening for diabetes-related microvascular complications should start immediately at the time of diagnosis of T2DM and within 5 years after the diagnosis of T1DM.

DSPN:

- Screening for DSPN is essential as around 50% of individuals with DSPN are asymptomatic and will not volunteer symptoms.
- Before diagnosing DSPN, HCP may need to rule out other causes of neuropathy.
- In clinical practice, nerve conduction studies and skin biopsy are rarely indicated.
- In individuals with DSPN, an annual foot examination may not be adequate and exam/inspection at every visit is suggested.
- Patients should be encouraged to check their feet daily.
- Foot care education should be provided to the patient at least at the initial visit and as indicated.
- In individuals who are at high risk for ulceration and amputations, HCP should prescribe diabetic shoes and consider a podiatry referral.

DKD:

- In individuals without DKD, annual serum creatinine and UACR are required.
- An abnormal UACR requires 2 to 3 abnormal specimens within a 3- to 6-month period to confirm the diagnosis of albuminuria.
- If the GFR is < 30 mL/min/1.73 m^2, there is a rapid worsening of renal functions, or the etiology is unclear, the patient should be referred to nephrology.
- The reliability of hemoglobin A1c is low in advanced DKD.
- In individuals with DKD, RAS blockade agent and/or SGLT-2i are recommended. Finerenone can reduce CKD progression and cardiovascular events.

DR:

- An eye examination by an expert is needed at least annually for the first 2 years.
- Individuals with diagnosed DR may require a more frequent monitoring schedule.
- Digital retinal photography with remote reading may be an option in locations with limited access to ophthalmologic evaluation.
- In patients seeking pregnancy, a comprehensive eye examination within 1 year before conception and then during pregnancy is indicated as pregnancy may exacerbate DR.
- The use of RAS inhibitor has shown to reduce the incidence and risk of progression of DR.

DISCLOSURE

BMM has served on Advisory Board Panels for AstraZeneca and Bayer with the consulting fees paid directly to East Carolina University. BMM also received a research grant (to East Carolina University) from Eli Lilly and Company.

DMC and JRP report no conflict of interest.

REFERENCES

1. Pop-Busui R, Boulton AJ, Feldman EL, et al. Diabetic neuropathy: a position statement by the American Diabetes Association. Diabetes Care 2017;40(1): 136–54.
2. Feldman EL, Callaghan BC, Pop-Busui R, et al. Diabetic neuropathy. Nat Rev Dis Primers 2019;5(1):41.
3. England JD, Gronseth GS, Franklin G, et al. Distal symmetric polyneuropathy: a definition for clinical research: report of the American Academy of Neurology, the American Association of Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation. Neurology 2005;64(2):199–207.
4. England JD, Gronseth GS, Franklin G, et al. Practice parameter: evaluation of distal symmetric polyneuropathy: role of autonomic testing, nerve biopsy, and skin biopsy (an evidence-based review). Report of the American Academy of Neurology, American Association of Neuromuscular and Electrodiagnostic Medicine, and American Academy of Physical Medicine and Rehabilitation. Neurology 2009;72(2):177–84.
5. Brownlee M, Aiello LP, Cooper ME, et al. Complications of diabetes mellitus. In: Williams Textbook of Endocrinology. 13th edition; 2016. p. 1484.
6. Vinik AI, Nevoret ML, Casellini C, et al. Diabetic neuropathy. Endocrinol Metab Clin North Am 2013;42(4):747–87.
7. Boulton AJ, Armstrong DG, Albert SF, et al. Comprehensive foot examination and risk assessment: a report of the task force of the foot care interest group of the American Diabetes Association, with endorsement by the American Association of Clinical Endocrinologists. Diabetes Care 2008;31(8):1679–85.
8. Feng Y, Schlösser FJ, Sumpio BE. The Semmes Weinstein monofilament examination as a screening tool for diabetic peripheral neuropathy. J Vasc Surg 2009;50(3):675–82, 682.e1.
9. Jeng C, Michelson J, Mizel M. Sensory thresholds of normal human feet. Foot Ankle Int 2000;21(6):501–4.
10. Olaiya MT, Hanson RL, Kavena KG, et al. Use of graded Semmes Weinstein monofilament testing for ascertaining peripheral neuropathy in people with and without diabetes. Diabetes Res Clin Pract 2019;151:1–10.
11. Tanenberg R, Donofrio PD. Neuropathic problems of the lower limbs in diabetic patietns. In: The diabetic foot. 7th edition; 2008. p. 33–40.
12. Miller JD, Carter E, Shih J, et al. How to do a 3-minute diabetic foot exam. J Fam Pract 2014;63(11):646–56.
13. Takahara M, Fujiwara Y, Sakamoto F, et al. Assessment of vibratory sensation with a tuning fork at different sites in Japanese patients with diabetes mellitus. J Diabetes Invest 2014;5(1):90–3.
14. Prabhakar AT, Suresh T, Kurian DS, et al. Timed vibration sense and joint position sense testing in the diagnosis of distal sensory polyneuropathy. J Neurosci Rural Pract 2019;10(2):273–7.
15. Thomson MP, Potter J, Finch PM, et al. Threshold for detection of diabetic peripheral sensory neuropathy using a range of research grade monofilaments in persons with Type 2 diabetes mellitus. J Foot Ankle Res 2008;1(1):9.
16. van Netten JJ, Lazzarini PA, Armstrong DG, et al. Diabetic foot Australia guideline on footwear for people with diabetes. J Foot Ankle Res 2018;11:2.
17. American Diabetes Association. 11. Microvascular complications and foot care: standards of medical care in diabetes-2021. Diabetes Care 2021;44(Suppl 1): S151–67.

18. KDIGO 2020 clinical practice guideline for diabetes management in chronic kidney disease. Kidney Int 2020;98(4s):S1–115.
19. KDOQI clinical practice guidelines and clinical practice recommendations for diabetes and chronic kidney disease. Am J Kidney Dis 2007;49(Suppl 2): S12–154.
20. Knicely DH, Myers D. Diabetic kidney disease. Johns Hopkins Diabetes Guide; 2019. Johns Hopkins Guide. Available at: www.hopkinsguides.com/hopkins/view/Johns_Hopkins_Diabetes_Guide/547097/all/Diabetic_Kidney_Disease. July 4, 2021.
21. Heerspink HJL, Stefánsson BV, Correa-Rotter R, et al. Dapagliflozin in patients with chronic kidney disease. N Engl J Med 2020;383(15):1436–46.
22. Perkovic V, Jardine MJ, Neal B, et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. N Engl J Med 2019;380(24):2295–306.
23. DeFronzo RA, Inzucchi S, Abdul-Ghani M, et al. Pioglitazone: the forgotten, cost-effective cardioprotective drug for type 2 diabetes. Diabetes Vasc Dis Res 2019; 16(2):133–43.
24. Schneider CA, Ferrannini E, Defronzo R, et al. Effect of pioglitazone on cardiovascular outcome in diabetes and chronic kidney disease. J Am Soc Nephrol 2008; 19(1):182–7.
25. Bakris GL, Agarwal R, Anker SD, et al. Effect of finerenone on chronic kidney disease outcomes in type 2 diabetes. N Engl J Med 2020;383(23):2219–29.
26. Yau JW, Rogers SL, Kawasaki R, et al. Global prevalence and major risk factors of diabetic retinopathy. Diabetes Care 2012;35(3):556–64.
27. Solomon SD, Chew E, Duh EJ, et al. Diabetic retinopathy: a position statement by the American Diabetes Association. Diabetes Care 2017;40(3):412–8.
28. Cummings DM, Morrissey S, Barondes MJ, et al. Screening for diabetic retinopathy in rural areas: the potential of telemedicine. J Rural Health 2001;17(1):25–31.
29. Newman R, Cummings DM, Doherty L, et al. Digital retinal imaging in a residency-based patient-centered medical home. Fam Med 2012;44(3):159–63.
30. Wong TY, Sun J, Kawasaki R, et al. Guidelines on diabetic eye care: the international council of ophthalmology recommendations for screening, follow-up, referral, and treatment based on resource settings. Ophthalmology 2018; 125(10):1608–22.
31. Antonetti DA, Klein R, Gardner TW. Diabetic retinopathy. N Engl J Med 2012; 366(13):1227–39.