CME Screening and Management of Diabetic Microvascular Complications in Older Adults

Microvascular complications of both Type 1 and Type 2 diabetes mellitus (DM) can be classified into three major categories: retinopathy, nephropathy and neuropathy. Numerous studies have consistently shown that the development of complications in both Type 1 and Type 2 diabetes is related to several factors. The most important ones, however, include glycemic control (as measured by hemoglobin A1c) and the duration of diabetes. This article reviews the details of screening and management of diabetic microvascular complications in older adults. It incorporates guidelines from both the Canadian and American Diabetes Associations, as well as reviews of recently published literature.

Key words: *diabetes mellitus, retinopathy, nephropathy, neuropathy, screening, management.*

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Diabetes mellitus (DM) exerts its deleterious effects through the development of long-term macrovascular and microvascular complications. Macrovascular complications include coronary artery disease and peripheral vascular disease, while microvascular disease includes retinopathy, nephropathy and neuropathy.

Retinopathy

Diabetic retinopathy is an important long-term complication of DM and is the most frequent cause of new cases of blindness among adults 20–74 years of age (Figure 1).[1] The mortality rate of patients with diabetic retinopathy is much higher than that of the general population.[2] Eye disease in general is much more common among older adults than in younger populations, and studies by Whitmore[3] and Mitchell, *et al.*[4] have shown that the prevalence is even higher in nursing home residents. Many of these eye conditions are potentially treatable. In the Oulu Eye Study, a 21% prevalence of diabetic retinopathy was found in individuals with diabetes aged 70 years or older.[5] An important point to note is that most patients are asymptomatic at the time that background diabetic retinopathy is detected. By the time patients notice any visual deterioration, retinopathy is usually well advanced.[6]

Screening

In a cost-effectiveness analysis, Javitt, *et al.* calculated that screening for diabetic retinopathy was a cost-effective health care intervention.[7] Arun, *et al.* showed that a retinal screening program for adults with Type 2 DM could reduce the incidence of blindness and partial loss of sight by up to one-third.[8]

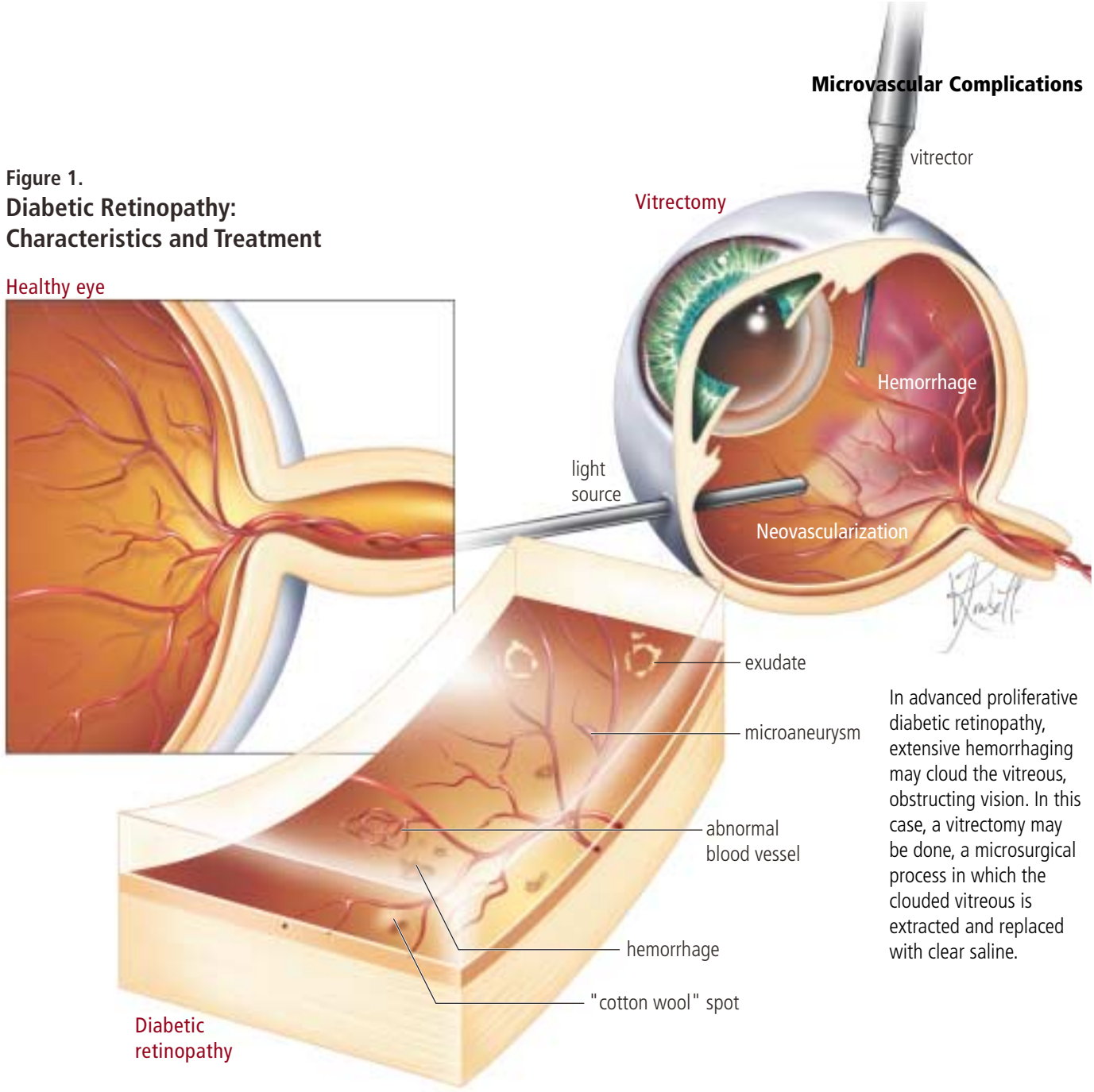
Older adults with Type 1 and Type 2 DM should be screened yearly for diabetic retinopathy through a dilated ophthalmologic examination. Early referral to an ophthalmologist is important, as a significant proportion of individuals with Type 2 DM will have baseline retinopathy at the time of diagnosis. In the United Kingdom Prospective Diabetes Study (UKPDS), at the time of diabetes diagnosis retinopathy was present in 39% of men and 35% of women. More advanced retinopathy with cotton wool spots or intraretinal microvascular abnormalities was present in 8% of men and 4% of women.[9]

Treatment

Individuals with either proliferative or non-proliferative diabetic retinopathy need close follow-up. The specifics surrounding the treatment of diabetic retinopathy are beyond the scope of this review, but in general treatment involves panretinal and/or focal laser photocoagulation. Appropriately timed panretinal photocoagulation has been shown to reduce the risk of vision loss from proliferative diabetic retinopathy compared to indefinite deferral.[10] Even subtle retinal changes such as the presence of microaneurysms are important, as these have a high predictive value for the future development of progressive retinopathy.[11]

Clearly, a major modality used to treat and prevent diabetic retinopathy includes strict glycemic control (Table 1). In the case of Type 1 DM, the Diabetes Control and Complications Trial (DCCT) showed that intensive glycemic control compared with conventional glycemic control reduced the progression of retinopathy by 76% in the primary prevention cohort (no retinopathy at baseline), and by 54% in the secondary intervention cohort (mild to moderate retinopathy at baseline).[12,13] The UKPDS, a study of blood pressure (BP) and glycemic control in older adults with Type 2 DM, demonstrated a 25% reduction in microvascular complications in patients receiving intensive

Figure 1.
Diabetic Retinopathy: Characteristics and Treatment



In advanced proliferative diabetic retinopathy, extensive hemorrhaging may cloud the vitreous, obstructing vision. In this case, a vitrectomy may be done, a microsurgical process in which the clouded vitreous is extracted and replaced with clear saline.

glucose-lowering therapy versus conventional therapy. The median HbA1c in the intensive glucose control group was 7.0% compared with a median HbA1c of 7.9% in the conventional glucose control group.[14]

In the blood pressure arm of the UKPDS, 1,148 hypertensive patients with Type 2 DM were divided into two groups and followed for a median of 8.4 years: 758 patients were allocated to tight BP control (target of < 150/85mmHg; mean BP achieved at follow-up = 144/82) and 390 patients were assigned to less stringent BP control (target of < 180/105; mean BP achieved at follow-up = 154/87). In the group with a lower BP target, there was a risk reduction of 24% in diabetes-related endpoints, 32% in mortality related to diabetes, 44% in stroke and 37% in microvascular endpoints over the study period. The reduction in microvascular endpoints was predominantly owing to a reduced risk of retinal photocoagulation.[15] After nine years of follow-up, the group assigned to tight BP control also had a 34% risk reduction in deterioration of retinopathy by two steps, and a 47% reduced risk of deterioration in visual acuity by three lines (equivalent to a change from 6/6 to 6/12 on the Snellen chart). The results suggested that tight BP control also prevented the development of diabetic maculopathy, which is the predominant cause of visual impairment in Type 2 DM. The UKPDS gave concrete evidence that the incidence and development of diabetic retinopathy can be reduced by tight BP control.[16] From a clinical perspective, it is important to note that 25–33% of patients needed three or more antihypertensive drugs in order to meet target BP values.

The Early Treatment of Diabetic Retinopathy Study was a randomized trial of aspirin 650mg per day versus placebo in 3,711 patients with mild to severe non-proliferative or early proliferative diabetic retinopathy. Aspirin did not alter the course of diabetic retinopathy, nor did it have

Table 1: Levels of Glucose Control for Older Adults with Diabetes Mellitus

	A1c* (%)	Fasting plasma/preprandial plasma glucose (mmol/L)	2-hour postprandial plasma glucose (mmol/L)
Target for most patients	≤ 7.0	4.0–7.0	5.0–10.0
Normal range (consider for patients in whom it can be achieved safely)	≤ 6.0	4.0–6.0	5.0–8.0

* An A1c of 7.0% corresponds to a laboratory value of 0.07.

Adapted from the 2003 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada published in the December 2003 issue of the *Canadian Journal of Diabetes*. It must be kept in mind that clinical judgement is required to determine which people can reasonably and safely achieve these targets. Treatment goals and strategies must be tailored to the patient, with consideration given to individual risk factors.

any clinically important harmful effects for patients with retinopathy.[17] The study concluded that there were no ocular contraindications to aspirin if it was required for cardiovascular disease protection. Finally, serum lipids also have been postulated to play a role in either the development and/or the progression of diabetic retinopathy,[18] but to date only one small study has shown a significant benefit of lipid-lowering agents on the progression of retinopathy.[19] The Working Group on Hypercholesterolemia and Other Dyslipidemias recently released new recommendations for the management of dyslipidemia. Adults with DM are considered to be at high risk of developing coronary artery disease; the target LDL cholesterol in these individuals is < 2.5mmol/L and the target total cholesterol:HDL cholesterol ratio is less than 4.0.[20]

Summary

To summarize, in any patient with diabetic retinopathy, both hyperglycemia and hypertension should be treated aggressively (Table 2, page 26). Ophthalmological assessment and follow-up are critical. Lipid-lowering agents may be helpful, but their potential role requires further evaluation before they can be recommended as a part of standard care.

Nephropathy

Diabetes is the single most common cause of end-stage renal disease in the Western world. Furthermore, proteinuria is the single most powerful predictor of end-stage renal disease in patients with diabetes.[21] Diabetic nephropathy begins with the excretion of low amounts of albumin (protein) in the urine. This is referred to as microalbuminuria and is defined as excretion of between 30 and 299mg/day of protein. It is important to remember that regular urine dipsticks are not adequately sensitive to detect microalbuminuria.

Microalbuminuria in both Type 1 and Type 2 diabetes was originally thought to be a marker for progressive disease, culminating eventually in end-stage renal failure. Recent evidence, however, suggests that microalbuminuria may show frequent regression.[22] Although the predictive or determining factors of progressive nephropathy are not yet completely understood, glucose control, blood pressure control and hyperlipidemia may all contribute, as for retinopathy. Nonetheless, the presence of microalbuminuria, apart from signaling renal injury, is a predictive marker for early mortality from cardiovascular disease.[23] In contrast, macroproteinuria—that is, a positive dipstick and quantitatively measuring > 300mg per day—is consistently associated with advanced nephropathy.

Ten years following the diagnosis of Type 2 diabetes in the UKPDS cohort, the prevalence of microalbuminuria was 24.9%, of macroalbuminuria was 5.3% and of elevated plasma creatinine or renal replacement therapy was 0.8%. Importantly, patients who have an elevated creatinine (≥ 175µmol/L) have been reported to have an annual death rate of 19.2%, and there is a strong correlation between worsening nephropathy and increasing risk of cardiovascular death.[24]

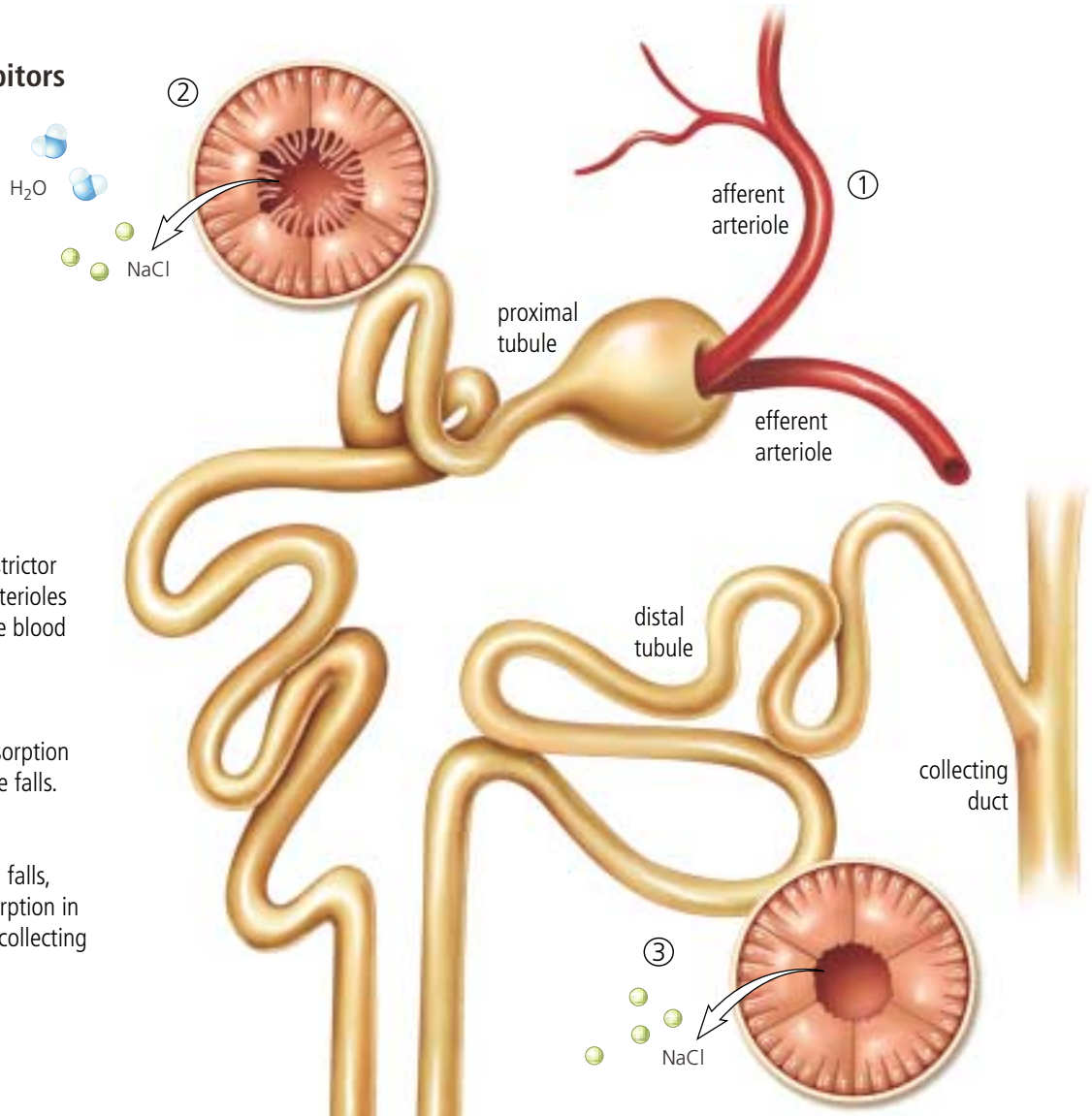
Screening

Screening for microalbuminuria should be performed at the time of diagnosis in those with Type 2 DM, and five years after diagnosis in those with Type 1 DM. If the initial screening is negative, then subsequent screening should be carried out on a yearly basis.

There are three generally accepted modalities for screening. A spot urine collection is easily performed in the ambulatory clinic setting. A diagnosis of microalbuminuria is made when the ratio of albumin to creatinine is 2–20mg/mmol in men and 2.8–28mg/mmol in women.

A 24-hour urine collection for microalbumin, creatinine and creatinine clearance is another screening modality but logistically is somewhat more cumbersome. An excretion of < 30mg/24hr of albumin is considered normal. A microal-

Figure 2.
Action of ACE Inhibitors for Treatment of Nephropathy



① Angiotensin vasoconstrictor effects on systemic arterioles are lifted and arteriole blood pressure falls.

② NaCl and water reabsorption by the proximal tubule falls.

③ Aldosterone secretion falls, reducing NaCl reabsorption in the distal tubule and collecting duct.

bumin concentration of 30–299mg/24hr establishes the diagnosis of microalbuminuria.

Finally, a timed urine collection (e.g., 4-hour, or overnight 12-hour) is consistent with microalbuminuria when the microalbumin concentration is 20–199µg/min. It should be emphasized that short-term hyperglycemia, recent exercise, urinary tract infections, heart failure, marked hypertension, hematuria and many acute febrile illnesses may result in a positive test for microalbuminuria and should be taken into consideration when screening is done. Some sources advocate performing a spot urine collection initially and then following up positive screening results with either a 24-hour collection or a timed overnight collection.[25] Due to the frequent difficulty in achieving accurate timed or 24-hour collections in older adults, serial spot urines, as long as albumin is corrected for creatinine, is a fairly reliable method for diagnosis and follow-up.

Treatment

Tight blood sugar control (Table 1) will reduce the rate of development and progression of nephropathy in both Type 1 and Type 2 DM. In Type 1 DM, the DCCT showed that intensive glycemic control decreased the development of microalbuminuria in the entire cohort by 39% and the development of clinical albuminuria (> 300mg/day) by 56%. For each 10% decrease in HbA1c, there was a 25% decrease in the risk of microalbuminuria.[26] For Type 2 DM, the UKPDS also showed a significant reduction in the progression of albuminuria in the intensive blood sugar treatment group.[14]

The relationship between hypertension and the development and progression of diabetic nephropathy has been well documented. Both systolic and diastolic hypertension significantly accelerate the progression of nephropathy. For this reason, blood pressure control is an integral component of the management of nephropathy in both Type 1 and Type 2 diabetes. Provided there

are no contraindications, angiotensin-converting enzyme (ACE) inhibitors are the choice for first-line therapy for individuals with diabetic nephropathy. ACE inhibitors not only improve blood pressure, but also slow the progression of diabetic nephropathy (Figure 2).[27]

There is increasing evidence that angiotensin-receptor blockers (ARBs) also prevent the progression of renal disease in patients with Type 1 and Type 2 diabetic nephropathy.[28-31] Recent studies have shown a benefit with the addition of an ARB to the therapy of patients with diabetic nephropathy (both Type 1 and Type 2) who are already being treated with an ACE inhibitor,[32,33] presumably due to incomplete blockage of angiotensin II production and/or action by either agent alone. It has been postulated that the renal protection afforded from both these agents is independent of their blood pressure-lowering capabilities. Although the use of this combination is not yet widespread, it is most indicated in cases of refractory hypertension and/or progressive proteinuria. However, it may be limited by hyperkalemia or, in some cases, by hypotension. Thus, special care must be taken in older diabetic patients.

Most individuals with DM will need multiple pharmacological agents in order to achieve target BP goals of < 130mmHg systolic and < 80mmHg diastolic.[34] In the UKPDS, each 10mmHg decrease in mean systolic BP was associated with a 12% risk reduction for any complication related to diabetes, 15% for deaths due to diabetes, 11% for myocardial infarction and a 13% risk reduction for microvascular complications.[35] It should be noted that there was no difference in outcomes for treatment based on the ACE inhibitor captopril versus the beta-blocker atenolol as the first agent of choice.[36] However, this may have been due to the fact that the majority of subjects in both groups ended up on multiple medications. Nonetheless, the clinical benefit of lowering BP is paramount.

Those with progressive nephropathy and/or worsening renal function despite treatment will need further specialized management. Early referral to a nephrologist should be made when there is significant proteinuria, a significantly reduced glomerular filtration rate (GFR) or ongoing problems with either hyperkalemia or difficult-to-manage hypertension.

With respect to the relationship between lipids and the progression of renal disease, the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group (DCCT/EDIC) showed that total triglycerides and total and LDL cholesterol, but not HDL cholesterol, were associated with albumin excretion rate and diabetic nephropathy.[37] In a cohort of 1,253 patients with Type 2 DM, elevated apolipoprotein B, lower HDL and higher fibrinogen levels were independently associated with progres-

Table 2: Summary of Recommendations for Screening and Management for Retinopathy, Nephropathy and Neuropathy

	Retinopathy	Nephropathy	Neuropathy
Frequency of screening	– yearly by ophthalmologist – more frequent follow-up if abnormalities detected	– yearly urine sample for albumin:creatinine ratio (normal is < 2mg/mmol for men and < 2.8 for women) – blood pressure measurement at every clinic visit	– yearly foot examination to check for skin integrity, bony deformities, sensation to pain, sensation to monofilament, vibration testing, deep tendon reflexes
Treatment of complications	– optimize blood sugar control, lipids and blood pressure – panretinal or focal laser photocoagulation at the discretion of ophthalmologist	– optimize blood sugar control and lipids – ACE inhibitor or ARB as first-line agents if microalbuminuria present (regardless of blood pressure); may need multiple medications to reach target blood pressure – treat hypertension if present (target BP < 130/80mmHg), regardless of microalbuminuria status	– optimize blood sugar control – education on proper foot care
Referrals	– ophthalmologist	– nephrologist if significant proteinuria, significantly reduced glomerular filtration rate, difficulty controlling BP despite multiple medications, elevated serum creatinine or significant hyperkalemia	– neurologist – chiropodist/podiatrist – foot care program

sion to overt nephropathy.[38] Although controlled prospective intervention trials have not been performed, this data strongly suggest a benefit from treating hyperlipidemia in cases of nephropathy.

Summary

In summary, screening of older patients with DM for microalbuminuria and follow-up annually thereafter with at least spot urine samples are indicated (Table 2). Attempts to optimize glycemic control, blood pressure and correction of hyperlipidemia will decrease the rate of development and progression of nephropathy and associated end-stage renal disease.

Neuropathy

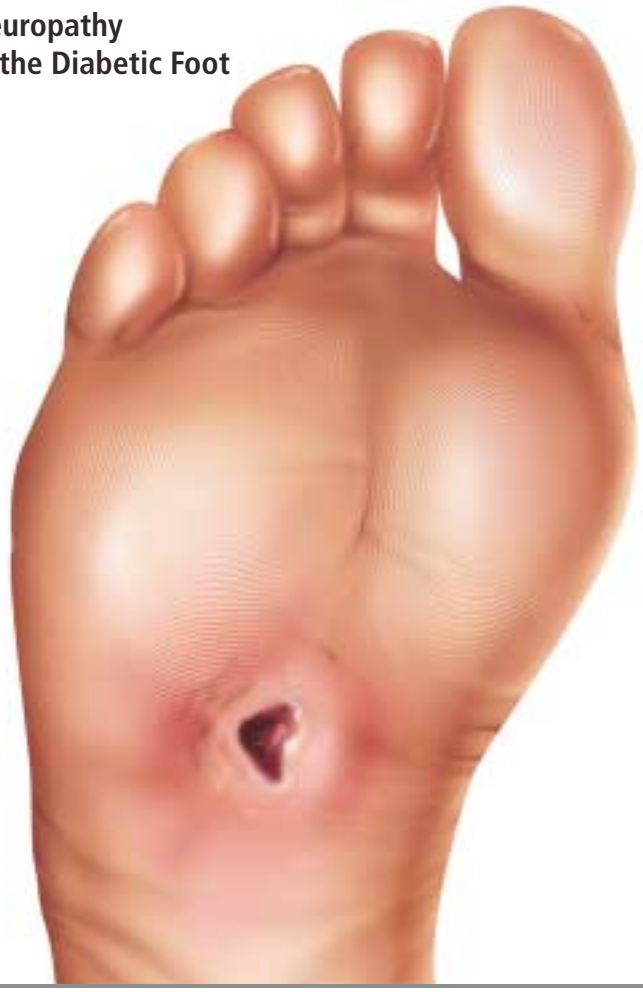
Diabetic neuropathy can present in many forms, but the most common is a distal symmetric polyneuropathy that affects both sensory and motor fibres. Neuropathy is common in both types of diabetes and, similar to many microvascular complications, has a greater prevalence among those with diabetes of longer duration and poorer metabolic control. Among 8,757 individuals (median age 56 years) with both Type 1 (15%) and Type 2 (85%) DM, an overall prevalence of diabetic neuropathy was found to be 32.3% using nerve conduction studies and neurological examination.[39]

Screening

Screening for neuropathy can be carried out using several modalities, including symptom assessment, nerve conduction studies and clinical examination. Since many patients with neuropathy are asymptomatic, relying on symptoms alone as a diagnostic tool is not reliable. Perkins, *et al.*[40] found that the 10g monofilament, vibration testing and superficial pain testing all had high specificity for the diagnosis of neuropathy.

Although there are no formal guidelines for the screening of neuropathy, the older adult with DM should have a careful foot examination at least once a year to assess for skin integrity, bony deformity, loss of sensation (monofilament, pain and vibration) and deep tendon reflexes. When appropriate, individuals should be referred to a neurologist, foot specialist or chiropodist for further diagnosis and management. Early detection of diabetic peripheral neuropathy and enrolment in a comprehensive foot care program has been

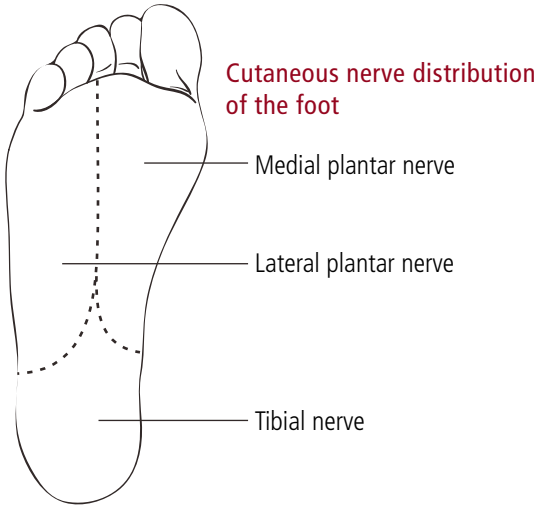
Figure 3.
Neuropathy in the Diabetic Foot



Ulcerated foot

A common complication of diabetes is neuropathy, often in the feet. Sensory neuropathy allows trauma to occur in the feet from ill-fitting shoes, for example. This may lead to ulcer formation, spur formation and bone fragmentation.

Annual screening for neuropathy in diabetic patients, such as with vibration testing or superficial pain testing, is of paramount importance.



shown to decrease the incidence of foot ulceration in people with diabetic neuropathy (Figure 3).[41]

Treatment

Similar to the many other complications of diabetes, there is a strong relationship between neuropathy and blood sugar control (Table 1). HbA1c has consistently been shown to be related to the incidence, severity and prevalence of diabetic neuropathy in multiple epidemiological studies. Although neuropathy was not a primary endpoint in the UKPDS, intensive blood glucose treatment resulted in a 40% relative risk reduction in deterioration of sensory nerve function as measured by a biothesiometer, compared to conventional treatment.[14]

In contrast to retinopathy and nephropathy, blood pressure control has not been associated with the progression of neuropathy. On the other hand, animal studies and some human data suggest the involvement of oxidative stress in the pathogenesis of neuropathy. In small studies, antioxidants such as alpha-lipoic acid have shown symptomatic benefit in diabetic neuropathy.[42] Similarly, aldose reductase inhibitors also have been found to inhibit progression of neuropathy, and at least one, sorbinil, has been approved for use in some countries other than Canada or the U.S. At this point, these therapies remain experimental.

Other than striving to obtain the best glycemic control possible, the management of painful diabetic neuropathy is challenging. There is, however, some evidence that agents such as tricyclic antidepressants, selective serotonin re-uptake inhibitors (e.g., paroxetine), anti-convulsants (e.g., gabapentin, phenytoin, lamotrigine and carbamazepine), nerve stimulation modalities (e.g., transcutaneous electrical nerve stimulation) and narcotic agents have beneficial effects. These are all summarized in an excellent recent review by Spruce, *et al.*[43] In a patient with painful diabetic neuropathy that is severe enough to disturb sleep, a reasonable approach would be to start with a low dose of a tricyclic antidepressant, such as amitriptyline, imipramine or nortryptyline. An increase in the dose over three to four weeks is usually necessary before maximum efficacy and tolerance are achieved. Gabapentin is an alternative and/or additional treatment, especially in those patients with more acute pain. In those who have severe but intermittent breakthrough pain, an opiate analgesic such as codeine can be used, but caution must be taken, especially in older patients. Topical creams such as capsaicin are difficult to apply and have not been particularly useful.

A frequent neuropathic complication is impotence. Diabetes is one of the greatest risk factors for erectile dysfunction (ED). In fact, it is estimated that between 25% and 75% of men with Type 2 DM will complain of ED at some point.[44] In the earliest stage, when ED is partial, there may be a good response to phosphodiesterase inhibitors such as sildenafil, vardenfil or tadalafil. Several studies have shown that these medications are well tolerated and can improve erectile dysfunction in men with both Type 1 and Type 2 diabetes.[45-47] It is important to remember that these agents are contraindicated in people taking nitrates in any form, and should be used cautiously in patients with concomitant hypertension or heart disease, both of which are common in older adults. Once impotence has been present for months or years, these agents are generally ineffective. Intracorporeal or intraurethral injection of prostaglandin-derived vasodilators may be attempted, but are often not accepted by and/or are ineffective in older patients.

More advanced, severe autonomic neuropathy may be manifested by postural hypotension, dizziness and falls. The easiest screening test is to monitor the R-R interval variability during respiration on the electrocardiogram, which is lost in cardiac autonomic neuropathy. Cardiac autonomic neuropathy results from damage to the autonomic nerve fibres that innervate the heart and blood vessels. Other clinical manifestations of this form of autonomic neuropathy include exercise intolerance, intraoperative cardiovascular complications and silent myocardial ischemia and myocardial infarction. This condition is associated with increased mortality, particularly during surgical procedures. A recent meta-analysis found an association between cardiovascular autonomic neuropathy and increased risk of mortality in patients with diabetes.[48] Cardiac autonomic neuropathy also plays a role in the high mortality rate seen in patients with diabetes after acute myocardial infarction.[49] Cardiovascular autonomic neuropathy creates difficulty in treating hypertension since supine blood pressure may be significantly elevated in the presence of low or normal upright blood pressure. Adjustment of antihypertensive medication may be required.

Summary

In summary, screening for neuropathy is important, as this complication is frequent and often asymptomatic (Table 2). Prevention of foot ulceration by instruction about proper footwear, protection from injuries and extremes of temperature (i.e., hot water) will reduce morbidity and mortality from sepsis and amputation. Prevention of onset and progression of neuropathy is achieved by optimization of glucose control. Autonomic neuropathy is an important marker of cardiovascular disease and a significant risk factor for falls.

Conclusions

Screening for microvascular complications in older adults is important, as early detection and treatment of retinopathy, nephropathy and neuropathy improve both morbidity and mortality. Complication screening should be carried out, at minimum, on a yearly basis. High-risk and affected individuals need more frequent follow-up.

In addition to morbidity and mortality, health care costs also will be reduced with appropriate screening and treat-

ment. The estimated direct medical (hospital services, physicians' services, prescription medicines) and mortality-related productivity cost of Type 1 and Type 2 diabetes in Canada for 1998 was $4.76–5.23 billion (U.S.).[50] Of the costs associated with the complications of diabetes, cardiovascular disease was the largest at $637 million, which represented approximately 35% of the total burden of diabetes. These costs are expected to increase as the prevalence of diabetes, especially Type 2 DM, increases in Canada and around the globe.[51] In North America alone, it is estimated that between 2000 and 2010, there will be a 23% increase in the number of people diagnosed with diabetes.

There are several challenges faced by health care providers who treat older adults with DM. In addition to the microvascular complications, older adults with DM are at greater risk than other older persons for several common geriatric syndromes, such as depression, cognitive impairment, urinary incontinence, injurious falls and persistent pain.[52] These associated conditions in the older patient may make it particularly difficult to reach optimal glycemic targets. However, the treating physician should not compromise the most effective therapy to reach glycemic targets (i.e., insulin if required) based on the age of the patient alone.[53] Furthermore, an extremely important consideration in managing these patients is their increased risk of macrovascular or large vessel disease, myocardial infarction, stroke, peripheral artery disease, amputation and sudden death. Thus, diabetes in the older adult must be considered a serious illness.[54] ◆

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