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Management of Retinopathy and Neuropathy in Diabetes

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ABSTRACT

A combination of metabolic and vascular dysfunction in patients with diabetes can often lead to the development of microvascular complications such as retinopathy and neuropathy. These complications are the cause of significant morbidity and mortality in patients with diabetes, potentially leading to blindness and lower limb amputation. A key aim in diabetes management is to slow the development of microvascular disease, as there are limited options for treatment of established disease. Past studies have demonstrated the importance of strict control of blood glucose levels in preventing or slowing progression of microvascular complications. There is strong evidence that aggressive treatment of hypertension, dyslipidemia, and lifestyle modifications are also important in preventing complications. This review aims to help future physicians understand the pathogenesis of diabetic retinopathy and neuropathy, and provides a summary of the current literature and evidence–based recommendations for screening and management of both conditions.

KEYWORDS: *diabetes mellitus, diabetes complications, diabetic retinopathy, diabetic neuropathy*

INTRODUCTION

Diabetes mellitus currently affects greater than 285 million people, a figure that is expected to increase to 366 million by the year 2030.[1] Diabetes is characterized by a state of chronic hyperglycemia resulting in many downstream effects including eventual organ dysfunction. Microvascular complications include diabetic nephropathy, retinopathy, and neuropathy, all of which can result in serious consequences if left untreated. The topic of chronic kidney disease and end–stage renal disease in diabetes has been reviewed in recent publications.[2,3] This review will focus on the pathophysiology and management of diabetic retinopathy and neuropathy.

The effects of microvascular disease in diabetes are most prominent in the kidneys, retina, and vascular endothelium, tissues in which glucose uptake is independent of insulin levels.[4] Metabolic changes, including increased production of reactive oxygen species, formation of advanced glycation end products (AGEs), activation of protein kinase C isoforms, and hyperactivity of the hexosamine pathway,[5] lead to altered blood flow, endothelial permeability, and extravascular protein deposition.[6] The U.K. Prospective Diabetes Study Group (UKPDS) and the Diabetes Control and Complications Trial Research Group (DCCT) have shown a direct relationship between microvascular disease and inappropriate glycemic control.[7,8] Other factors also contribute to the risk of developing complications, including the patient's type of diabetes, gender, duration of diabetes, and hemoglobin A1c level.[9] The importance of controlling cardiovascular risk factors to prevent the development of microvascular complications is well–established.[1] For example, reduction of arterial hypertension, cessation of smoking, reduction of body mass index, and treatment

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of dyslipidemia can all slow progression of diabetic retinopathy and neuropathy.[7,10-12]

Current clinical practice guidelines for both neuropathy and retinopathy recommend starting annual screening of type 1 diabetic patients five years after diagnosis and screening type 2 patients at the time of diagnosis and subsequently every one or two years.[1,13]

RETINOPATHY

Diabetic retinopathy is a leading cause of adult blindness in developed countries.[14] At diagnosis, retinopathy is rarely present in type 1 diabetic patients, but is seen in 20 % of type 2 diabetic patients.[14-16] After 15-20 years, nearly all type 1 and 60 % of type 2 diabetic patients will develop retinopathy.[14-16] The classification of diabetic retinopathy as defined by the Early Treatment Diabetic Retinopathy Study (ETDRS) is summarized in Table 1.[17] The formation of asymptomatic microaneurysms in retinal capillaries is an early ophthalmoscopic finding that is pathognomonic for nonproliferative diabetic retinopathy.[18] As vascular damage progresses, leakage of serum proteins and fluid into the retina manifests as retinal thickening and hard exudates.[19] Late stage nonproliferative retinopathy is characterized by severe microvascular dysfunction and diagnosed through the observation of "venous beading," indicating retinal ischemia and preceding the proliferative phase of retinopathy.[20] Ischemia stimulates the expression of vascular endothelial growth factor (VEGF), leading to the growth of new vessels and the eventual onset of proliferative retinopathy.[21] These new vessels can result in hemorrhage, retinal detachment, and macular edema.[20] While nonproliferative retinopathy is often asymptomatic, proliferative retinopathy can cause disabling vision loss. Proliferative retinopathy is more likely to develop in early type 1 diabetes whereas macular edema may be more prominent in patients with type 2 diabetes.[20] Loss of central vision due to macular edema, defined by the presence and location of retinal thickening as evaluated by an ophthalmologist,[22] can occur at any stage.[23] The UKPDS and the Wisconsin Epidemiologic Study of Diabetic Retinopathy found that 5 % of patients progress to proliferative retinopathy ten years after diagnosis in the absence of appropriate management.[24] For patients with type 1 diabetes, use of an insulin pump can lower the incidence of retinopathy by 76 % compared to daily subcutaneous insulin injections with once–daily monitoring.[25]

> " **Current clinical practice guidelines for both neuropathy and retinopathy recommend annual screening of type 1 diabetic patients beginning five years after the diagnosis, and screening type 2 patients at the time of diagnosis and subsequently every one or two years.**

Table 1. Classification of diabetic retinopathy, adapted from the Early Treatment of Diabetic Retinopathy Study.[17] These findings on dilated indirect ophthalmoscopy, coupled with biomicroscopy and seven–standard field stereoscopic fundus photography, can be used to evaluate the extent of retinopathy present.

Disease Severity	Findings on Dilated Ophthalmoscopy
Mild nonproliferative retinopathy	At least one microaneurysm.
Moderate nonproliferative retinopathy	Hemorrhages and/or microaneurysms, and/or soft exudates, venous beading, or intraretinal microvascular abnormalities.
Severe nonproliferative retinopathy	Soft exudates, venous beading, and intraretinal microvascular abnormalities all definitely present.
Early proliferative retinopathy	New vessels not meeting the definition for high–risk proliferative retinopathy.
High–risk proliferative retinopathy	New vessels on or within one disc diameter of the optic disk, or vitreous and/or preretinal hemorrhage with new vessels.

The extent of retinopathy, as defined in Table 1, helps to guide management decisions. Diabetic macular edema (DME) can be managed with corticosteroids, laser treatment, or surgery. While intravitreal corticosteroid injections or implants can improve visual acuity in patients with DME,[26,27] these treatments carry a high risk for development of glaucoma, cataracts, and other adverse effects.[27] Focal laser treatment can significantly reduce vision loss due to macular edema compared to observation alone [28] and is the standard of care therapy for DME.[29] Vitrectomy may reduce macular thickening and improve visual acuity in DME refractory to laser treatment; however, existing studies are limited by small sample sizes.[30,31]

Proliferative diabetic retinopathy can be treated with laser treatment and anti–VEGF therapy. Panretinal laser photocoagulation (PRP) reduces the oxygen demands of photoreceptor cells and improves retinal oxygenation from the choroidal circulation.[32,33] PRP combined with vitrectomy reduced the risk of vision loss in a study of patients with severe proliferative retinopathy from 50 % to 4 % at five–year follow–up.[34] However, PRP is associated with pain and an increased risk of complications compromising visual function, including macular edema.[35-37] VEGF is expressed throughout the retina and is important in pathological neovascularization.[21] Therefore, medical management of proliferative retinopathy includes targeted anti–VEGF therapy. Three anti–VEGF agents currently available are pegaptanib (Macugen®), ranibizumab (Lucentis®), and bevacizumab (Avastin®).[21] These agents may be useful adjuncts to current therapeutic interventions. Bevacizumab has been shown to reduce macular edema and result in greater regression of new vessels when given with PRP treatments.[21] Additionally, anti–VEGF agents may reduce the incidence of postoperative vitreous cavity hemorrhage when given prior to vitrectomy.[38] With the appropriate injection technique, no increased risk of infection has been demonstrated.[39] However, a recent multicenter randomized controlled trial (RCT) reported a higher incidence of adverse events in the bevacizumab treatment group (24.1 %) compared with ranibizumab (19.0 %).[40] Overall, there is a lack of robust safety data available for the use of intravitreal bevacizumab,[41] despite the fact that it comprises the majority of intravitreal anti–

VEGF injections currently given in the United States.[42] Additional RCTs or meta–analyses would be beneficial to gain further insight into the role and safety profile of anti–VEGF agents in the treatment of diabetic retinopathy.

NEUROPATHY

Neuropathic complications occur in 40-50 % of patients with diabetes within ten years of diagnosis.[1,43] The pathogenesis of diabetic polyneuropathy (DPN) involves both metabolic and vascular dysfunction resulting in degenerative damage beginning in the distal terminals of peripheral nerves.[43,44] Heightened expression of the receptor for advanced glycation end products (RAGE) may have an important role in diabetic neuropathy, with RAGE–deficient mouse models demonstrating attenuated neuropathic features and reduced activation of harmful signaling pathways.[45] The pathophysiology remains controversial and may involve polyol flux, microangiopathy, and growth factor deficiency.[46]

Diabetic neuropathy includes a spectrum of disease manifestations, ranging from cranial nerve palsies to mononeuropathies and polyneuropathies.[47,48] The most common manifestation of DPN is a symmetrical, sensorimotor polyneuropathy, affecting the long fibers in a glove–and–stocking distribution. Longstanding DPN leads to the progressive destruction of bone and soft tissues at weight–bearing joints known as Charcot's arthropathy, which can result in joint dislocations, pathologic fractures, debilitating deformities, and commonly leads to foot and lower limb amputations.[49] Neuropathic pain can manifest in conjunction with DPN in up to 25 % of patients,[48] making it an important target for therapeutic intervention.

DPN screening includes evaluation of tactile sensitivity to a 10 g Semmes–Weinstein monofilament and/or vibration sensitivity using a 128 Hz tuning fork at the dorsum of the great toe, as well as assessment of pinprick sensation and/or reflexes.[50] Nerve conduction tests may be used to objectively quantify any abnormalities. The 10 g monofilament may not be as sensitive as alternative methods of screening, in particular for detection of less severe neuropathy. A recent study found that the modified neuropathy disability score and biothesiometry demonstrated a sensitivity of 0.92 for detection of individuals at risk for foot ulcers, higher than either the 10 g monofilament or tuning fork.[51]

Upon detection of an abnormality, the severity of DPN can be graded according to the stages outlined by Dyck [47] or defined according to the minimal criteria for diagnosis of DPN.[52] In these

> ## Neuropathic complications occur in 40-50% of patients with diabetes within ten years of diagnosis.

guidelines, possible DPN is defined by the presence of neuropathic sensory symptoms such as "prickling or stabbing, burning or aching pain and a symmetric decrease in distal sensation."[52] There are a number of validated tools available to quantify the degree of neuropathic pain in diabetes, including the McGill Pain Questionnaire and the Neuropathic Pain Symptoms Inventory.[53] However, a consistent pain scale for use across clinical trials remains to be developed.[54]

The mainstay of current treatment for DPN involves treating neuropathic pain.[1,55-57] Recent reviews have noted that pregabalin (Lyrica®) alone has level A evidence for efficacy to reduce pain and improve physical function and quality of life in patients with painful diabetic neuropathy, whereas venlafaxine (Effexor®), duloxetine (Cymbalta®), amitriptyline (Elavil®), gabapentin (Neurontin®), valproate (Depakene®), opioids (morphine sulfate, tramadol, and oxycodone), and capsaicin have level B evidence.[54] In one study, treatment with pregabalin at 75-300 mg twice a day significantly reduced neuropathic pain compared to placebo after two days.[58] Another study demonstrated that topical preparations of high concentration capsaicin (8 %) on a patch for 60 minutes daily decreased pain scores by 32 % over a 12–week period.[59] A major criticism of the existing randomized controlled trials (RCTs) for the medical treatment of DPN is that the short duration of most trials (2-20 weeks) is not adequate to demonstrate long–term therapeutic effects.[54] Foot ulceration is an extremely challenging complication of DPN to manage.[60] A recent Cochrane meta–analysis of six RCTs evaluating diabetic foot ulcer debridement concluded that hydrogels are significantly more effective in healing diabetic foot ulcers compared to gauze dressings or standard pressure–alleviating care, while larval therapies had the greatest reduction in wound size.[60]

SUMMARY

The microvascular complications of diabetes are the cause of significant morbidity and mortality in diabetic patients. This review summarized the major pathophysiologic changes in retinopathy and neuropathy and provides physicians with an introduction to the screening as well as currently established and new treatments for patients with diabetes. Importantly, treatment of patients with diabetes requires a multi–faceted approach, including evaluation of lifestyle and cardiovascular risk factors such as hypertension, smoking, and dyslipidemia. As the prevalence of diabetes continues to increase at a dramatic rate, the appropriate treatment of microvascular complications remains highly relevant to clinical practice and must continue to evolve as ongoing developments in basic science research translate into innovations in patient care.

> ## At diagnosis, retinopathy is rarely present in type 1 but may be seen in 20% of type 2 diabetic patients.
> ## After 15-20 years, nearly all type 1 and 60% of type 2 diabetic patients will develop retinopathy.

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