Diabetic Retinopathy and Neuropathy: 2018 Clinical Practice Guidelines

Richard Arakaki, M.D.
Phoenix Area Diabetes Consultant

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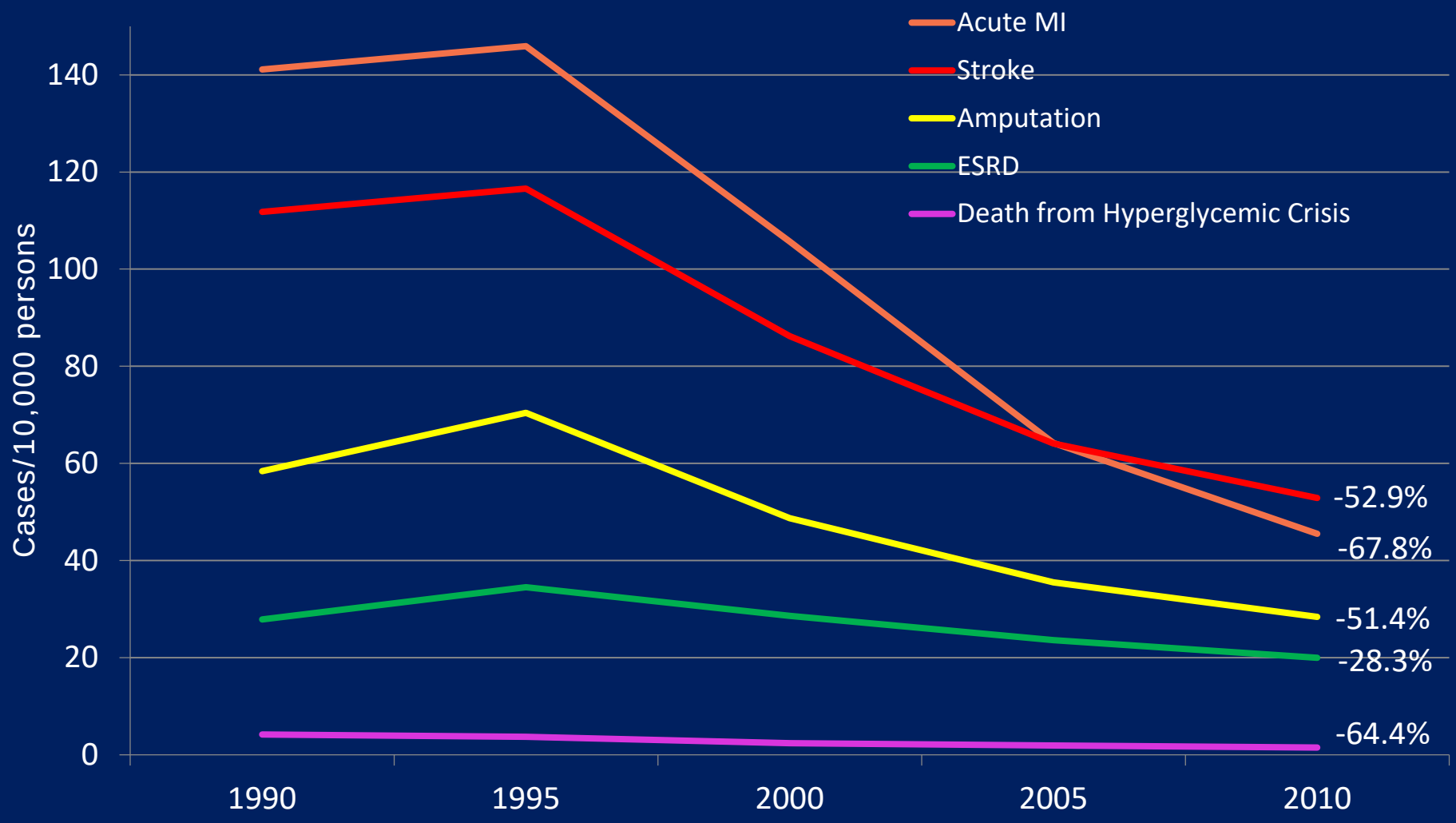
Disclose no conflict of interest

Complications and Co-morbidities of Diabetes

- Macrovascular Complications
  - Heart disease, peripheral arterial, CHF, and stroke
- Microvascular Complications
  - Retinopathy: Blindness, eye problems
  - Nephropathy: CKD and ESRD
  - Neuropathy
- Foot Disease
  - Ulcers and Amputations
- Co-morbid conditions
  - Hypertension; hyperlipidemia; obesity

National Diabetes Information Clearinghouse. National Diabetes Statistics, 2014. Available at: http://diabetes.niddk.nih.gov/dm/pubs/statistics/

Trends in age-standardized rates of diabetes-related complications among U.S. adults with diabetes, 1990-2010

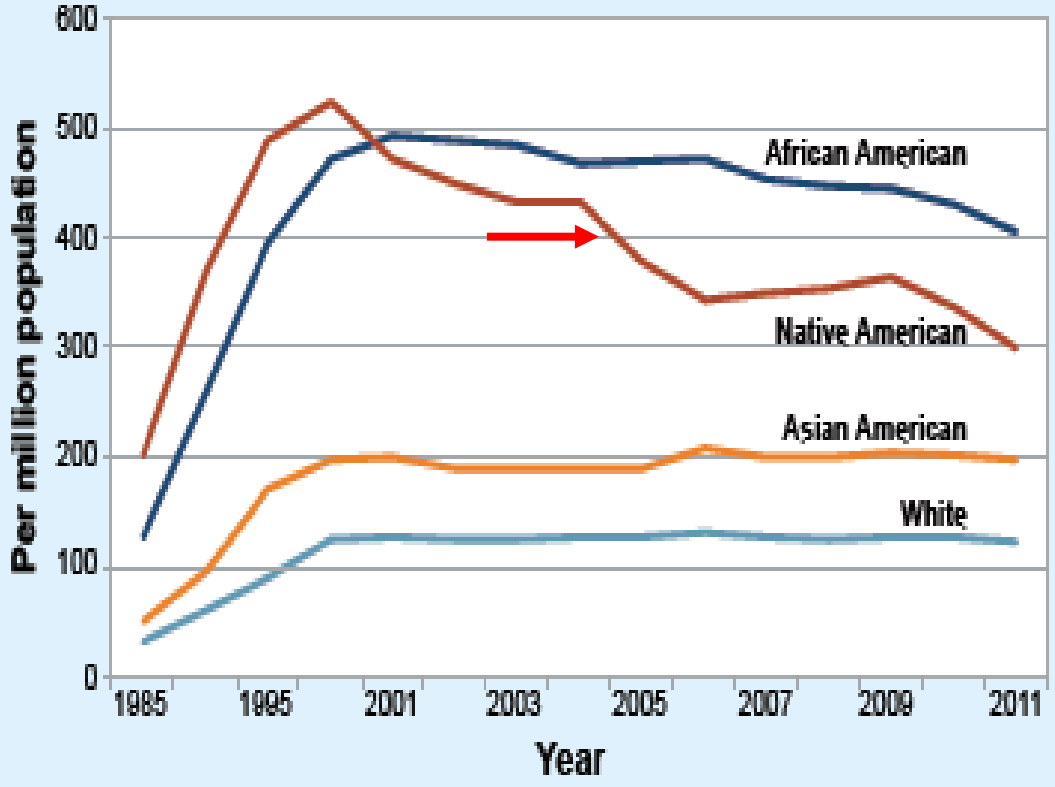


Gregg et al. N Engl J Med 370: 1514—1523, 2014

A Decade of Dramatic Reduction in Rates of ESRD

- End Stage Renal Disease (ESRD) in AI/AN persons with diabetes has been reduced by over 40%.
- This reduction is greater than that achieved in any other racial group.
- The average medical costs of one year of care of a patient on dialysis in 2011 dollars was $88,000.
- Savings to Medicare, IHS and other payers are thus measured in $millions, freeing up resources for other pressing health needs.

Figure 8. Incidence Rates of ESRD due to Diabetes, by Race



Source: United States Renal Data System 2013

Reduction of Diabetes ESRD in AI/AN: Addressing Multiple Factors

- Blood Pressure Control
  - Average BP: 132/76 mmHg in 2016
- Blood Sugar Control
  - Mean A1c level decreased by 10% between 1996-2016
- Use of Renin Angiotensin System Inhibitors
  - 76% of patients prescribed medications in 2014
  - 36% higher than in NHANES cohort (2009-2014)
- Increase Screening for diabetes nephropathy
  - 62% of patients over the age of 65 yrs had UACR test in 2015
  - Compared with 40% among Medicare patients with diabetes in 2013

IHS, Division of Diabetes Treatment and Prevention

Improvement in DM Retinopathy among AI/AN: JVN Program Data

- IHS Joslin Vision Network Teleophthalmology Program (JVN)
  - Established in 2000
  - Exemplary telemedicaine program
- Retrospective data analysis of 54,000 A1/AN people with diabetes who participated in the JVN program 2011-2016
- Compare with studies done in the 1980s and 1990s, the *prevalence of diabetic retinopathy* **decreased by over 50%**

Table 2. Numbers (n) and percentages (%) of IHS-JVN patients by level of DR and DME.

Severity level	n	%
DR		
No Apparent DR	36381	80.0
Mild NPDR	4284	9.4
Moderate NPDR	3698	8.1
Severe NPDR	67	0.1
PDR	1052	2.3
Total	45482	100.0
DME		
Absent	44806	97.7
Not Clinically Significant	653	1.4
CSDME	394	0.9
Total	45853	100.0
STR		
Absent	43055	95.8
Present	1904	4.2
Total	44959	100.0

Conclusions

Prevalence of DR in this cohort was approximately half that in previous reports for AI/AN, and prevalence of DME was less than that reported in non-AI/AN populations. A similar reduction in diabetes related end-stage renal disease in the same population and time period has been reported by other researchers. Since these two diabetic complications share a common microvasculopathic mechanism, this coincident change in prevalence may also share a common basis, possibly related to improved diabetes management.

Bursell S-E, et al. Prevalenc of diabeteic retinopathy and diabetic macular edema in a primary care-based teleophthalmology program for AI and AN. PLoS One. https//doi.org/10.1371/journal.pone.0198551

Vascular complications of diabetes: mechanisms of injury and protective factors

Fig. 1. Selected mechanisms of injury and protective factors determining development of diabetic vascular complications

This diagram illustrates that in the normal state, factors with protective functions in the vasculature can render blood vessels less susceptible to vascular disease and can counteract mechanisms which promote vascular injury. In diabetes, however, glucose and lipid metabolites promote mechanisms of injury and, at the same time, inhibit factors with protective functions in the vasculature. Abbreviations: AGE, advanced glycation end-products; APC, activated protein C; FFA, free fatty acids; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NFκB, nuclear factor κB; PDGF platelet-derived growth factor; PKC, protein kinase C; ROS, reactive oxygen species; VEGF, vascular endothelial growth factor. Artwork by Leah A. Klein.

Christian Rask-Madsen and **George L. King** *Cell Metab.* 2013 January 8; 17(1): 20–33. doi:10.1016/j.cmet.2012.11.012.

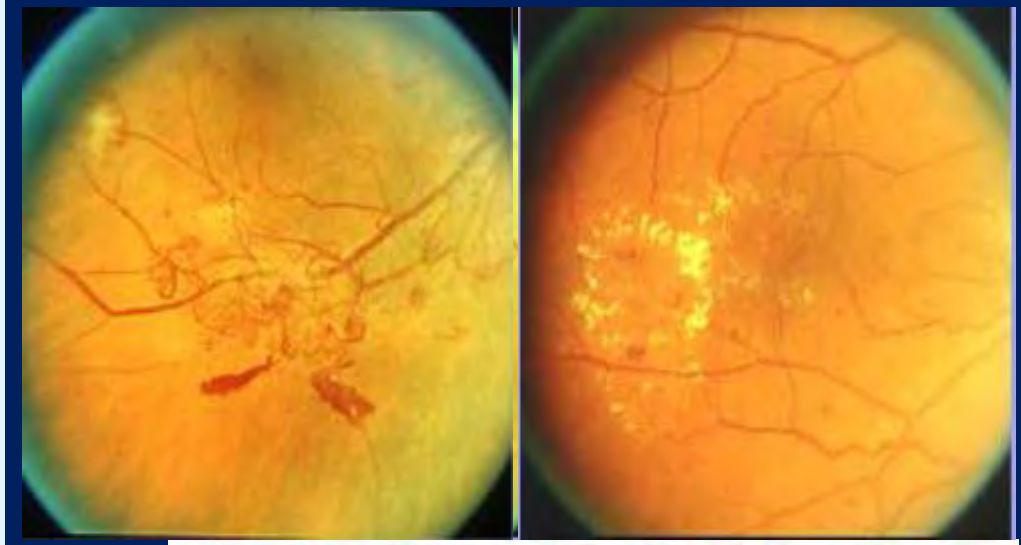
Complications of Diabetes: Retinopathy

- About 40% prevalence of retinopathy among all patients
- Approximately 20% of patients have retinopathy at DM diagnosis
- Diabetes is leading cause of new cases of blindness among adults ages 20–74 years; 12 – 24 K new case/yr
- 655,000 (4.4% of those with diabetes) had advanced diabetic retinopathy that could lead to severe vision loss
- 1.5%/year of patients with DM need Laser treatment

National Diabetes Information Clearinghouse. National Diabetes Statistics, 2014. Available at: http://diabetes.niddk.nih.gov/dm/pubs/statistics/

Diabetic Retinopathy

Stage	Features
Background retinopathy	Microaneurysms (saccular pouches due to capillary distension)
	Dot/blot haemorrhages
	Hard exudates (lipid deposits related to extravascular leaks)
Pre-proliferative	Cottonwool spots (areas of retinal ischaemia)
	Venous beading
	Intraretinal microvascular abnormalities
Proliferative retinopathy	Neovascularisation:
	• new vessel disc
	• new vessel elsewhere
Advanced eye disease	Vitreous haemorrhage
	Traction retinal detachment
	Rubeosis iridis
	Rubeotic glaucoma
Maculopathy	Macular oedema
	Hard exudates in macular region



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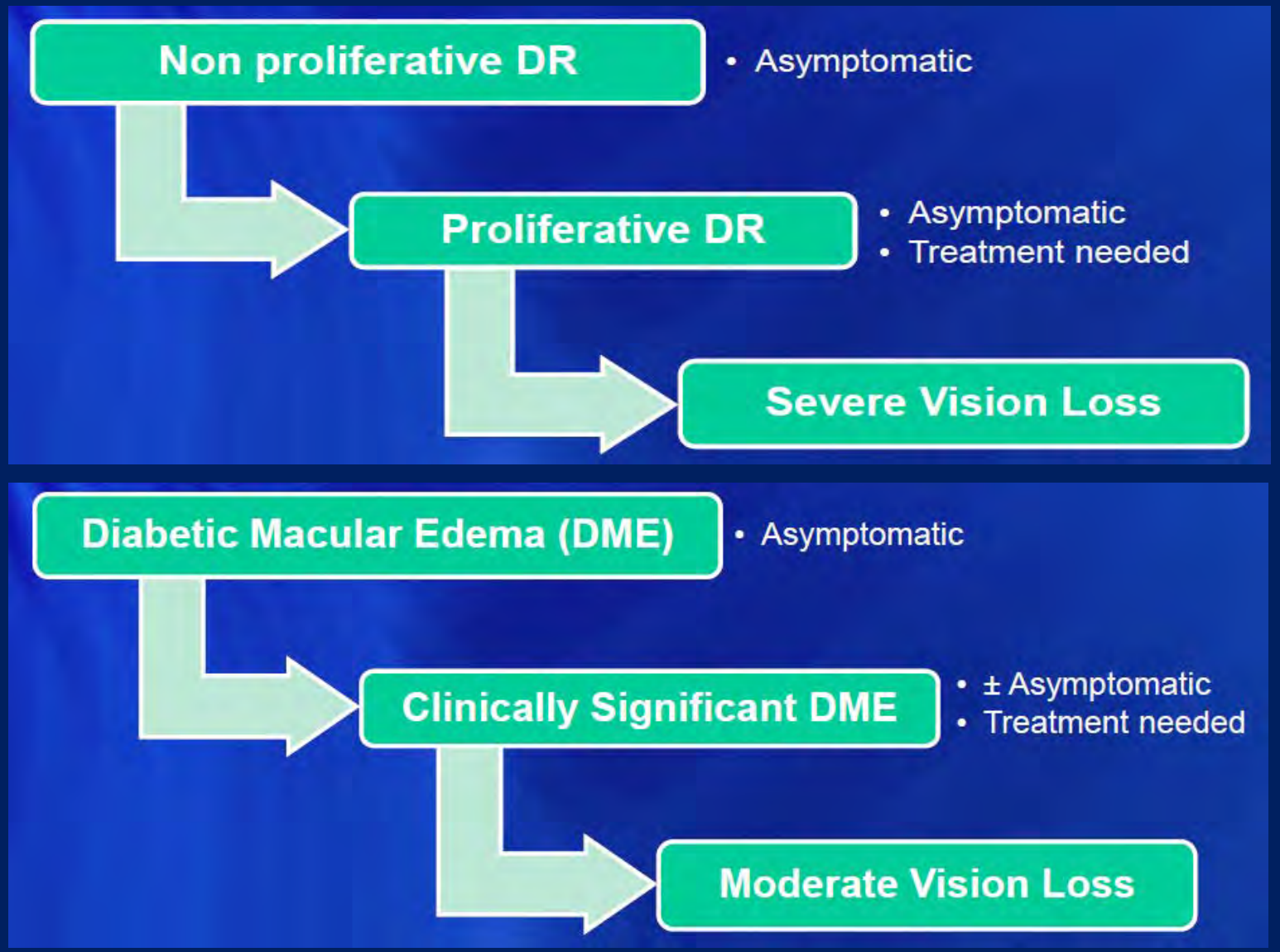
Diabetic Retinopathy: Clinical Consequence



Scheme and Photos courtesy of Dr. Dawn Clary, Director JVN Tele-ophthalmology Program

10. Microvascular Complications and Foot Care: *Standards of Medical Care in Diabetes—2018*

Diabetes Care 2018;41(Suppl. 1):S105–S118 | https://doi.org/10.2337/dc18-S010

DIABETIC RETINOPATHY

Recommendations

- Optimize glycemic control to reduce the risk or slow the progression of diabetic retinopathy. A
- Optimize blood pressure and serum lipid control to reduce the risk or slow the progression of diabetic retinopathy. A

Screening

- Adults with type 1 diabetes should have an initial dilated and comprehensive eye examination by an ophthalmologist or optometrist within 5 years after the onset of diabetes. B
- Patients with type 2 diabetes should have an initial dilated and comprehensive eye examination by an ophthalmologist or optometrist at the time of the diabetes diagnosis. B

Screening

- If there is no evidence of retinopathy for one or more annual eye exam and glycemia is well controlled, then exams every 1–2 years may be considered. If any level of diabetic retinopathy is present, subsequent dilated retinal examinations should be repeated at least annually by an ophthalmologist or optometrist. If retinopathy is progressing or sight-threatening, then examinations will be required more frequently. B
- While retinal photography may serve as a screening tool for retinopathy, it is not a substitute for a comprehensive eye exam. E

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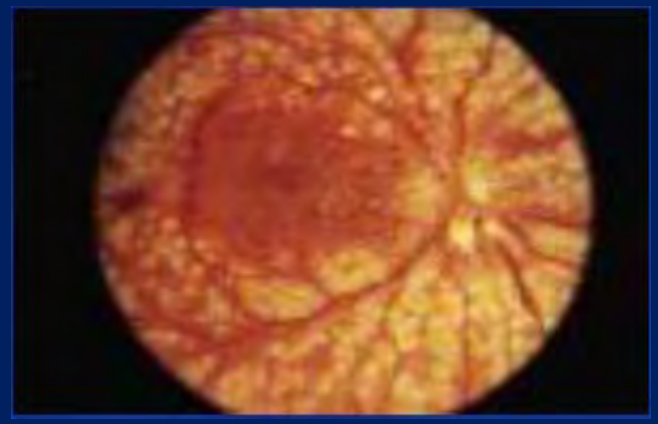
DIABETIC RETINOPATHY

Treatment

- Promptly refer patients with any level of macular edema, severe nonproliferative diabetic retinopathy (a precursor of proliferative diabetic retinopathy), or any proliferative diabetic retinopathy to an ophthalmologist who is knowledgeable and experienced in the management of diabetic retinopathy. A
- The traditional standard treatment, panretinal laser photocoagulation therapy, is indicated to reduce the risk of vision loss in patients with high-risk proliferative diabetic retinopathy and, in some cases, severe nonproliferative diabetic retinopathy. A
- Intravitreous injections of anti–vascular endothelial growth factor ranibizumab are not inferior to traditional panretinal laser photocoagulation and are also indicated to reduce the risk of vision loss in patients with proliferative diabetic retinopathy. A



Treatment

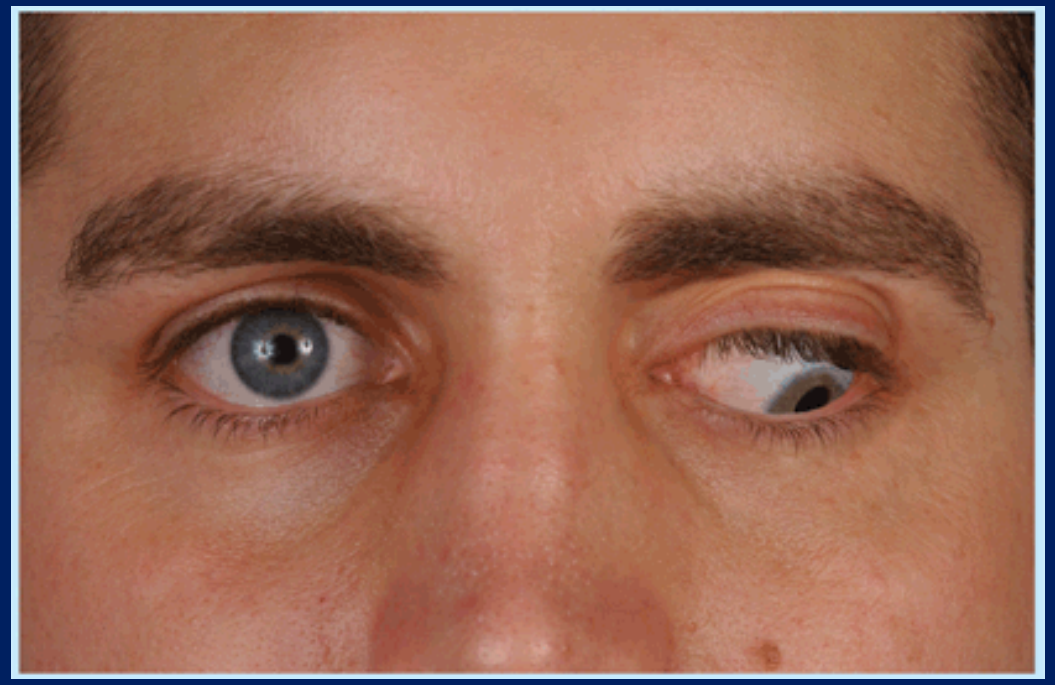
- Intravitreous injections of anti–vascular endothelial growth factor are indicated for central-involved diabetic macular edema, which occurs beneath the foveal center and may threaten reading vision. A
- The presence of retinopathy is not a contraindication to aspirin therapy for cardioprotection, as aspirin does not increase the risk of retinal hemorrhage. A

Complications of Diabetes: Retinopathy

- Diabetic Retinopathy is PREVENTABLE by adhering to accepted standards of care and established best practices

  - Identify all patients with diabetes
  - Control for confounding factors and co-morbidities
  - Assess level of retinopathy year
  - Provide timely treatment

National Diabetes Information Clearinghouse. National Diabetes Statistics, 2014. Available at: http://diabetes.niddk.nih.gov/dm/pubs/statistics/



50 yo man with DM type 1 presented with ABRUPT and PAINLESS left eye droop and diplopia. Slight orbital for days prior to onset

Examination showed pupils equal and reactive to light.

Diplopia and Ptosis

Summary Table

Condition	*Characteristics*
Aneurysm of the posterior communicating artery	May compress the oculomotor nerve, leading to third nerve palsy; pupil constriction is typically impaired
Diabetic third nerve palsy	Caused by microvascular infarction of the blood supply to the oculomotor cranial nerve; manifests as inferolateral deviation of the eye with diplopia and ptosis; recovery generally occurs over weeks to months, although deficits that are present after six months are usually permanent
Myasthenia gravis	Caused by autoimmune destruction of postsynaptic acetylcholine receptors; may manifest as pupil-sparing third nerve palsy with ptosis, but usually also affects multiple other nerves; application of ice may relieve ptosis
Orbital myositis	Inflammation of at least one extraocular muscle; manifests as orbital pain, diplopia, and conjunctivitis; pupil is spared; diagnosis confirmed with neuroimaging
Vertebrobasilar occlusion	May affect the oculomotor nucleus located in the midbrain, resulting in nausea, vertigo, and other cranial nerve deficits; bilateral ptosis also occurs

KRISTINE J. PFEIFFER, DO,
STEVEN K.F. ROPERS, MD,
MATTHEW W. SHORT, MD,

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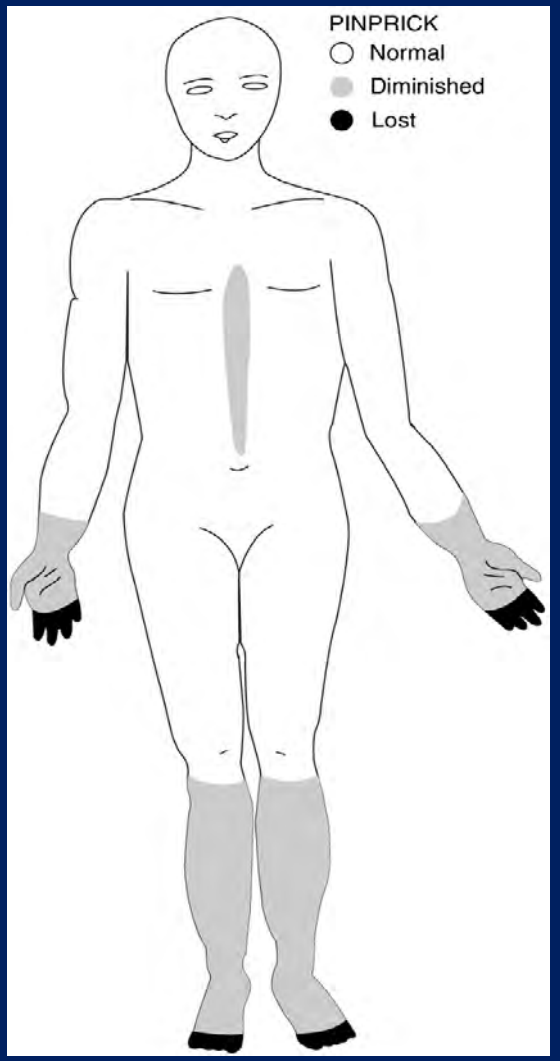
Complications of Diabetes: Neuropathy

Type of neuropathy	Clinical phenotype
Hyperglycaemic neuropathy	Reversible, influenced by glucose levels
Symmetrical sensorimotor neuropathy	Most common presentation, glove and stocking pattern
Focal neuropathy	Entrapment syndromes (carpal tunnel/meralgia paraesthetica)
	Cranial nerve palsies
	Diabetic amyotrophy
Autonomic neuropathy	Postural hypotension
	Erectile dysfunction
	Gastroparesis
	Gustatory sweating

Cuirass Distribution



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Pathology and pathogenetic mechanisms of diabetic neuropathy: Correlation with clinical signs and symptoms

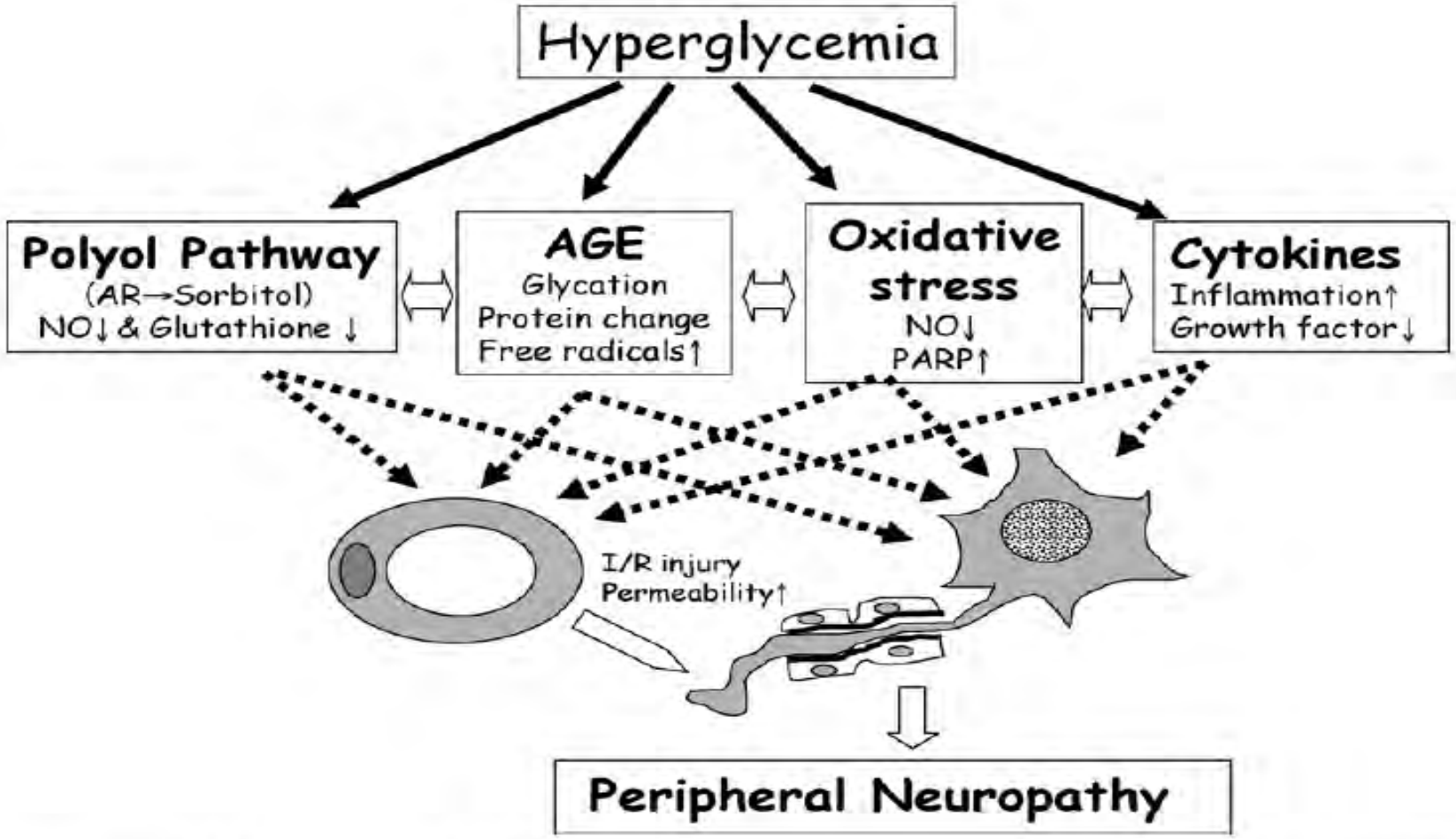

Fig. 3. Multifactorial etiology of diabetic neuropathy. Hyperglycemia exerts increased polyol pathway, enhanced AGE formation, increased oxidative stress as well as cytokine release. These factors are complicatedly interactive or independently operate for the cause and development of diabetic neuropathy directly affecting nerve tissues or through nutrient vascular tissues.

S. Yagihashi et al./Diabetes Research and Clinical Practice 77S (2007) S184–S189

Pathology and pathogenetic mechanisms of diabetic neuropathy: Correlation with clinical signs and symptoms

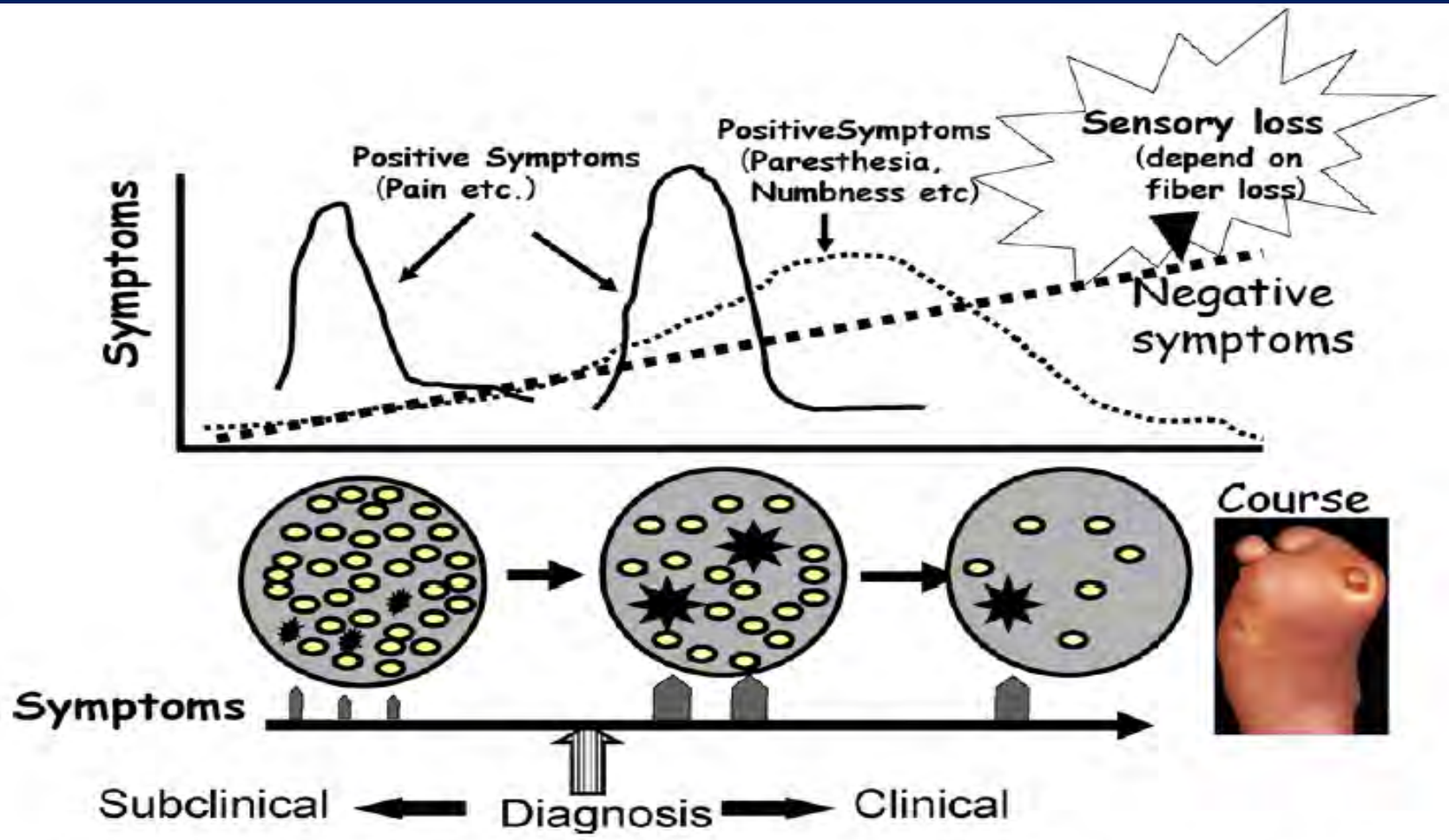

Fig. 2. Natural history of diabetic neuropathy and clinical signs and symptoms with pathological background. With increasing stage of neuropathy, there is a progressive loss of nerve fibers that convey sensation. When the fibers undergo degeneration or impaired remyelination, they release impulse of positive symptoms. With progression of disease, negative symptoms of sensory loss are increased.

S. Yagihashi et al./Diabetes Research and Clinical Practice 77S (2007) S184–S189

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NEUROPATHY

- Diabetic Peripheral Neuropathy: Patient with type 1 diabetes, duration > 5 yrs and all type 2 patients should be annually assessed. Primary complaints are discomfort or pain or loss of sensations
- Diabetic Autonomic Neuropathy: elicited through H and P
- Gastrointestinal Neuropathies: suspected in individuals with erratic glycemic controls or GI symptoms without other causes
- Genitourinary Disturbances: symptoms of sexual and bladder dysfunction

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NEUROPATHY | Treatment

- Improve Glycemic Control
- Neuropathic Pain: Pregabalin (anti-convulsant) and duloxetine (selective norEpi and serotonin reuptake inhibitor) and tapentadol (opioid analgesic) are FDA approved medications. Tricyclic antidepressants, venlafaxine, carbamazepine, tramadol, and topical capsaicin are effective but not approved for DPN pain.
- Orthostatic Hypotension: difficult to treat; compressive garments, or midodrine and droxidopa are approved by the FDA
- Gastroparesis: dietary changes (small meals, reduce dietary fat and fiber), avoid certain medications, metocloprpamide approved by FDA (5 days only)
- Genitourinary Disturbances: erectile dysfunction – PDE-5 in

Approach to Peripheral Neuropathy for the Primary Care Clinician

https://doi.org/10.1016/j.amjmed.2017.12.042

Christopher T. Doughty, MD,[a,b] Reza Seyedsadjadi, MD[a,b]

[a]Massachusetts General Hospital, Boston, Mass; [b]Harvard Medical School, Boston, Mass.

Table 6 Pharmacologic Agents for the Management of Neuropathic Pain in Patients with Neuropathy

Name	Instructions for Starting	Goal Dose	Maximum Dose	Good for Patients with:	Consider Alternatives if:	Common Side Effects
Gabapentin	100 mg TID or 300 mg at bedtime	300 mg TID	3600 mg/d	Seizure disorder	Renal insufficiency	Dizziness, sedation, gait disturbance, confusion, peripheral edema
Pregabalin	75 mg BID	150 mg BID	600 mg/d	Seizure disorder	Renal insufficiency	Dizziness, sedation, gait disturbance, confusion, peripheral edema
Amitriptyline/ Nortriptyline	10-25 mg at bedtime	50-100 mg at bedtime	150 mg/d	Insomnia Migraine	Cardiac disease, arrhythmia, other serotonergic medications	Dry mouth (more common with amitriptyline), sedation, dizziness, confusion, QT-prolongation, orthostatic hypotension
Duloxetine	30 mg/d	60 mg/d (daily or split BID)	120 mg/d	Depression, anxiety, fibromyalgia	Hepatic failure, other serotonergic medications, anticoagulants	Nausea, dyspepsia, constipation, sedation, dry mouth, dizziness, hyperhidrosis, sexual dysfunction
Venlafaxine	37.5 mg/d (XR)	150 mg/d (XR)	225 mg/d	Depression, anxiety	Uncontrolled hypertension, other serotonergic medications	Nausea, dyspepsia, sedation, dizziness, nervousness, insomnia, hypertension, sexual dysfunction

Neuropathy: Overview

Early recognition and management is important because:

1. Diabetic neuropathy (DN) is a diagnosis of exclusion.
2. Numerous treatment options exist.
3. Up to 50% of diabetic peripheral neuropathy (DPN) may be asymptomatic.
4. Recognition & treatment may improve symptoms, reduce sequelae, and improve quality of life.

Microvascular Complications and Foot Care:
Standards of Medical Care in Diabetes - 2018. *Diabetes Care* 2018; 41 (Suppl. 1): S105-S118

Neuropathy: Recommendations

Screening:

- All patients should be assessed for DPN starting at diagnosis for T2DM and 5 years after diagnosis of T1DM and at least annually thereafter. B
- Assessment for distal symmetric polyneuropathy should include a careful history and assessment of either temperature or pinprick sensation (small-fiber function) and vibration sensation using a 128-Hz tuning fork (for large-fiber function). All patients should have annual 10-g monofilament testing to identify feet at risk for ulceration and amputation. B
- Symptoms and signs of autonomic neuropathy should be assessed in patients with microvascular complications. E

Microvascular Complications and Foot Care:
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Neuropathy: Recommendations (2)

Treatment:

- Optimize glucose control to prevent or delay the development of neuropathy in patients with T1DM A and to slow the progression in patients with T2DM. B
- Assess and treat patients to reduce pain related to DPN B and symptoms of autonomic neuropathy and to improve quality of life. E
- Either pregabalin or duloxetine are recommended as initial pharmacologic treatments for neuropathic pain in diabetes. A

Microvascular Complications and Foot Care:
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Diabetic Retinopathy and Neuropathy: Summary

Diabetes is associated with significant microvascular complications: retinopathy, neuropathy and nephropathy

Diabetic retinopathy remains the most common cause of blindness in working-age adults in the developed world.

Neuropathy may manifest in different ways and can be difficult to manage

Prevention and reduction in progression of microvascular complications requires intensive management of glucose, blood pressure and lipids

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Thank you for your attention.

Questions or Comments?