Diabetes Head to Toe


What Optometrists Should Know About Systemic Diabetes, non-Ocular Comorbidities & Their Link to Eye Disease

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Disclosures

- **I have spoken for, consulted for, or been paid honorarium by the following:**

Bausch & Lomb, Optos, ZeaVision, VSP, Risk Medical Solutions, Regeneron, Zeiss, Genentech, American Diabetes Association, EyeNuk, AI Optics

- **These associations did not unduly influence the content of this presentation or my patient care recommendations**

Increasing Prevalence of DM

- 34.1 million Americans now have diabetes (13%)
  - 7.3 million undiagnosed Incidence: 1.5 million (2018)
- 88 million Americans have prediabetes (34.5%) and 85% unaware
- NHANES analysis (2012) suggested 50+% of Americans adults had diabetes or prediabetes
- 100+ million have NAFLD associated with insulin resistance
- **You won't lose vision to DR if you don't develop diabetes**

https://www.cdc.gov/diabetes/pdfs/data/statistics/national-diabetes-statistics-report.pd accessed 5/15/2020
JAMA. 2015;314(10):1021-1029.
PLoS One. 2017; 12(3): e0173499

PROJECTED FUTURE PREVALENCE OF DIABETES

2012 1 in 10

2050 1 in 3 to 5

✓ Significant increase in prevalence of total diagnosed and undiagnosed diabetes in adults in the US over the next 40 years.

Mean Estimate: 100 million Americans by 2050

Boyle JP, et al. *Population Health Metrics.* 2010;8:29. http://www.pophealthmetrics.com/content/8/1/29. Accessed February 11, 2015.

Worldwide Statistics

- **1 billion will have diabetes by 2050**
- **Highest increases in diabetes & prediabetes in Asia and Sub-Saharan Africa**

International Diabetes Federation, 2015; www.diabetesatlas.org

Why Things Can Go Terribly Wrong in Diabetes

Clinician error

Patient ignorance or lack of health care literacy

Patient non-compliance or non-adherence

Why Things Go Wrong

A health care system focused on treatment of acute disease more than management of chronic disease

Maintaining metabolic control is a fine and difficult balancing act requiring collaboration between pts, family members and HCPs

It's a little late….

- Up to 60% of pancreatic beta cells are non-functional AT Dx of T2DM *Diabetologia* 2001;**44**:929–945
- Estimated duration of T2DM AT Dx is a mean of 6.2 YEARS! Diabetes Care. 2014 Jun;37(6):1668-74
- 1 in 5 patients with newly Dx T2DM has DR/ DME! (3% have CSME) and both entities are associated with increased CV mortality
- BioTrends Research Group, TreatmentTrends®: Diabetic Retinopathy/Diabetic Macular Edema (U.S.) 2013.

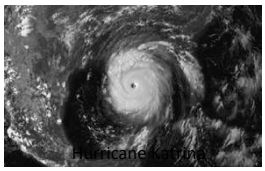
Circ Cardiovasc Qual Outcomes. 2015 May;8(3):260-7

Cost of Diabetes to the US Economy

- $327 Billion in 2017
  - $92 Billion in lost productivity
  - 1 in 4 health care dollars

Up from $245 Billion in 2021

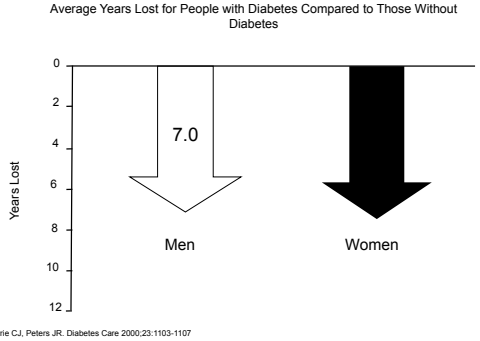
Diabetes Care. 2018 May;41(5):917-928



x 2.2 =

Cost of Diabetes Every Year in the US

Diabetes Reduces the Lifespan



Morgan CL, Currie CJ, Peters JR. Diabetes Care 2000;23:1103-1107

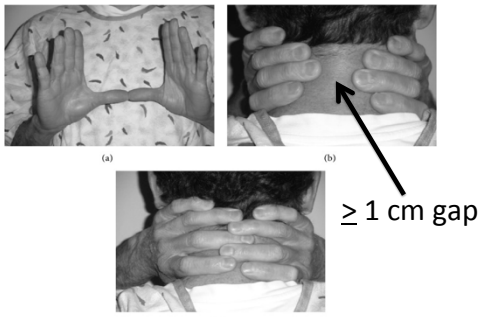
A Patient for Your Consideration

45 YO Man

- Presents for initial evaluation
  - He has not visited a physician in > 5 years
  - Recently gained 20 pounds
- Complaint: "Blurry Vision"
- Meds: none
- Physical exam:
  - BP 152/95
  - Height 5'-9"
  - Weight 226 Lbs.
  - BMI 33 & Waist 40"
  - Reports being tired all the time → + ESAP

Ocular Dx:
1+ NS
Presbyopia
20/20 OD/OS
Retina appears normal
IOP = 17/16

+ ESAP = Easy Sleep Apnea Predictor



Neck Grasp Predicts Obstructive Sleep Apnea in Type 2 Diabetes Mellitus. Sleep Disord. 2019 Jul 1;2019

In-office Random Blood Glucose =212 mg/dl

→ Refer to primary care physician

Lab Results: What do they mean?

- **Fasting glucose 165 mg/dl (65-99 mg/dl)**
- **AST 42 IU/L (0-40 IU/L)**
- **ALT 54 IU/L (0-44 IU/L)**
- ALK PHOS 110 IU/L (39-117 IU/L)
- BUN 18 mg/dl (6-24 mg/dl)
- Cr 1.2 mg/dl (.76 – 1.27 mg/dl)
- **Total Chol 232 mg/dl (100-199 mg/dl)**
- **Trig 302 mg/dl (0-149 mg/dl)**
- HDL 30 mg/dl (>39 mg/dl)
- **LDL 164 mg/dl (0-99 mg/dl)**
- **Urine Albumin / Creatine 110 mcg/mg (<30 mcg/mg)**

HbA1c of 8.2%

Diagnoses:

Elevated LFTs
→ ?NAFLD

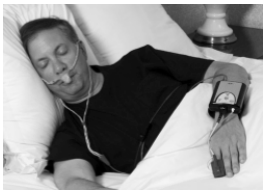
Metabolic Syndrome
High TG/Low HDL
HTN (>130/85)
FBG ≥ 100
waist ≥ 40 inches

Diabetes mellitus

DKD

→ Referred for Sleep Study by PCP

- In-home polysomnography (PSG)
  - **Apnea-Hypopnea Index: 32 events/hour**



Severe OSAS

Definitions

- **Diabetes mellitus (DM) is characterized by hyperglycemia secondary to insulin deficiency, insulin resistance, or both**
- **type 1 diabetes = autoimmune destruction of beta cells with absolute insulin deficiency**
- **type 2 diabetes = insulin resistance overlaid on progressive beta cell failure**

"Diabetes" literally means "siphon"

Mellis = sweet

Insipidus = dull, boring

Diabetes mellitus or 'DM'

Nomenclature

- **T1DM, T2DM, GDM are accepted acronyms**
- **NOT Type I and Type II**

- **NOT insulin-dependent and non-insulin dependent**
  - **NOT IDDM or NIDDM**
  - **Many T2DM patients require insulin**

- **NOT 'juvenile diabetes' or 'adult-onset diabetes'**
  - **Many children develop T2DM**
  - **Many adults develop T1DM**

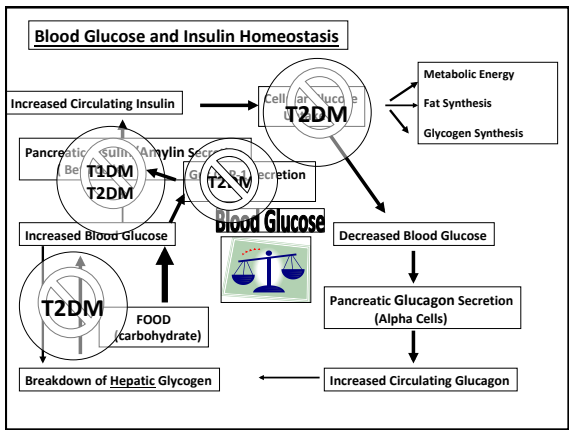
Common Misunderstandings

- Use of insulin means a person with type 2 DM now has type 1 DM
- Only overweight/obese people get type 2 diabetes
- type 2 diabetes is the 'good kind' of diabetes

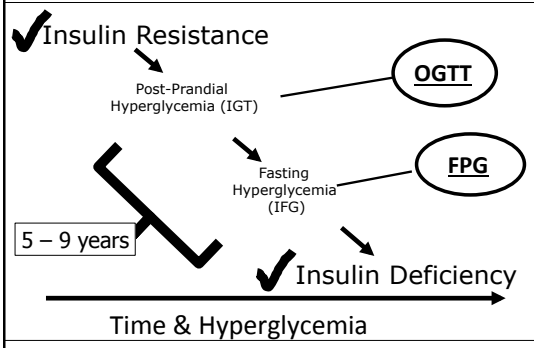
Diagnosis of DM

- FPG ≥ 126mg/dl on two occasions (Fasting > 6)
- RPG ≥ 200mg/dl with polyuria, weight loss (Random with Symptoms)
- OGTT ≥ 200mg/dl at 2 hours (Sugar Water Test)
- HbA1c ≥ 6.5% (2009) (2-3 month Average)
- Pre-diabetes (IFG and/or IGT) now defined as FPG ≥ 100mg/dl or OGTT ≥ 140mg/dl or HbA1c ≥ 5.7%

Diabetes Care 2015 Jan; 38(Supplement 1): S8-S16

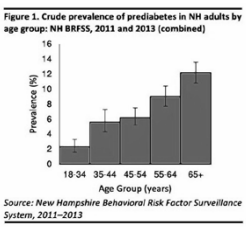


Natural History of T2DM



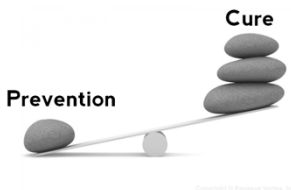
Optometry is on the Front Lines

- ODs perform the majority of eye examinations in the US
- Presbyopia onset aligns with increasing DM risk
- Diabetes is associated with myriad ophthalmic symptoms & signs
- Optometry is about prevention



Best Way To Prevent Diabetic ALL Diabetes Complications, including Retinopathy??

- **Don't Get Diabetes!!!**



Who Gets Diabetes

RISK

- Older pts > Younger pts
- Men > Women in mid-life
- People with a strong family history
- People with essential HTN
- People who are physically inactive
- African, Latino, Native, Asian and Pacific Island Americans > European Americans
- Those with increased abdominal fat

Who Gets Diabetes?

- Transmission of type 2
  - If 1 parent with T2DM, then 20% risk
  - If 2 parents with T2DM, then 60% risk
  - 60-75% in identical twins
- Transmission of type 1
  - If father hasT1DM, then 5-15% risk
  - If mother has T1DM, 1-5% risk
  - If both parents have T1DM, then 10-25%
  - 25-50% in identical twins

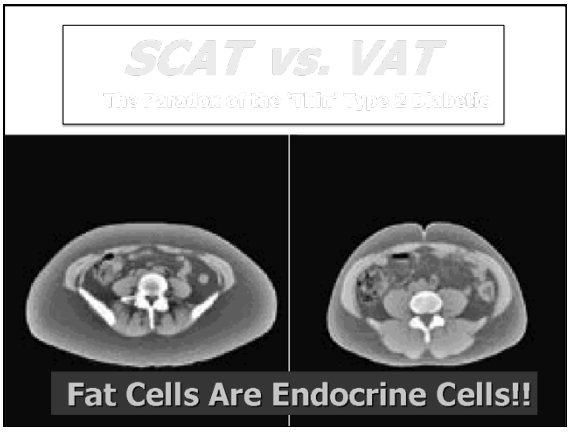
T2DM is Far More 'Transmissable' thanT1DM!!

- **After controlling for age, gender, BMI, BP, race, and socioeconomic status, patients with high familial diabetes risk (≥2 first order relatives or ≥ 1 first + ≥ 1 second order relative) are 5.5 times more likely to develop T2DM than the population average**
  - **Source: NHANES 163,000 USAdults**

Diabetes Care. 2007 Oct;30(10):2517-22. Epub 2007 Jul 18
Public Health Genomics. 2010;13(6):353-9.

Visceral Adipose Tissue:
Bad Fat Releases Bad Hormones

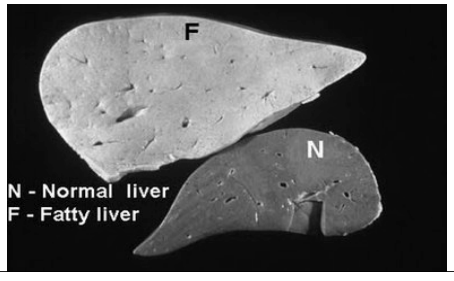
- Visceral fat releases substances that cause insulin resistance and mobilize non-esterified fatty acids (Free Fatty Acids)
- High Abdominal Fat is BAD



NAFLD

➔ 70-80% of T2DM pts
➔ 35% of US adults
➔ 10% of pediatric pts

Annals of Hepatology 2009
World J Gastroenterol. 2014 Jul; 20(27): 9072–9089
Arch Dis Child. 2015 Jul;100(7):673-7



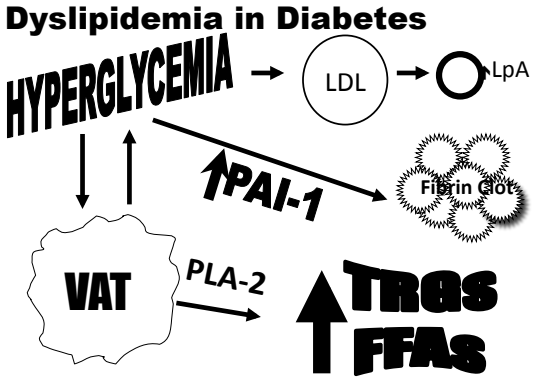
Metabolic Abnormalities Associated With Diabetes

- Hyperglycemia
- Inflammatory Dyslipidemia
- Hypertension
- Increased Formation of Reactive Oxygen Species (ROS)

These abnormalities individually and synergistically damage the retina

Metabolic Abnormalities Associated With Diabetes

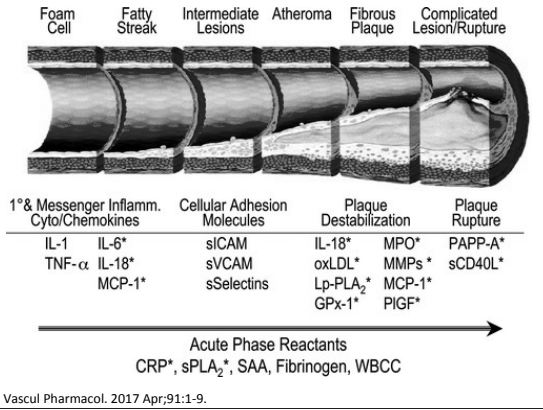
- Hyperglycemia:
  - Insulin deficiency (type 1 & type 2)
  - Faulty inhibition of gluconeogenesis in the liver (type 2)
  - Insulin resistance (IR) resulting from increased visceral fat (type 2)



Inflammatory Dyslipidemia:

- Glucose sticks to LDL cholesterol particles making them small and dense & also ↑ lipoprotein A (promoting plaque formation)
- Visceral Fat increases triglycerides and mobilizes harmful free fatty acids via the enzyme phospholipase A2 (PLA_2)
- Insulin resistance makes platelets sticky

These processes worsen insulin resistance and damage retinal vessels

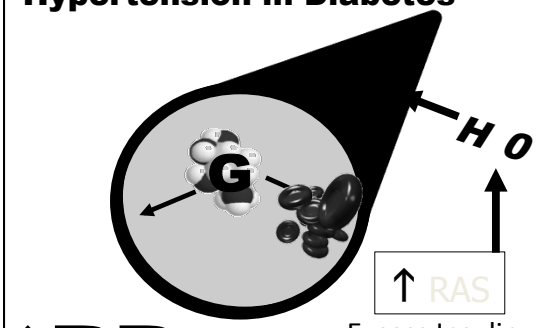


Vascular Pharmacol. 2017 Apr;91:1-9.

- Hypertension:
  - Glycation of vascular endothelium increases vessel rigidity
  - Glycation of RBCs increases blood viscosity
  - Hyperinsulinemia due to IR activates the renin-angiotensin system causing renal sodium retention and increased extracellular fluid volume

HTN causes inflammation and accelerates vessel leakage

Hypertension in Diabetes



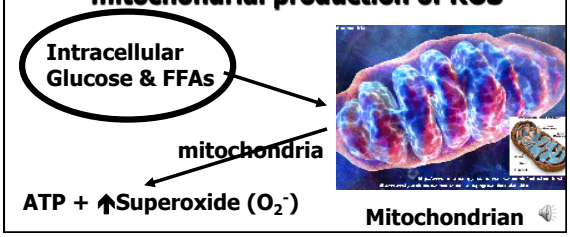
- Excess Generation of Reactive Oxygen Species (ROS) is caused by:
  - Intracellular Glucose
  - Intracellular Free Fatty Acids

Within VASCULAR Endothelium

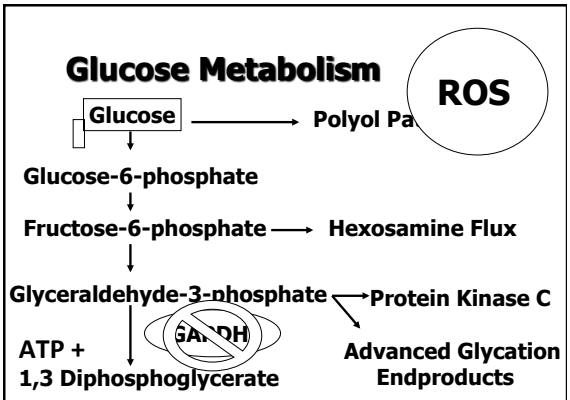
ROS increase inflammation & damage retinal cells

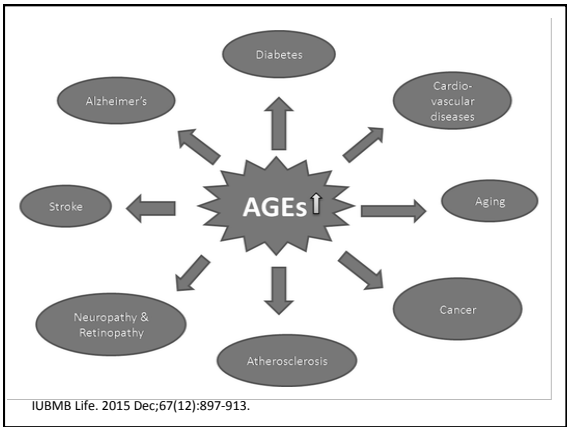
Pathophysiology

- Blood vessel damage in diabetes is mediated by four distinct biochemical pathways driven by mitochondrial production of ROS



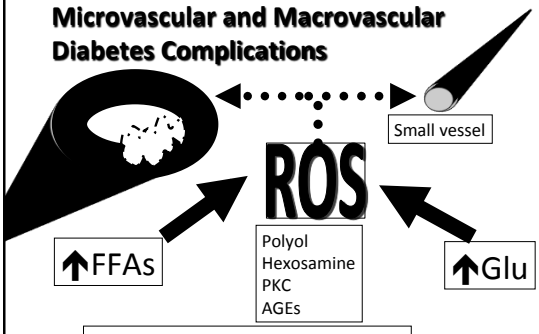
Glucose Metabolism





IUBMB Life. 2015 Dec;67(12):897-913.

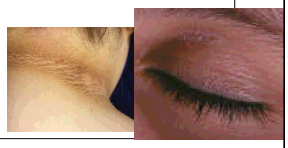
A Unifying Mechanism for Microvascular and Macrovascular Diabetes Complications



Adapted source: Michael Brownlee, M.D.

Optometric Findings That Increase DM Risk

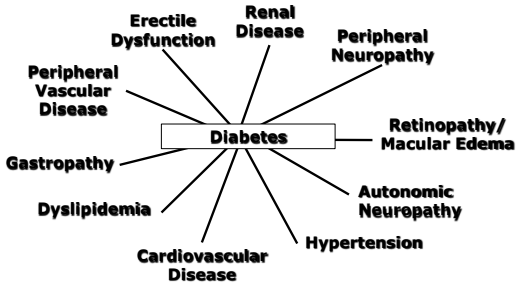
-
-
- hordeoli
- acanthosis nigricans
-



J Neurol Sci. 2009 Sep 15;284(1-2):24-8.

"
who discovered that I have diabetes."

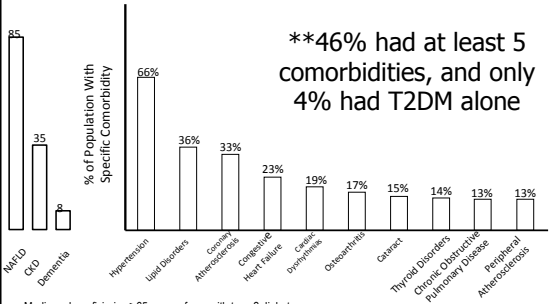
A Constellation of Complications



Diabetes Complications

- Only occur in tissues containing:
- **Blood Vessels**
- **Nerves**
- **Proteins**……..

Prevalent Comorbidities Among Older Patients With Type 2 Diabetes



**46% had at least 5 comorbidities, and only 4% had T2DM alone

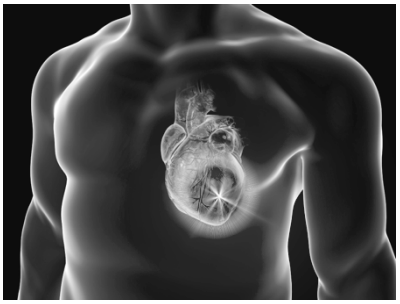
Medicare beneficiaries ≥65 years of age with type 2 diabetes.
Niefeld MR, et al. *Diabetes Care*. 2003;26:1344-1349. Copyright © 2003 American Diabetes Association. Reprinted with permission from The American Diabetes Association.

Extraocular Complications of DM

- Cardiovascular/Cerebrovascular Disease ✔
- Renal Disease ✔
- Podiatric disease ✔
- Neurologic disease ✔
- Sleep disordered breathimg ✔
- Dermatologic disorders ✔
- Sexual/Reproductive dysfunction ✔
- Anxiety/Depression ✔
- Cancer
- Musculoskeletal dysfunction✔
- Periodontal disease ✔
- Thyroid Disease ✔

Many are Associated With DR

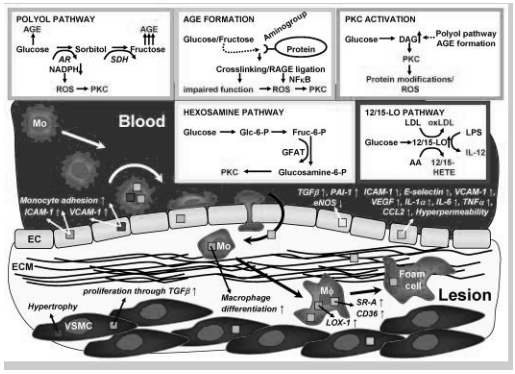
Heart Disease



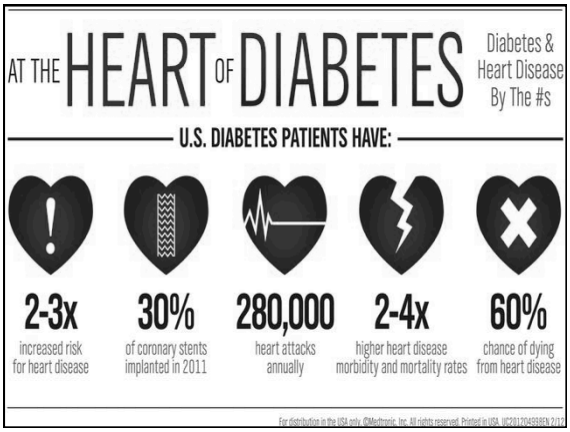
Pathobiology of CVD/Stroke in Diabetes

- Hypertension
- Cardiac autonomic neuropathy → arrhythmia
- Inflammatory dyslipidemia with atheroma formation/arterial stiffness due to AGEs
  - FFAs and hyperglycemia damage vascular endotheilium via ROS & ↑ cellular adhesion molecules with foam cell formation
  - CRP disrupts vulnerable plaques
- CHF 2X risk in men/5X risk in women from cardiac muscle exposure to glucose and FFAs

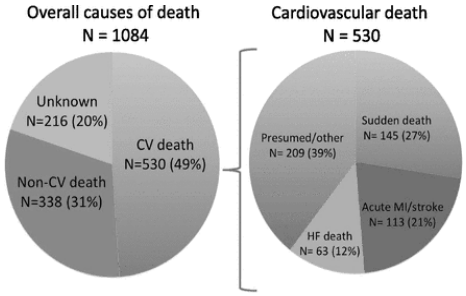
Drug Discov Today Dis Mech. 2007; 4(3): 131–140.
Card Fail Rev. 2017 Apr; 3(1): 52–55.



Drug Discov Today Dis Mech. 2007; 4(3): 131–140



Mortality in T2DM in CV saftety study of sitagliptin added to usual care



Diabetes Care 2017 Dec; 40(12): 1763-1770

DR/DME Are Associated with Cardiovascular and CVA Risk

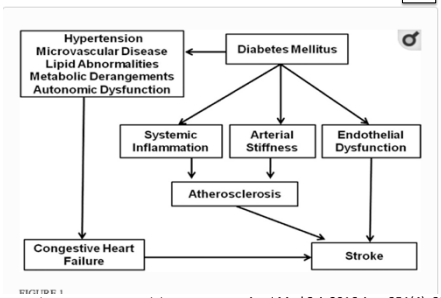
CHD = coronary heart disease

More Evidence: DR and CV Risk

- In meta-analysis of 25 observational studies (145,000+ patients), the presence of any diabetic retinopathy increased the risk of :
  - Stroke ↑74% Medicine (Baltimore). 2017 Jan;96(3):e5894
  - Congestive Heart Failure ↑124%
- PDR and/or DME increased risk of CV mortality 2.33 fold compared to subjects with NPDR or no DR
  - Meta-analysis of 8 prospective trials (n= 7000+) JAMA Ophthalmol. 2017 Jun 1;135(6):586-593.

Brain Disease: Stroke & Dementia

→ **Ischemic Stroke Risk is 1.7X Higher in Diabetes**
→ **Presence of DR in ACCORD-Eye Study increased incident CVA risk by 52% (p=0.026)**



Am J Med Sci. 2016 Apr; 351(4): 380–386.

Am J Med Sci. 2016 Apr; 351(4): 380–386.

Increased Dementia Risk?

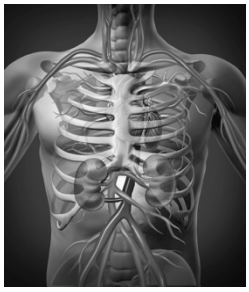
- **Meta-analysis: Diabetes increases risk for vascular & non-vascular dementia 60% compared to age-matched controls**
  - 2.3 million patients, 102K+ cases
  - 90% derived from Asian populations
  - HR for vascular dementia was 2.34X/1.73 in women/ men
  - Non-vascular dementia risk was 1.5X higher in both genders

Diabetes Care. 2016 Feb; 39(2): 300–307

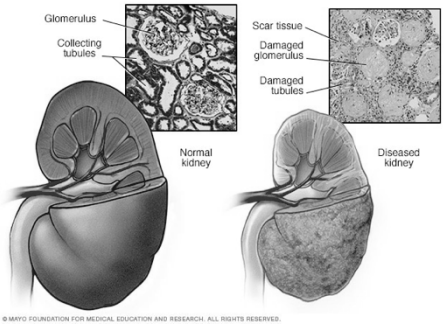
- AD referred to as 'type 3 diabetes' due to prevalent loss of hippocampal insulin sensitivity

Nat Rev Neurol. 2018 Mar; 14(3): 168–181.

Renal Disease

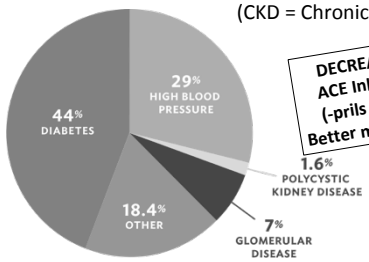


Diabetic Nephropathy



Diabetes is the main cause of CKD

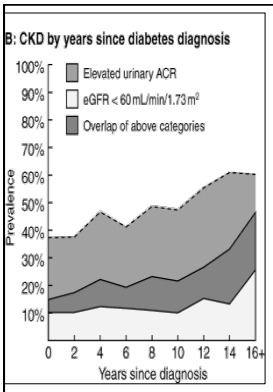
(CKD = Chronic Kidney Disease)



DECREASES DUE TO ACE Inhibitors/ARBs (-prils and –sartans) Better metabolic control

Diabetes is the leading cause of ESRD in the US - 45% 42K+ cases/year, but has decreased 33% from 2000-2014

MMWR Morb Mortal Wkly Rep 2017;66:1165–1170.



J Renal Inj Prev. 2015; 4(2): 28–33.

Diabetic Kidney Disease (DKD)

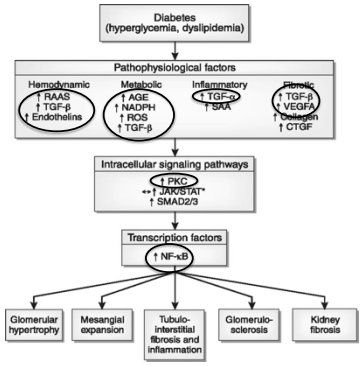
↑ Urinary albumin: creatinine ratio
ACR > 30mcg/mg = renal disease

↓ Estimated glomerular filtration rate (eGFR))
< 60ml/min = renal disease
(eGFR < 15 = kidney failure)

ESRD: ↑Urea (uremia) & Fluid Overload

Transplantation **Dialysis**
11 yr mean survival **5.2 yr**

DR and DKD Share Common Biology

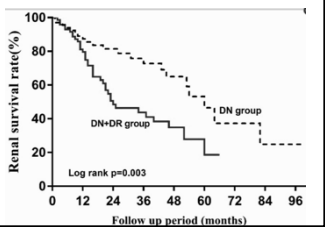


- **INCREASED**
- ROS
- VEGF-A
- TGF-α
- TGF-B
- RAAS
- AGEs
- Endothelins
- Protein Kinase C
- Nf-κB

DR and Kidney Outcomes

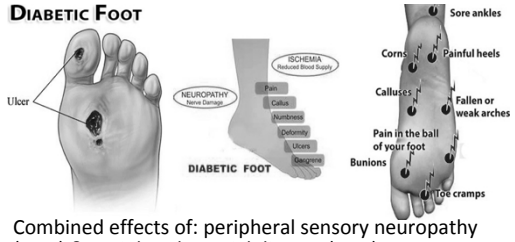
- **Diabetic retinopathy increases the risk of developing end-stage renal disease 2-3 fold**
- **ESRD survival was reduced by 3 years in pts with DR**

Ren Fail. 2018 Nov;40(1):243-251.



Foot Disease

Diabetic Foot Disease

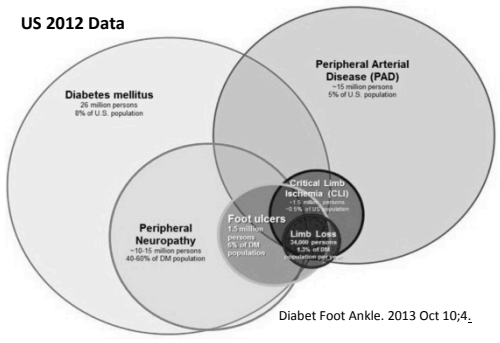


Combined effects of: peripheral sensory neuropathy (DPN) & peripheral arterial disease (PAD)

DM is the leading cause of non-traumatic lower-extremity amputations (US mean ≈ 73,000 per year)
→7.5 to 41X increased risk of LEA versus non-diabetes LEA = lower extremity amputation

PLoS One. 2017; 12(8): e0182081

Foot Disease: Overlapping Risks



Diabet Foot Ankle. 2013 Oct 10;4.

Diabetic Foot Ulcer Linked to DR

- **In retrospective analysis, 90% of patients with DFU had some degree of retinopathy (n = 100, all T2DM)**
- **55% of DFU patients had PDR**

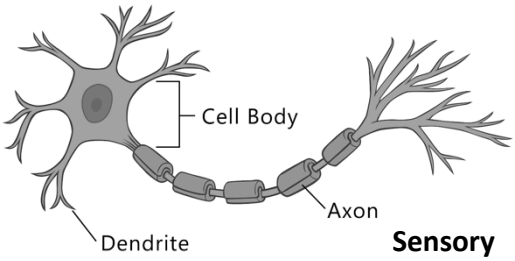
PLoS One. 2017 Apr 7;12(4):e0175270.

Diabetic Hand

- Microvascular and neuronal damage
- AGE deposition in collagen & muscle
- Cross-sectiona case-control study (n = 400) 2/3 of DM patients had one or more of the following compared to 19% of controls:
- Limited joint mobility (cheiroarthropathy)
- Dupuytren's contracture (palmar fascia thickening)
- Stenosing Tensosynovitis (trigger finger → pain)
- Carpal Tunnel Syndrome
- Charcot neuroarthropathy (fracture due to nerve loss)

Diabetes Care. 1983;6:140–143 Ann Med Health Sci Res. 2013 Jul-Sep; 3(3): 349–354
Nutr Metab (Lond). 2018; 15: 72 Cureus. 2018 Jun; 10(6): e2772.

Neuropathy



Sensory
Motor
Autonomic

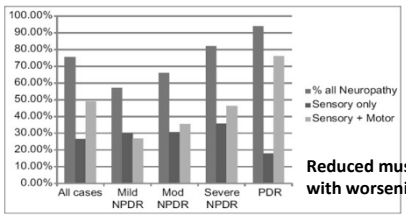
Diabetic Neuropathy

- 2/3 have DPN (pins/needles, burning, hypothesia → DFU; 20% asymptomatic): ↑duration & hyperglycemia
  - Decreased myelin & axon density/ ↓blood supply
  - Corneal sensory neuropathy linked to DPN
  - Poor pupil dilation linked to cardiac autonomic neuropathy (CAN)
- Autonomic neuropathy in 14-70% (↓vasovagal reflex, pupil response/accommodation, heart, stomach, orthostatic hypotension, neurogenic bladder/bowel, sexual dysfunction)
- TIND = treatment-induced neuropathy of diabetes (pain with rapid glucose reduction and worsening DR) – formerly called 'insulin neuritis'

Diabetol Int. 2020 Apr; 11(2): 87–96 Invest Ophthalmol Vis Sci. 2020 Mar; 61(3): 48

DR and Risk of Neuropathy

- 234 T2DM with known DR but asymptomatic for DPN –> nerve conduction studies
- 16X higher risk with PDR versus mild NPDR
- 6X higher risk with moderate/severe NPDR



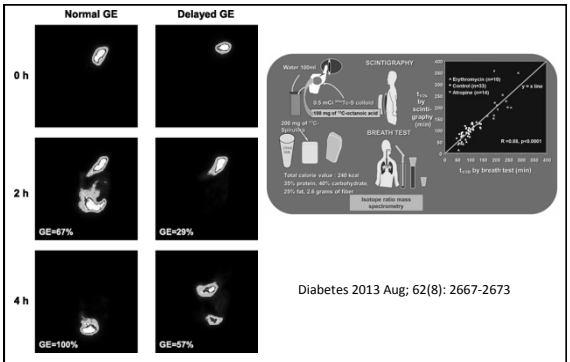
Reduced muscle strength with worsening DR

J Family Med Prim Care. 2020 Apr; 9(4): 1891–1895.

Diabetic Gastropathy & Esophogeal Dysmotility

- Autonomic neuropathy delays transit of food in/out of stomach
- Studies report prevalence of 1 to 64%!
  - More common in T1DM than T2DM
  - Prevalence thought to be 50+%/35%
- Symptoms bloating, stomach pain, nausea
- May Interfere with blood glucose control
- **DG/ED Strongly associated with DR (50%/ 61%)**

Mol Imaging Radionucl Ther. 2017 Feb; 26(1): 17–23
Rev Diabet Stud Summer 2011;8(2):268-75.



Diabetes 2013 Aug; 62(8): 2667-2673

Delayed Gastric Emptying (GE) is demonstrated by Technitium-sulfur scintigraphy or breath testing

Sleep Disordered Breathing

Apnea is Common in Diabetes

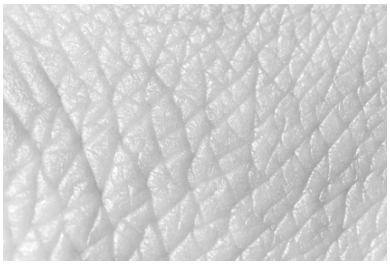
- Obstructive sleep apnea (OSA) is 2-3 fold more common in both T1DM and T2DM
  - Higher BMI and neck circumference
  - Neuropathy affecting upper airway muscles

AHI = Apneic+ Hypopneic events / Time

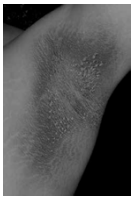
- After all adjustments, OSA increased odds of progressing to severe NPDR/PDR 5-fold
- **AHI > 11.9 vs < 4.8 increased odds of STDR 7.5-fold**

Am J Respir Crit Care Med. 2017 Oct 1;196(7):892-900.
J Diabetes Complications. 2017 Jan;31(1):156-161 Sleep Med. 2016 Sep;25:156-161

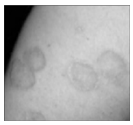
Skin Manifestations



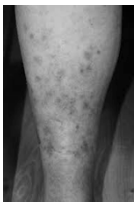
Common Skin Manifestations



Axillary acanthosis nigricans



Granuloma annulare



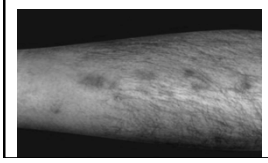
Diabetic dermopathy

- Fungal infections (hyperglycemia) − tinnea pedis
- Pruritis (reduced blood flow)

Am J Clin Dermatol. 2017 Aug;18(4):541-553

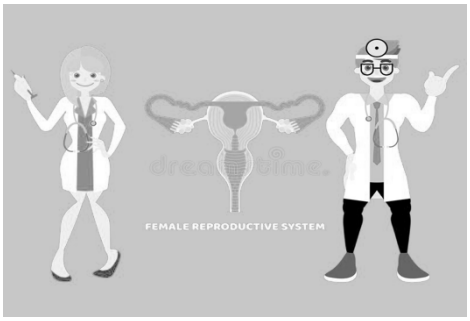
Diabetic Dermopathy (DD)

- Subjects with diabetic retinopathy were found to have a 3.6 X increased risk of dermopathy ($p < 0.003$)
  - **44% of DD patients had DR in one analysis**
- Well-demarcated hyperpigmented brownish papules, on the shins



Dermatology 2007;214:133–136
Clin Diabetes. 2015 Jan; 33(1): 40–48.

Sexual & Reproductive Dysfunction



Male Sexual/Reproductive Dysfunction in Diabetes

- Erectile dysfunction (ED) is 2-3 X more common in men with diabetes
  - T2DM has 2X the risk of T1DM
  - After age-adjustments, ED is 2X more common in T1DM vs T2DM
  - Improved HbA1c lowered risk in men < 60

  Diabet Med. 2017 Sep;34(9):1185-1192 J Sex Med. 2009 Jun;6(6):1719-1728
- Hypogonadism (low testosterone, desire, sperm count) is present in 25% of men with DM (c/w 2-12% in the general population Urol Clin North Am. 2016 May;43(2):163-76
- ED is highly associated with diabetic retinopathy and its severity independently of age and diabetes duration Urology. 2011 May;77(5):1133-6.

Female Sexual/Reproductive Dysfunction

- FSD is 2X higher using Female Sexual Function Index (FSFI) compared to women without diabetes in meta-analysis of T1DM/T2DM (n = 6+K)
  - Higher BMI/depression were associated with low FSFI
- In T1DM, self-reported sexual function was lower if HbA1c > 8% and frequent UTI
- ↑Menstrual disorders & polycystic ovary syndrome (25%) in T1 and T2 vs 6-15% in non-DM
- Women with pre-existing DM have significantly increased risk of fetal macrosomia (birth weight > 4 Kg = 8.8 lbs), perinatal death & congenital malformation

Curr Diabetes Rev. 2017;13(6):573-581. Minerva Endocrinol. 2016 Mar;41(1):122-37.
Int J Environ Res Public Health. 2020 Jun 22;17(12):4468 J Sex Med. 2013 Apr;10(4):1044-51

Polycystic Ovary Syndrome (PCOS)

Table 1. Some Common Signs and Symptoms of PCOS[a]

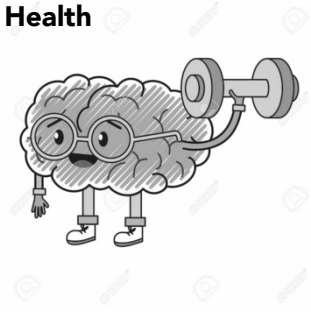
Menstrual Disturbances
Oligomenorrhea, amenorrhea, dysfunctional uterine bleeding Infertility and/or recurrent miscarriages
Hyperandrogenism
Hirsutism Acne Male-pattern alopecia (in 40%-70% of PCOS patients)
Other
Obesity/weight gain/inability to lose weight Obstructive sleep apnea Acanthosis nigricans (black or brown hyperpigmentation) on dermal areas, especially behind neck and in skin folds Episodes of depression Elevated prolactin levels and galactorrhea Hyperlipidemia, hypertension Presence/history of multiple ovarian cysts, sometimes accompanied by episodes of pelvic pain

[a] *This is not a comprehensive list.*
PCOS: polycystic ovarian syndrome.
Source: References 15-18.

Untreated PCOS
- insulin resistance
- sleep apnea
- HTN
- dyslipidemia
- CV disease
- endometrial hyperplasia
- endometrial cancer

Clin Epidemiol. 2014;6:1-13.

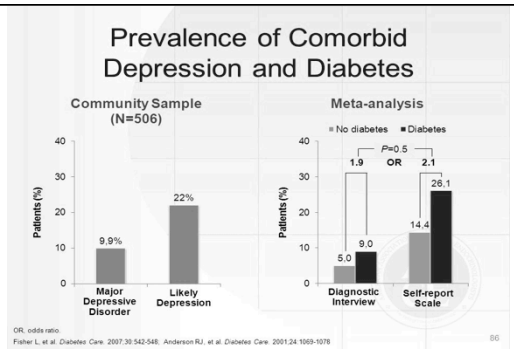
Mental Health



Mental Health & Diabetes

- Acute & Situational depression are doubly likely in diabetes JAMA. 2014 Aug 20; 312(7): 691–692.
- Anxiety disorder is 2.5 times more likely in diabetes and increases with onset of diabetes complications Gen Psychiatr. 2019; 32(4): e100076.
- Prevalence of depression and anxiety higher in pts w DR (95K with DM/5% with DR)
  - Higher depression in all DR but lowest for PDR
  - Anxiety only increased in mild & severe NPDR
  - Less anxiety in >65yo vs younger

  Olson D, ARVOLearn 2020, published on-line



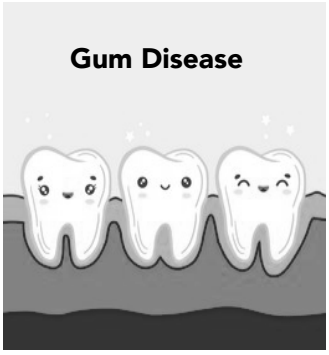
There is a reciprocal direct association between depressive symptoms and glycosylated hemoglobin

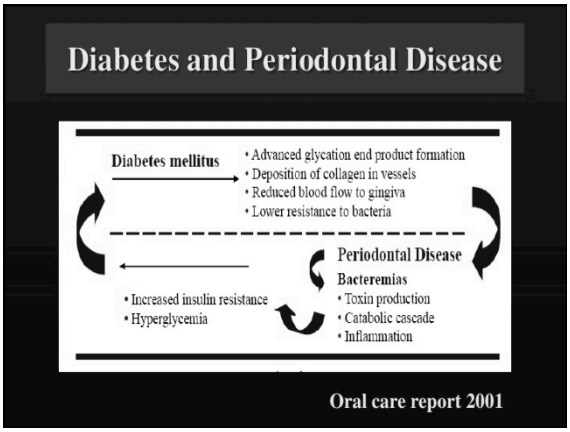
Psychol Med. 2016 Apr;46(5):945-55.

Why some people with DR/DME are Lost to Follow-up (LTFU)

- A study from San Francisco looked at risk for non-compliance with DR/DME follow-up
- 209 patients mean age 58yo w A1c 8.5
- 46% of patients attended <80% of f/u
- Risk factors for missing f/u:
  - **Foot involvement OR 2.4**
  - **Foot/kidney OR 3.7**
  - **Major depressive disorder OR 2.1**
  - **MediCal or SF Health insurance. OR 5.01/6.79**

Chen et al. Compliance with DR f/u. Ophthal. Epidemiol. 8/18.

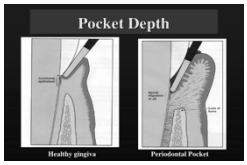




Periodontal Disease

- Non-obese type 2 diabetes patients with any periodontitis were doubly likley to have any DR Endocrine. 2017 Apr;56(1):82-89
- Presence of periodontitis is associated with a 2.8X increased risk of PDR

Diabetes Care. 2004 Feb;27(2):615



Thyroid Disorders

Thyroid Disease (TD) in Diabetes

- Up to 30% of T1DM pts have autoimmune thyroiditis (Hashimoto's Disease), and 3% have hyperthyroidism, including Grave's Dz
  - 2-4X risk compared to general population
- TD is 1.9 more common in T2DM
  - Sub-clinical hypothyroidism (SCT) most common
- HyperT associated with higher glucose & CV risk; HypoT associated with hypoglycemia, CV risk & microvascular complications
- SCT is associated with a 2 to 4-fold higher risk of sight-threatening diabetic retinopathy in meta-analysis after all adjustments (↑IR/CRP/endo dysfunction)

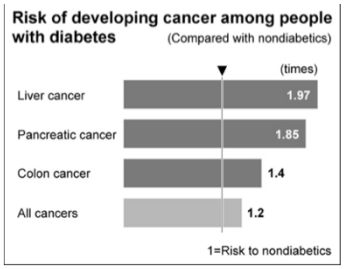
Endocr Rev. 2019 Jun 1;40(3):789-824
Trends Cardiovasc Med. 2020 Feb;30(2):57-6
Sci Rep. 2015 Jul 20;5:12212

Complication Potpourri

- Hearing loss is doubly likely in T2DM and 7X more likely in T1DM
  - "*We face an epidemic of another microvascular complication*" Semin Hear. 2019 Nov;40(4):281-291. . Int J Pediatr Otorhinolaryngol. 2018 Oct;113:38-45.
- Olfactory impairment is 60% more liklely in DM compared wih age-matched controls
  - High correlation with cognitive impairment
    Laryngoscope Investig Otolaryngol. 2019 Aug 7;4(5):465-475
- Leaky lymphatics ↓transport of lipids from organs hypothesized to → atherosclerosis
  Front Physiol. 2020 May 5;11:404.

Increased Cancer Risk

- Hyperinsulinemia upregulates IGF
- IGF promotes tumor growth



Tsilidis KK, Kasimis JC, Lopez DS, Ntzani EE, Ioannidis JP. Type 2 diabetes and cancer: umbrella review of meta-analyses of observational studies. BMJ. 2015 Jan 2;350:g7607.

Acute Complications of Diabetes that CAN Kill Patients

- **Hyperglycemia**
  - DKA → hypokalemia, cerebral/pulmonary edema
    - Hyperglycemia, metabolic acidosis, urine/blood ketones
    - < 5% fatality, more common in elderly, T1DM > T2DM
  - Non-ketotic hyperglycemic hyperosmolar syndrome (HHS) → osmotic diuresis with 20% mortality
    - Profound hyperglycemia (> 600 g/dl) with ↑ plasma osmolarity
    - 90+% T2DM
- **Hypoglycemia**
  - Common in patients using exogenous insulin: 4-10% mortality reported in T1DM
  - Dead-in-Bed Syndrome (fatal cardiac arrythmia) with glucose < 30 mg/dl; young T1DM and elderly T2DM on insulin
  - Vision loss

Treat Endocrinol. 2003;2(2):95-108
Diabetes Care. 2014 Nov;37(11):3124-31.
Diabetes Care 2012 Sep; 35(9): 1814-1816

Avoid SEVERE Hypoglycemia

- Kills retinal cells in animal models
  PLoS One. 2011;6(6):e21586.
- Fremantle Diabetes Study (Western Australia) showed that risk of 2+ lines of vision loss in T2DM was significantly & independently linked to hospitalization for severe hypoglycemia and cigarette smoking (n = 1551 over 4 years)
  - Smoking HR = 3.17
  - Severe Hypoglycemia HR = 5.59 p < 0.0001

Drinkwater, Jocelyn J., et al. "Incidence and Predictors of Vision Loss Complicating Type 2 Diabetes: The Fremantle Diabetes Study Phase II." Journal of Diabetes and Its Complications, Elsevier, 22 Feb. 2020

Symptoms of Acute Hypoglycemia

- **Perspiration (diaphoresis)**
- **Confusion**
- **Tremor**

Hypoglycemia
Level 1: BG < 70 mg/dl
Level 2: BG < 55 mg/dl

Who Gets:

Patients on insulin

Or

Sulfonylureas (Glipizide, Glyburide, Glimepreride)

Hypoglycemia

- **Always have a rapid-acting carbohydrate in the office (juice, sugared soda, glucose gel)**

15gm CHO will ↑ ~ 30-40 mg/dl (1.7-2.2 mmol/L)

The Rule of 15

- **For confirmed or suspected hypoglycemia**
- **Give 15 grams rapid-acting carbohydrate → wait 15 minutes & re-test glucose, if possible → if still < 70 mg/dl, give an additional 15 g CHO until glucose > 70 mg/dl or symptoms remit**
  - **If BG < 55 mg/dl & patient is unresponsive/unable to eat/drink, call 911**
- **Follow with fat/protein to stabilize blood glucose (e.g. cheese, peanut butter)**

CDC 2021 recommendations

Summary

- **Diabetes complications affect every organ system**
- **Chronic complications are mediated by small and large vessel vasculopathy, neuropathy and ROS-mediated insult**
- **Diabetic retinopathy coexists with many of these non-ophthalmic comorbidities**
- **Maintenance of excellent metabolic control mitigates many of these processes**

Thank You!

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