Diabetes:
Treatment and Management

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What is diabetes?

- DM is a chronic disorder characterized by a lack of insulin or increased resistance to insulin
- Insulin is needed for proper uptake of glucose
- Clinical result is hyperglycemia
  - retinopathy
  - nephropathy
  - neuropathy

Statistics

- Approximately 9.3% of US population
  - 29.1 Million Americans
  - 2012: 1 out of 10
  - 2050: 1 out of 5 to 1 out of 3
- Another **79 million** Americans have pre-diabetes and are likely to develop diabetes if do not change habits
  - 37% of adults age 20 or older

Cost of Care

- ⇧ from $172 Billion in 2007 to $245 Billion in 2012- ⇧41%
  - $ 176 B direct costs
  - $ 69 B indirect
- In CA alone, $24.5 Billion (July 2015)
- Medical cost 2.3X higher in pts with DM
- Care of people with DM accounts for 1 out 5 healthcare dollars in US

TYPE 1

- Formerly IDDM or juvenile onset
- Prevalence: 0.2%
- 10% of all DM
- Most common age of onset < 30
- Destruction of insulin producing B-cells in pancreas (auto-immune? viral?)
- Total lack of endogenous insulin
- Need to be on insulin to survive

TYPE 2

- Formerly NIDDM or adult onset
- Prevalence: ≈8.0%
- 90% of all DM
- Most frequent age of onset > 40
- Often asymptomatic
- Characterized by insulin resistance
- Strong genetic predisposition
  - One parent, 50% likelihood
  - Both parents , 80%

Gestational Diabetes

- Affects 4% of all pregnancies
- High risk populations:
  - Pregnant woman greater than age 25
  - Abnormal body weight
  - Have first degree relatives with diabetes
  - Hispanic, Asian, Native American , African American descent
- Screen in 24th to 28th week of pregnancy
- NO ADDITIONAL RETINAL SCREENING NEEDED

Symptoms

- Often asymptomatic, especially Type 2
- Classic symptoms
  - polydipsia
  - polyphagia
  - polyurea
- Others: weight loss, delayed wound healing, dry mouth, dry skin, recurrent infections, refractive changes

Risk Factors

- Family history
- Specific ethnic backgrounds
  - African Americans
  - Native Americans
  - Hispanic
  - Asian American
  - Pacific islander
- Sedentary Lifestyle
- Pertinent medical history
  - obesity
  - cardiovascular disease
  - HTN
  - High cholesterol
  - Polycystic ovarian syndrome
  - Psychiatric illness
  - Gestational DM
  - IFG/IGT

Traditional Diagnosis

- **Fasting blood glucose > 126 mg/dL**
- OGTT > 200 mg/dL (2 hour sample)
- Any random testing >200 mg/dl should be referred for further testing
- Random testing > 200 mg/dL with symptoms very suggestive of DM

New Diagnosis Criteria

- Panel of "experts" at ADA annual meeting now recommend A1C be used for diagnosis of diabetes
- Glycosolated hemoglobin
- Tells blood sugar control over 3 months
  - normal range 4% to 6%

HgbA1c	BS Level	HgbA1c	BS Level
4	**60**	**9**	**210**
5	**90**	**10**	**240**
6	**120**	**11**	**270**
7	**150**	**12**	**300**
8	**180**	**13**	**330**

New Diagnosis Criteria

- **≥ 6.5 would be indicative of DM**
  - First major change in 30 years
  - In adults and children, not pregnant women
    - Advantages:
      - Convenience: no fasting
      - More accurate: average over 3 months
    - Disadvantage:
      - Cost?

Treatment of Type 2 DM

- Goal: to produce desirable blood glucose levels with minimal adverse effects and maximal patient compliance
- Treatment begins with diet and exercise and ends with insulin
- Often, adequate control can be achieved with oral agents
  - If not, insulin is utilized

Medical Management of DM

Oral Agents[1]

DRUG CLASS	EXAMPLES Generic (Trade)
Biguanide	Metformin (Glucophage®)
α-Glucosidase Inhibitors	Acarbose (Precose®), miglitol (Glyset®)
Sulfonylureas	Glipizide (Glucotrol®), glyburide (Micronase®), glimepiride (Amaryl®)
Meglitinides	Repaglinide (Prandin®), nateglinide (Starlix®)
TZDs (glitazones)	Pioglitazone (Actos), rosiglitazone (Avandia®)
DPP-4 Inhibitors (dipeptidyl peptidase-4 inhibitors)	Sitagliptin (Januvia®), saxagliptin (Onglyza®), linagliptin (Tradjenta®), alogliptin (Nesina)
SGLT2 Inhibitors (sodium-glucose cotransporter 2 inhibitors)	Canagliflozin (Invokana®), dapagliflozin (Farxiga®), empagliflozin (Jardiance®)

1. Garber AJ, et al. American Association of Clinical Endocrinologists comprehensive diabetes management algorithm 2013 consensus statement. *Endocr Pract.* 2013;19(3):536-557.

Medical Management of DM

Injectable Non-Insulin Agents[1]

DRUG CLASS	EXAMPLES Generic (Trade)
GLP-1 Agonists (incretin mimetics)	Liraglutide (Victoza®), exenatide (Byetta®), exenatide ER (Bydureon®), dulaglutide (Trulicity®), albiglutide (Tanzeum®)
Amylin Analogs	Pramlintide (Symlin®)

1. Garber AJ, et al. American Association of Clinical Endocrinologists comprehensive diabetes management algorithm 2013 consensus statement. *Endocr Pract.* 2013;19(3):536-557.

Medical Management of DM

Insulin Therapy[1,2]

DRUG CLASS	EXAMPLES Generic (Trade)
Basal Insulin	Glargine (Lantus®), detemir (Levemir®), glargine U-300 (Toujeo®)
Rapid-Acting Insulin Analogs	Aspart (NovoLog®), lispro (Humalog®), glulisine (Apidra®), lispro U-200 (Humalog® U-200)
Premixed Insulin	70:30, 75:25, 50:50 (Humulin®, Novolin®)
Regular Insulin	U-500 (Humulin® R)
Inhaled Insulin	Afrezza

1. Garber AJ, et al. American Association of Clinical Endocrinologists comprehensive diabetes management algorithm 2013 consensus statement. *Endocr Pract.* 2013;19(3):536-557.
2. American Diabetes Association. Insulin basics. http://www.diabetes.org/living-with-diabetes/treatment-and-care/medication/insulin/insulin-basics.html. Accessed October 14, 2015.

Medical Management of DM

Insulin Delivery Devices

INSULIN PUMP THERAPY COMPANY	EXAMPLES
Medtronic	MiniMed® 530G, Paradigm® Revel™
Tandem	t:slim®, t:flex®
Insulet	OmniPod®
Animas®	Vibe™, OneTouch® Ping®
Accu-chek®	Combo

Current recommendations for Treatment of DM

- Control BS levels
  - HgbA1c < 7
- Control HTN
- Control Cholesterol levels
  - Total cholesterol < 200
- No smoking
- Exercise
- Yearly foot exams, dental exams, and dilated retinal exams

Diabetic Retinopathy

- Leading cause of blindness 20-74 year old
- 8-12% of all new cases of legal blindness
- 50,000 Americans legally blind
- Early diagnosis and treatment can decrease vision loss by 50-60%
- Factors which influence development of DR
  - duration of disease
  - control of BS

Duration of disease

- Type 1 Pts:
  - Retinopathy rare in 1st 3- 5 years
  - After 10 yrs, 60% have some retinopathy
  - After 20 yrs, almost always present
    - 50-60% PDR
- Type 2:
  - ≈ 20% to 39% have retinopathy at time of diagnosis
  - After 15 years, 60-80% have some retinopathy
    - 20% chance of PDR

Control of Blood Sugar

- DCCT Trial: 1993
  - Intensive blood glucose control reduced risk of developing retinopathy by 76%
  - Slowed the progression by 54% if already had retinopathy
- UKPDS: 1998
  - for every 1% decrease in HgbA1C there is a 35% reduction in risk for retinopathy
  - 34% reduction in retinopathy progressing with good HTN control

Diabetic Retinopathy

- Joslin Diabetes Center study
  - Only 60% of DM's receive "timely eyecare"
  - $624 million and 400,000 patients' sight saved if annual eye exam and appropriate treatment
- March 2001: *Ophthalmology* 35% of DM reported no annual DFE

Diabetic Retinopathy

- Non-proliferative Diabetic Retinopathy (NPDR)
  - mild
  - moderate
  - severe
  - very severe
- Proliferative Diabetic Retinopathy (PDR)
  - Including high-risk

Nonproliferative Diabetic Retinopathy (NPDR)

- Loss of retinal capillary pericytes
- Weakens capillary walls
- Causes non-perfusion in capillary beds and hypoxia
- Divided into mild, moderate, and severe (and very severe)

Mild NPDR

- Microaneurysms (ma)
- Dot/blot hemorrhages

- Follow-up: 1 yr
  - 5-10% of pts with no retinopathy will progress to retinopathy within 1 year
  - 5-10% with mild NPDR will also progress within 1 year

Moderate NPDR

- Marked hemorrhages/ma
- Cotton wool spots (CWS)
- Venous beading (VB)
- Intra-retinal microvascular abnormalities to mild degree (IRMA's)

- Follow Up: 6 months
  - as many as 16% of pts with mod NPDR can progress to proliferative disease within 4 years

Severe/ Very Severe NPDR

- 4-2-1 Rule:
  - Marked hemes/ma in all 4 quadrants
  - VB in 2 or more quadrants
  - Marked IRMA's in one quadrant
- Very severe: 2 of the 3 above criteria

- Follow-up: 3-4 months
  - Between 10-50% of pts with this level progress to PDR within 1 year
- Laser is sometimes recommended
  - Type 2 DM, associated with a 50% reduction in the rate of severe vision loss, vitrectomy and progression to high-risk PDR

Rate of Progression to PDR

	1 yr	**5 yr**
Mild	5%	14%
Moderate	12-26%	30-48%
Severe	52%	71%

Proliferative Diabetic Retinopathy (PDR)

- Hallmark is retinal neovascularization
  - response to ischemia from capillary closure
  - grow onto lattice of vitreous
  - new vessels are fragile and easily rupture
- Neo divided into 2 categories
  - NVD: on or within 2 DD of optic disc
  - NVE: neovascularization elsewhere

- Follow-up: Retinal consult within 2 weeks

High Risk PDR

- NVD >1/4 to 1/3 disc area
- Any NVD with a PRH or VH
- Moderate to severe NVE with VH or PRH
- Poses very high risk of severe VH and vision loss within 2 years

- Follow-up: Immediate Retinal consult (24-48 hours)

Clinically Significant Macular Edema(CSME)

- Characteristics
  - retinal thickening at or within 500 microns (1/3 DD) of center of macula
  - hard exudates at or within 1/3 DD if associated with thickening of adjacent retina
  - thickening greater than 1 DD in size part of which is within 1 DD of center of macular
- May occur at any stage of retinopathy
- Treatment: retinal consult within 2 weeks

CSME

- Level of Retinopathy
  - mild NPDR≈ 3% incidence of DME
  - moderate to severe NPDR ≈40%
  - Proliferative ≈ 71%
- Type 2: Duration and Insulin
  - no insulin
    - 10 years 5%
    - 20 years 15%
  - on insulin
    - 10 years 10%
    - 20 years 30-35%

DME

- ETDRS
  - 3711 pts, 22 centers, 10 years
  - Established focal macular laser (FML) as treatment for CSME
- PROS:
  - Reduced risk of moderate vision loss by 50%
  - 95% chance of maintaining vision when guidelines followed
- CONS:
  - 12% lost >15 letters at 3 years
  - <3% gained 15 letters
  - Diffuse, chronic, lipid deposits respond poorly

Steroids for DME

- Early 2000's, before anti-VEGF, IVT was looked at treatment for DME
  - Inhibit reduction of PGs
  - Decreases permeability
  - May Decrease VEGF proliferation
- DRCR.net *Ophthalmology* September 2008
- 848 eyes with CSME and VA from 20/40 to 20/320 were evaluated
  - At 2 yrs, laser is more effective and has fewer side effects than either 1 or 4 mg intravitreal triamcinolone

antiVEGF

- Lucentis, Avastin, Eylea
- Shown in multiple studies to be beneficial for DME
  - RISE
    - 18.1% of pts in sham gained ≥ 15 letters vs. 44.8% (0.3 mg) or 39.2% (0.5 mg)
    - 2.6 letters gained in sham vs. 12.5 (0.3mg) or 11.9 (0.5mg)
  - RIDE
  - READ
  - VISTA
  - VIVID

Protocol –T: Lucentis vs Avastin vs Eylea

- One year
  - Eylea gained 13.3 letters
  - Lucentis 11.2
  - Avastin 9.7
  - No statistical difference
- If VA was 20/50 or worse
  - Eylea gained 18.9
  - Lucentis 14.2
  - Avastin 11.8

Protocol –T

- 2 year results
  - No statistically significant difference between 3 drugs, even in those worse than 20/50
    - But better acuity with Eylea
  - Bottom line:
    - It may matter which drug
    - May matter more with worse vision
    - Economics may dictate
      - In order to justify use of lucentis/eylea vs avastin, price would have to decrease by 70-80%

PDR

- ETDRS
  - Established benefit of immediate PRP in patients with PDR
- PROS
  - Showed an overall reduction rate of severe vision loss (ie 5/200) of approximately 50% in treated vs. untreated eyes
  - <4% chance of severe vision loss in 5 years w/ tx
- CONS
  - Decreased VF
  - Decreased night vision
  - CME

Protocol S

- Non-inferior study evaluating Lucentis vs. PRP
- 55 sites, 203 pts with PRP, 191 with Lucentis, as frequent as q 4 weeks
- At 2 years:
  - VA improved 2.8 letters with Lucentis vs. 0.2 with PRP
  - More VF loss with PRP:. 531db vs. 213db loss
  - More vitrectomies in PRP group: 15% vs 4%

Protocol S

- Bottom line:
  - Longer Study needed
  - Economics may dictate
  - May be best with concurrent DME
  - Pt must be complaint
  - Perhaps combo of both treatments will be best?
  - Role in severe NPDR?

LUCENTIS FDA approved April 17, 2017 for treatment of ALL forms of diabetic retinopathy

Care of the diabetic patient

- Dilated retinal exams
- Timely intervention and referral to retinal specialist
- Patient education
  - inform of ocular side effects
  - retinopathy possible even with good vision
  - report ocular symptoms associated with DM
  - advise about organizations for support