Diabetes

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Diabetes

What are we trying to accomplish ?

Let the target serve the patient,
not the patient the target!

Per the ADA

- 33-49% of patients do not meet targets for A1C, blood pressure, or lipids
- Only 14% of all diabetic patients meet all requirements for a1c, lipid, BP and smoking goals

Goals in Diabetes

- Macrovascular changes
- Microvascular changes

Goals in Diabetes

- Macrovascular changes
  - Reducing the A1c by 1 point = 45% reduction in MI risk
  - Study reduced A1c from 7.8% to 7.0%
    - **Glycemic Control in Patients with Type 2 Diabetes Significantly Lowers Cardiovascular Disease Risk.** Value-Based Care in Cardiometabolic Health August 2012, Vol 1, No 2 - *Cardiometabolic Health*
  -
  - Stratify Heart Risk by presenting A1c
    - A1c 5.0= heart attack risk is normal for person that age with similar health conditions
    - A1c 5.5%-6.%= 23 % relative risk increase
    - A1c 6.0%-6.5%=78% relative risk increase
    - A1c 6.5% or greater=200% relative risk increase
      - **Glycated Hemoglobin, Diabetes, and Cardiovascular Risk in Nondiabetic Adults. Selvin et al. New England Journal of Medicine. 2010; 362:800-811**

How low is low enough?

Advance/U.K. Prospective Diabetes Study (UKPDS) 5 yr. f/u

- Safe to reduce a1c to 6.5
- Mortality fell by 12% in the intensive treatment, but not statistically significant
- No change in MI risk
- Microvascular changes
  - 25-50% reduction in microvascular changes

- U.K. Prospective Diabetes Study Group Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998; 352: 837– 853
- Stratton IM, Adler AI, Neil HA, Matthews DR, Manley SE, Cull CA, Hadden D, Turner RC, Holman RR: Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ 2000; 321: 405– 412

STENO-2

- Longitudinal study, 20 plus years
  - At 21 years, intensive therapy gained 8 years of life vs. non-intensive therapy

- A Cost Analysis of Intensified vs. Conventional Multifactorial Therapy of Patients with Type 2 Diabetes—The Steno 2 Study," presented at the American Diabetes Association's® (ADA's) 78th Scientific Sessions® at the Orange County Convention Center

ACCORD TRIAL.

- 5 year. Intensive treatment treatment stopped 17 months early
  - Less than 8 show reduction in MI risk
  - Less than 6 showed an increase in MI risk

- **Clinical Implications of the ACCORD Trial.** S. Genuth, F. Ismail-Beigi .*The Journal of Clinical Endocrinology & Metabolism*, Volume 97, Issue 1, 1 January 2012, Pages 41–48, https ://doi.org/10.1210/jc.2011-1679

Goals in Diabetes

- Microvascular changes
  - Retinopathy, neuropathy, chronic renal disease
  - Reduce by 30-40%
    - Primarily retinopathy
      - advance/UKPDS

American Diabetic Association recommendations

- Under 7.0%: majority of adults with diabetes
- Under 6.5%: patients who can tolerate the treatment, younger patients
- Under 8.0%: patients with a history of hypoglycemia, limited life expectancy, or those with longstanding diabetes and vascular complications

A1c limitations

- Weighted mean average
  - Weights last six weeks higher than other
  - A1c value will be disproportionately affected by the most recent glucose levels
    - Ex. recent steroid injection
- Conditions that change A1c
  - Certain anemias-false increase
  - Severe hypertriglyceridemia-false increase
  - Chronic alcohol assumption- false increase
  - Anemia from acute or chronic blood loss-false decrease
  - Splenomegaly- false decrease
  - Pregnancy-false decrease

- Saudek CD, Brick JC. Clinical advances in hemoglobin A1c measurement: the clinical use of hemoglobin A1c. J Diabetes Sci Technol. 2009;3(4):629–634. doi: 10.1177/193229680900300402. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
- 8Tahara Y, Shima K. Kinetics of HbA1c, glycated albumin, and fructosamine and analysis of their weight functions against preceding plasma glucose level. Diabetes Care. 1995;18:440–447. doi: 10.2337/diacare.18.4.440. [PubMed] [CrossRef] [Google Scholar]
- Nathan DM, Kuenen J, Borg R, et al. Translating the A1c assay into estimated average glucose values. Diabetes Care. 2008;31(8):1473–1478. doi: 10.2337/dc08-0545. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

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Medications for Diabetes

Lifestyle Changes

Biguanide

Metformin

- What it does
  - Suppresses glucose production from the liver
  - increases insulin sensitivity
  - decreases absorption of glucose from the GI tract
  - DOES NOT increase insulin levels
- Side effects
  - GI: diarrhea/nausea
  - Renal
    - Not indicated in CC under 30
    - Stop at creatinine around 1.5
    - Oral contrast
  - ADA recommends monitoring b12 levels ‘periodically’

Sulfonylurea

Glipizide, glimepiride, glyburide

- What they do
  - Stimulates the beta cells of the pancreas to release insulin
    - Not for type I
    - The less beta cell production, the less effective the medicins become
- Side effects
  - Hypoglycemia
  - Weight gain

Thiazolidinediones

Actos (pioglitazone), Avandia (rosiglitazone)

- At one point, avandia+metformin was the best selling diabetic medicine in the world
- What do they do
  - Increase insulin sensitivity
- Side effects
  - Edema
    - Exacerbate or uncover CHF
  - Bone loss
  - Cardiac risk
    - 2007-2013 avandia use was restricted
    - Increase cardiac risk
    - Since lifted
  - Bladder cancer
    - Conflicting data,
    - FDA considers this a risk

Role of Glucagon in diabetes

Glucagon

- Opposite of insulin
- Turns glycogen (stored in liver) into glucose
- In Type II diabetes, glucagon is not suppressed after a meal

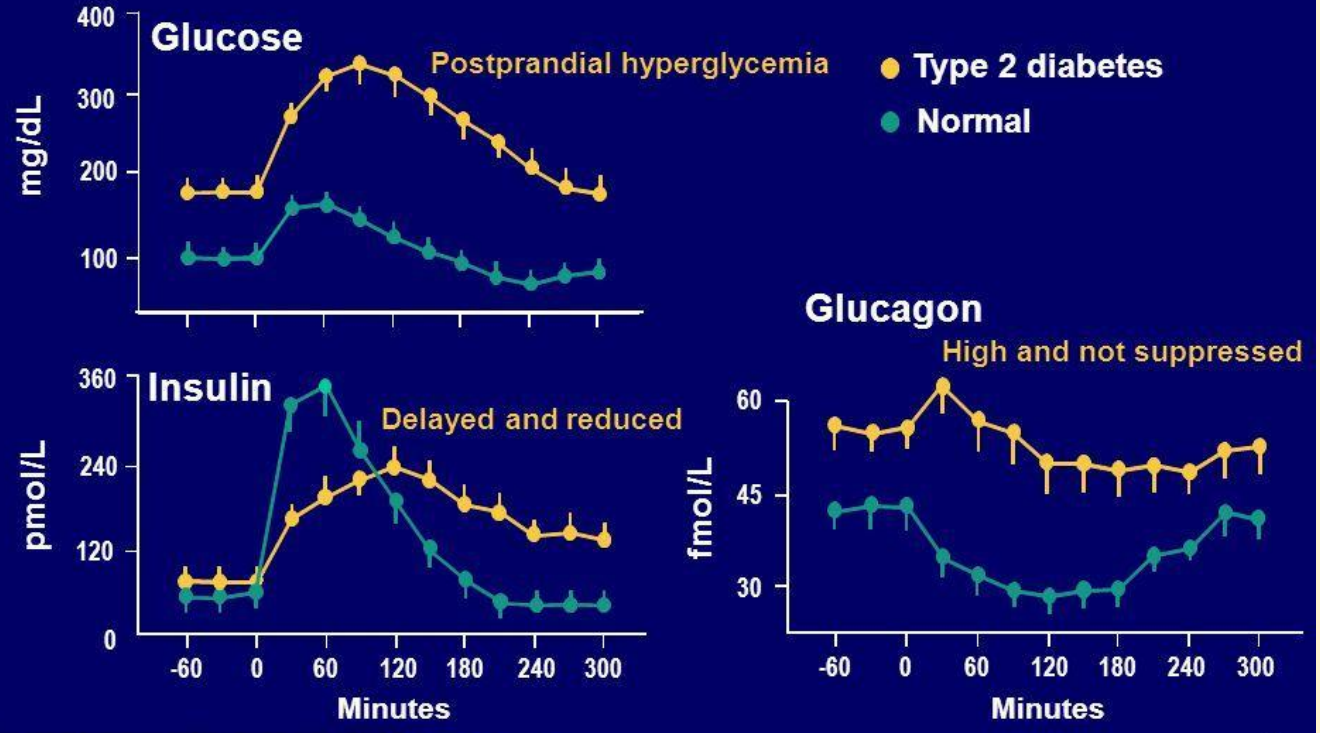
GLP-1

- Released by the intestine AFTER meals
    - Decreases glucagon production
    - Stimulates insulin production

DDP-4

    - Breaks down GLP-1

Patterns of Glucose, Insulin, and Glucagon in Type 2 Diabetes



Mitrakou A et al. *Diabetes.* 1990;39:1381-1390

DDP-4 Inhibitor

Januvia, Onglyza, Tradjenta

- Complete market domination by januvia

- What they do
  - DDP-4 breaks down GLP-1
  - This inhibits DDP-4, increasing GLP-1
- Side effects
  - Fairly neutral
  - Possible increase in CHF (onglyza)
  - Possible increase in pancreatitis
  - Weight neutral

GLP-1 agonist

Bydureon, Victoza, Trulicity, Ozempic

- All injectables

- What they do
  - Mimics natural GLP-1
    - Slow food absorption/gastric emptying
    - Stimulate insulin from beta cells
    - Decreases glucagon production
    - Decrease appetite
- Side effects
    - Weight loss
    - Cardiac protection
      - Victoza
      - Bydureon-no more events.

- Side Effects (cont)
  - Renal protection?
    - Award-7
    - liraglutide
  - Nausea
    - Gastroparesis
    - Dose at night to reduce nausea
  - Pancreatitis
  - Medullary thyroid cancer
- Per ADA, GLP-1 preferred to insulin
    - Not approved for type I

SGLT-2 inhibitor

Invokana, Jardiance, Steglatro, Farxiga

- What they do
  - Inhibits SGLT-2 in the distal tubule
  - Tosses sugar out in the urine
- Side effects
  - Mycotic and genital infections
  - Decreased bone mineral density
    - Lower limb amputation
      - Black box invokana
      - Not reproducible in other trials
      - Labeling for steglatro
      - Assumed to be class effect in Europe

- Side Effects (cont)
  - Weight loss
    - Off-loads around 60-100 grams of sugar a day
  - Decrease in blood pressure
  - Decrease in progression to renal failure
    - Creedence trial
      - Invokana
    - Reduction in admission in heart failure
  - Reduction in death from cardiac causes/reduction MI/CA
    - Invokana
    - jardiance

Insulin

- Two Types
  - Human insulin
    - More variable
  - Analog insulins
- Three parts of insulin
  - Onset, peak, duration
- Side effects
  - Hypoglycemia
  - Weight gain

Insulin

Onset	Peak	duration
Short-10-20 minutes Humalog/Novolog/ “R”	1-3 hours	3-5 hours
Intermediate-1-2 hours NPH	4-8 hours	12-14 hours
Long acting (basal)-1-4	No peak	24 hours 48 hours-tresiba
Combination NPH/regular-70/30		

Other Medicines

- Metaglinides
  - Stimulated insulin from beta cell
    - Prandin
  - Side effects
    - Similar to sulph.
- Alpha-glucosidase inhibitors
  - Acorbose
    - Starch blocker: inhibits release of glucose from carbs
  - Side effects:
    - Diarrhea
    - Gas (78%)
  - Popular in china
  - Only monosaccharides such as glucose tablets work to reverse hypoglycemia
- Amylin mimetic
  - Symlin
    - Similar to GLP-1
    - Approved type I and type II diabetes
  - Side effects
    - Nausea
    - Black warning for hypoglycemia with insulin
- Bile acid sequestrants
  - Wellchol
    - Unknown mechanism of action
    - Side effects
      - constipation

Other Medicines

Statins

- Under 40
  - ASCVD risk less than 20%-no treatment
  - ASCVD risk greater than 20%-high intensity
- Over 40
  - ASCVD risk less than 20%-moderate intensity
  - ASCVD risk greater than 20%-high intensity
- If ASCVD, continue adding medicine until LDL is under 70

zetia

Repetha

Triglycerides

- Trigs over 500: treat to reduce risk of pancreatitis
  - Fenofibrate
  - Vascepa
    - Reduce CV trial
- Trigs 150-499: lifestyle changes and stop medicines that elevate trigs

Renal function

- Asses for microalbumin
- Secondary prevention, not primary
  - ACE/ARBS
  - Invokana?

Gastric Bypass

- 87% better control with less medicine, 78% achieve normal glucose with no medicine
  - Buchwald H, Estok R, Fahrbach K, et al. Weight and type 2 diabetes after bariatric surgery: systematic review and meta-analysis. Am J Med. 2009;122:248–256
- Metabolic surgery **should** be recommended with BMI ≥40 kg/$m^2$and in adults with BMI 35.0-39.9 kg/m^2 (32.5-37.4 kg/m^2 in Asian Americans) who do not achieve durable weight loss and improvement in comorbidities (including hyperglycemia) with reasonable nonsurgical methods.
- Metabolic surgery **may** be considered as an option for adults with type 2 diabetes and BMI 30.0-34.9 kg/m^2How to treat

How do we treat Diabetes?

Metformin, then everything else in what every order you want

How do we treat Diabetes?

Metformin, then assess for secondary prevention of Coronary Disease

- Prioritize secondary cardiac prevention
- “In patients with type II diabetes and additional risk factors for CVD, it may reasonable to initiate these two classes of medications for primary prevention of CVD”
    - Victoza
    - Jardiance
    - Invokana

- 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol* 2019;March 17:[Epub

How do we treat Diabetes?

Metformin, then assess for secondary prevention of Coronary Disease

- Prioritize secondary cardiac prevention

In the future, Metformin,then assess for secondary prevention of Coronary Disease, then assess for renal disease

- SGLT-2
  - SGLT-2s

How do we treat Diabetes?

Do you prioritize the cost control to the system?

Do you prioritize the extra benefits to the patient?

Do you prioritize the extra effort to the staff?

Do you prioritize the ease visit?

What is your patient population?

How comfortable are you with starting an injectable?

How comfortable are you with explaining certain side effects?

How comfortable are you with dealing with patient’s side effects

What I do

Metformin first, unless there is a reason not to

GLP-1 or SGLT-2, depending on circumstance

Actos or sulfonylurea depending on circumstance

Basal insulin

Pt examples

69 white male.

HX of CABG, CAD.

No medicines for Diabetes.

A1c 6.6%

- Referred to dietician
- Recheck the a1c in three months
  - Lifestyle changes work
- If the a1c is still high
  - Metformin first, but
  - Consider cardioprotective
- I always titrate metformin
- Can consider insulin if a1c over 10
  - Remember to transition off the insulin

Pt examples

43 white male.

HX: DM, HTN.

Meds: Chlorthalidone. Metformin.

A1c: 8.2%, potassium: 3.1

- Pt deferred an injectable
- Held SGLT-2
  - Decreased potassium secondary to the chlorthalidone
  - Pt deferred to change the fluid pill
- With SGLT-2
  - Be careful with any pt already on a diuretic or blood pressure medicine

Pt examples

59 white male.

Hx: factory worker. DM, HTN.

medicines: janumet 50/1000 1 BID. lisinopril 20/12.5.

A1c 8.0%

- Already on janumet, no GLP-1
  - I could stop the janumet and add GLP-2
  - No study suggests GLP+DDP is effective
- Held sulfonylurea due to risk of low sugar with hard work
  - Sometimes they don't eat on 12 hour shifts
- Held SGLT-2. Already on diuretic, risk of dehydration
  - If I did this, consider adjusting or stopping the HCTZ
- Added actos.

Pt examples

70 BM, Hx of: DM, CHF, pacemaker, CRD.

medicine: glimepiride 2.5mg.

A1c: 7.5, creatinine 1.93.

- What medicines do you not use?
  - DDP-4
  - Actos
  - Metformin
- SGLT-2
  - Possible renal protective
  - Possible reduce risk of HF admissions
  - May not work with reduced eGFR
- Insulin
- Continued current meds

Pt examples

63 year old truck driver, HTN, CAD, DM.

Medicines: Metoprolol 25, glimepiride 2mg, lipitor 10, lisinopril 20.

A1c: 7.0%

- Changed the glimepiride to jardiance
- High incidence of hypoglycemia. Dangerous as a truck driver
- Jardiance shows a decreased risk CVA deaths
    - Foot exams
    - Push fluid
        - 3-4 bottles of water in the AM
    - Watch other diuretic type medicines

Pt examples

62 White female. HX: HTN, DM, Obesity. New onset DM.

A1C: 6.9%.

One of her concerns was weight loss

- Started ozempic
  - Not indicated for first line
  - Dose at night to help with the nausea
  - Document no gastroparesis/medullary thyroid cancer
  - Give the first dose in the office
    - Improves compliance
- Is a GLP-1 worth the conversation vs DDP-4?

Pt examples

51 BM HX: DM, HTN.

Medicine: glimepiride 4mg BID, invokana 300 mg, metformin 500 2 po AM, 1 po noon 1 po Qpm, Bydureon, Actos 45.

A1c 8.5%

- Stop sulfonylurea
- Basal insulin at 10-20 units
  - Go up 1 unit every 2-3 days
  - Give pt schedule
- Insulin
  - Basal will drop the higher a1c, the closer to 7, the harder it gets
    - Postprandial
  - Meal time insulin
    - Postprandial

- Consider stopping all orals
  - Cuts down on cost

Let the target serve the patient,
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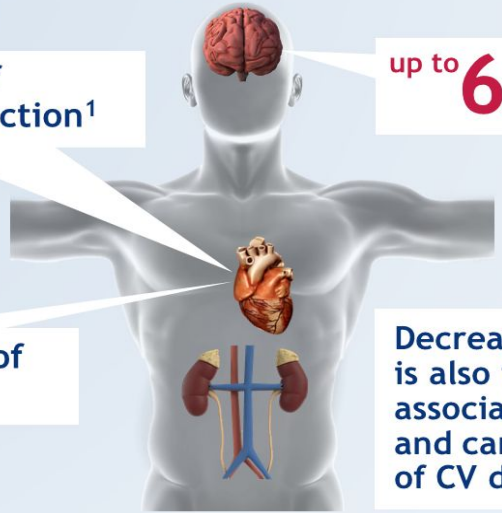
Diabetes Increases the Risk of Cardiovascular Disease

Patients With Diabetes Compared to Those Without Diabetes

5x increased risk of myocardial infarction[1]

up to **6x** increased risk of stroke[3]



2x increased risk of CV death[2]

Decreased renal function is also frequently associated with diabetes and can contribute to risk of CV disease and stroke[4]

- Stroke is a life-changing event for patients, their families, and caregivers[3]
  - In a 2015 survey of 186 patients in the US at risk of stroke, patients responded that avoiding a disabling nonfatal stroke was 1.7x more important than avoiding death[5]