DIABETES MANAGEMENT INTERN IMMERSION BLOCK

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Attending, Roosevelt General Internal Medicine Center
Outline

• Classification
• Screening
• Prevention
• Therapy
• Complications/Chronic disease management
Case

A 42 year old male presents to clinic for evaluation of weight loss and fatigue. He has no family history of diabetes. On review of symptoms he reports urinary frequent and excessive thirst, otherwise negative. Physical exam is notable for a BMI of 24, BP 108/70, HR 105, otherwise normal. Random blood sugar during clinic visit is elevated at 215. You order a hemoglobin A1c and a chemistry panel.

What additional blood test is likely to aid in the diagnosis of this patient?
## Classification

<table>
<thead>
<tr>
<th>Type</th>
<th>Pathophysiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1</td>
<td>Autoimmune β-cell destruction</td>
</tr>
<tr>
<td>Type 2</td>
<td>Insulin resistance with relative insulin deficiency, may progress to complete insulin deficiency</td>
</tr>
<tr>
<td>Gestational diabetes</td>
<td>Increased insulin resistance with relative maternal insulin deficiency</td>
</tr>
<tr>
<td>Secondary diabetes</td>
<td>Multiple causes: corticosteroid use, hemochromatosis, chronic pancreatitis</td>
</tr>
</tbody>
</table>
Type 1 DM

- Epidemiology: Young, slender patients
- Risk factors: genetic predisposition, likely environmental triggers
- Classic presentation: Diabetic ketoacidosis
- Auto-antibodies include: islet-cell antibodies (ICA), and antibodies to glutamic acid decarboxylase [anti-GAD]
Latent Autoimmune Diabetes in Adults: LADA

- Adult onset Type 1 diabetes
- Suspect in patients without classic risk factors
- Diagnosis supported by presence of auto-antibodies, send glutamic acid decarboxylase (GAD65) antibody assay
- More likely to require insulin, respond poorly to oral medications, prone towards DKA
Type 2 Diabetes

- Non-modifiable risk factors: H/o gestational diabetes, race (Native Americans, Hispanics, African and Asian Americans, Pacific Islanders), family history
- Modifiable risk factors: obesity, inactivity
- Disease associations: PCOS, dyslipidemia, hypertension, impaired fasting glucose
- Medication side-effects: antipsychotics, protease inhibitors, corticosteroids
Case

A 42 year old female with hypertension presents for a preventative medicine visit. She has a family history of hypertension, hyperlipidemia and type 2 diabetes. On exam her BMI is 31 and her BP is 135/86.

Do you screen her for diabetes?
Screening

- Testing options: fasting blood sugar, hemoglobin A1c, 2 hr 75 g OGTT
- USPSTF:
  - Pt with BP >135/80 (treated or untreated)
- ADA:
  - All pt at age 45
  - Earlier in overweight pts (BMI >25) with additional risk factors (inactivity, 1st degree relative with DM, high-risk population, h/o gestational DM, CVD, HTN, dyslipidemia, PCOS)
  - Screen q 3 yrs
Case

Fasting lab results:
- total cholesterol 192, triglycerides 219 (normal is <150), HDL 40, LDL 108
- sodium 138, potassium 4.9, creatinine 0.8, blood sugar 106.

How do you discuss these results with your patient?
Diagnosis

<table>
<thead>
<tr>
<th>Test</th>
<th>“Impaired”</th>
<th>Diagnostic for DM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting blood sugar*</td>
<td>100-125 mg/dL</td>
<td>≥126 mg/dL</td>
</tr>
<tr>
<td>Random blood sugar (+ symptoms)</td>
<td></td>
<td>≥ 200 mg/dL</td>
</tr>
<tr>
<td>Hemoglobin A1c*</td>
<td>5.7% - 6.4%</td>
<td>≥ 6.5%</td>
</tr>
<tr>
<td>2 hr 75 g OGTT*/**</td>
<td>140-199 mg/dL</td>
<td>≥ 200 mg/dL</td>
</tr>
</tbody>
</table>

*: Confirm by repeat testing  
**: Rarely used in practice
**Type 2 DM Prevention = Life-style modifications +/- metformin**

- Finnish Diabetes Prevention Study

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Weight loss at 2 yrs</th>
<th>Cumulative incidence of DM @ 4 yrs</th>
<th>RRR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>0.8 kg</td>
<td>23%</td>
<td></td>
</tr>
<tr>
<td>Lifestyle counseling</td>
<td>3.5 kg</td>
<td>11%</td>
<td>58%</td>
</tr>
</tbody>
</table>

- Diabetes Prevention Program

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Incidence of DM/100 person-yrs</th>
<th>RRR</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metformin</td>
<td>7.8</td>
<td>31%</td>
<td>14</td>
</tr>
<tr>
<td>Lifestyle intervention</td>
<td>4.8</td>
<td>58%</td>
<td>7</td>
</tr>
</tbody>
</table>


N Engl J Med 2002;346:393-403
Other clues to test...

Symptoms:
- Polyuria, polydipsia
- Unexplained weight loss

Physical exam findings:
- Acanthosis nigricans
- Recurrent vaginal yeast infections
- Peripheral neuropathy
General Treatment Options

- Dietary counseling
- Physical activity
- Oral hypoglycemic agents
- Insulin
- Other injectables
- Anti-obesity measures
Case

59 yo male presents for management of type 2 diabetes, hypertension and coronary artery disease. He has a history of subarachnoid hemorrhage with residual cognitive deficits. Initial labs reveal a HgbA1c of 9.9%.

What is your goal HgbA1c for this pt?
Recent Studies of Macrovascular Outcomes

- Long-standing, poorly controlled T2DM, aggressive A1c lowering results in:
  - ACCORD: ↑ all cause death, no benefit/harm re:CV outcomes
  - ADVANCE: no benefit/harm re:CV outcomes
  - VADT: no benefit/harm re:CV outcomes

- Newly dx’ed T2DM
  - UKPDS 10 yr f/u:
    - “legacy” effect
    - CV benefits of metformin tx > insulin or sulfonylurea

ACCORD (NEJM 2008;358:2545-59)
ADVANCE (NEJM 2008;358:2560-72)
VADT (NEJM 2009;360:129-39)
UKPDS 10-yr F/U (NEJM 2008; 359:1577-89)
Putting it all together…

What does hemoglobin Ac1 mean?

<table>
<thead>
<tr>
<th>Hb A1c (%)</th>
<th>Blood glc mg/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>126</td>
</tr>
<tr>
<td>7</td>
<td>154</td>
</tr>
<tr>
<td>8</td>
<td>183</td>
</tr>
<tr>
<td>9</td>
<td>212</td>
</tr>
<tr>
<td>10</td>
<td>240</td>
</tr>
<tr>
<td>11</td>
<td>269</td>
</tr>
<tr>
<td>12</td>
<td>298</td>
</tr>
</tbody>
</table>

Average BS = 125 + 30 for every % point > 6
Case

You are caring for a 59 year old female in the hospital, admitted with an UGIB. You are now planning for discharge, she has no diagnosis of diabetes but has had persistent blood sugar elevations (fasting blood sugars 155-185, pre-meal blood sugars 175-215) and has been getting small amounts of insulin since she began eating again. You tested her hemoglobin A1c, it was 5.5%.

Do you think this patient has diabetes?
Accuracy of A1c

• Falsely elevated values:
  • Low RBC turnover: untreated iron, B12 or folate def. anemia

• Falsely depressed values:
  • Increased RBC turnover: hemolysis, treated iron, B12, folate def. anemias, erythropoietin
  • Hemodialysis
  • RBC transfusion
# Oral diabetes medications

<table>
<thead>
<tr>
<th>Class</th>
<th>Specific Agents</th>
<th>Mechanism of action</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biguanides</td>
<td>Metformin/Glucophage</td>
<td>↓ hepatic gluconeogenesis, ↑ insulin sensitivity</td>
<td>$4 drug plans</td>
</tr>
<tr>
<td>Sulfonylureas</td>
<td>Glipizide/Glucotrol Glimepiride/Amaryl Glyburide/Diabeta, Micronase, Glynase</td>
<td>β-cell stimulation</td>
<td>$4 drug plans</td>
</tr>
<tr>
<td>Glinides</td>
<td>Repaglinide/Prandin Nateglinide/Starlix</td>
<td>Shorter acting β-cell stimulation</td>
<td>$240/90 tabs $180/90 tabs</td>
</tr>
<tr>
<td>Thiazolidinediones</td>
<td>Pioglitizone/Actos Rosiglitazone/Avandia</td>
<td>↑ insulin sensitivity</td>
<td>$270/30 tabs $140/30 tabs</td>
</tr>
<tr>
<td>α-Glucosidase inhibitors</td>
<td>Acarbose/Precoce Miglitol/Glycet</td>
<td>Delay glucose absorption in gut</td>
<td>$90/100 tabs $110/90 tabs</td>
</tr>
<tr>
<td>Dipeptidyl peptidase IV (DPP IV) inhibitors</td>
<td>Sitagliptin/Januvia Saxagliptin/Onglyza Linagliptin/Tradjenta</td>
<td>Decrease incretin metabolism</td>
<td>$215/30 tabs $205/30 tabs</td>
</tr>
</tbody>
</table>
Mechanisms of action

Liver: metformin

Pancreas:
sulfonylureas, glinides

Intestine: acarbose

Blood stream

Metformin, TZDs

Muscles
Dipeptidyl peptidase IV inhibitors

Food eaten → Intestinal GLP-1 release → GLP-1 active

GLP-1 active → DPP-4 inhibitor → DPP-4

GLP-1 inactive

Oral diabetes medication

• Generalities:
  • Monotx lowers HgbA1c by an absolute 1% (exception: DDP IV inhibitors)
  • Addition of a second agent lowered A1c by an additional 1%
  • Take home:
    • Medication choice is more dependent on secondary benefits/side-effects/cost than effectiveness
    • Not likely to achieve tight control without insulin for patients with HgbA1c>9%

Treatment

62 year old obese male presents to establish care after his cardiologist noted that he had a fasting blood sugar of 147, follow up testing with a HbA1c of 7.2%. He has hyperlipidemia and a history of an aortic valve replacement. No other medical problems.

What medication would you start him on?
Metformin

• First line therapy
• Benefits include:
  • CVD risk reduction (decreased rates of MI and all-cause mortality)
  • Weight loss
  • No risk of hypoglycemia
  • Possible lower risk of cancer

Metformin

• Cons:
  • Lactic acidosis
  • Standard contraindications:
    • Creatinine ≥ 1.5 in men, ≥ 1.4 in women
    • Liver dysfunction
    • Unstable CHF
    • Chronic hypoxia
    • Advanced age
  • Hold in the hospitalized patient
  • Hold for 48 hrs after IV contrast studies
Metformin

• But how significant is the lactic acidosis concern?
  • Large Cochrane Review calls it into question
    • 347 trials, 70,490 patient-years metformin tx, no increased risk c metformin compared to other tx
    • 97% of the studies included of patients with ≥ contraindication, 26% of all participants > 65 yo

Metformin

- B12 deficiency?
  - Absolute risk of vitamin B12 deficiency (<150 pmol/L):
    - 7.2% higher in metformin group
    - NNH 13.8 per 4.3 years
  - Absolute risk of low vitamin B12 level (150-220 pmol/L):
    - 11.2% higher in metformin group
    - NNH 8.9 per 4.3 years

Metformin

- Common side-effects: Loose stool, bloating, gas
- Dosing:
  - start low to minimize side-effects, e.g. 500 mg po q day
  - titrate up to 1000 mg po BID
Case

• Back to our patient, does he need a home glucose monitor?
Home glucose monitoring

• Role in care of patients not on insulin is unclear
• Medicare will cover:
  • 100 test strips and lancets every month if on multiple daily insulin injections
  • 100 test strips and lancets every 3 months if not on insulin

If one medication isn’t enough: ADA treatment algorithm

Case

61 yo female c venous insufficiency and lower extremity edema, DM on sulfonylurea monotherapy, and CKD, placed on Bactrim for cellulitis. She is hospitalized for hypoglycemia 2 days later.

What went wrong?
Sulfonylureas

- Sulfonylureas
  - Pros: Cheap, convenient dosing
  - Cons:
    - Weight gain (≈2 kg)
    - Hypoglycemia
      - Caution in the elderly and CKD
    - Long half-lives:
      - Avoid Glyburide (Diabeta)
    - Drug interactions:
      - Sulfonamides, gemfibrazole increase ½ life

My opinion: First choice is glipizide ➔ shortest half life.
Case

73 yo female with poorly controlled T2DM, HgbA1c 9.4%, h/o CVA, and osteoporosis. On metformin, no longer on SU d/t recurrent severe hypoglycemia. Is hesitant to change her medications d/t fear of low blood sugars.

What oral medications could be considered here?
Dipeptidyl peptidase IV inhibitors

- Agents: Sitagliptin (Januvia), saxagliptin (Onglyza) and linagliptin (Tradjenta)
- Pros:
  - Weight neutral, no hypoglycemia
- Cons:
  - Expensive
  - Relatively less effective as monotherapy
  - Long-term safety data lacking
  - Dose reduce in patient’s with renal insufficiency
Thiazolidinediones

- Options: Pioglitizone (Actos) and rosiglitizone (Avandia)
  - Black box warning on rosiglitizone: increased cardiovascular risks - MI, CHF and death
  - Bottom line: don’t start anyone on rosiglitizone
- Pros:
  - Preservation of beta-cell function
  - Possible benefits: treatment of NASH and impaired glucose tolerance
- Cons:
  - Both increase risk of CHF, fractures, and cause weight gain

Don’t use ‘em.

Meglitinides

- **Agents:** Repaglinide (Prandin), nateglinide (Starlix)
- **Pros:** Short acting
  - Patients who eat one large meal a day
  - Post-prandial hyperglycemia d/t steroids
  - Replaglinide safe in renal insufficiency (<10% renal excretion)
- **Cons:**
  - Expensive
  - TID dosing (taken with meals)
α-Glucosidase inhibitors

- **Agents:** Acarbose
- **Pros:**
  - No hypoglycemia
- **Cons:**
  - Less effective than other agents
  - GI side-effects result in poor tolerability
# Oral Therapy Summary

<table>
<thead>
<tr>
<th>Drug</th>
<th>A1c decrease *</th>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin</td>
<td>1% (1-2%)</td>
<td>CV benefits, weight loss/neutral, no hypoglycemia</td>
<td>GI SE, contraindications</td>
</tr>
<tr>
<td>Sulfonylurea</td>
<td>1% (1-2%)</td>
<td></td>
<td>Weight gain, hypoglycemia</td>
</tr>
<tr>
<td>TZD</td>
<td>1% (0.5-1.4%)</td>
<td>No hypoglycemia</td>
<td>$$$, Weight gain, CHF, bone fractures</td>
</tr>
<tr>
<td>Glinide</td>
<td>1% (0.5-1.5%)</td>
<td></td>
<td>$$$, TID dosing, weight gain</td>
</tr>
<tr>
<td>DPP4 inhib</td>
<td>0.5% (0.5-0.8%)</td>
<td>Weight neutral/ no hypoglycemia</td>
<td>$$$</td>
</tr>
<tr>
<td>A-Glucosidase inhib</td>
<td>0.5-0.8%</td>
<td>Weight neutral</td>
<td>$$, GI SE</td>
</tr>
</tbody>
</table>

* Comparative effectiveness data (monotherapy trial data)

1. CV benefits
2. Weight loss
3. No hypoglycemia
4. GI SE
Injectable Therapies

- Insulins
- Incretin based therapies
# Insulin

<table>
<thead>
<tr>
<th>Insulin</th>
<th>Onset</th>
<th>Peak</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapid (lispro/Humalog, aspart/Novolog, glulisine/Apidra)</td>
<td>5-15 min</td>
<td>0.5-1.5 hrs</td>
<td>&lt; 5 hrs</td>
</tr>
<tr>
<td>Short (regular/Humulin R)</td>
<td>30 min – 1 hr</td>
<td>1-5 hrs</td>
<td>5-7 hrs</td>
</tr>
<tr>
<td>Intermediate (NPH/Humulin N)</td>
<td>3-4 hr</td>
<td>4-10 hrs</td>
<td>10-18 hrs</td>
</tr>
<tr>
<td>Long (glargine/Lantus, detemir/Levemir)</td>
<td>1-2 hrs</td>
<td>None</td>
<td>24 hrs</td>
</tr>
</tbody>
</table>
Insulin in Type 1 DM

• Require intensive insulin therapy:
  • Prandial blood glucose: rapid-acting insulin
  • Basal blood glucose: long-acting insulin
  • Total insulin requirement 0.5-1 U/kg/d, divided 50:50 long:short acting
  • Insulin pump: basal and bolus rates of a continuous infusion of rapid-acting insulin
• Without insulin will go into DKA within 1-2 days (even if NPO)
Case

55 yr old overweight female with uncontrolled type 2 DM, recent Ac1 12.9% on metformin 1000 BID and glipizide 10 mg with dinner, presents for follow up. You decide she needs insulin therapy.

How do you start her on insulin? What do you do with her oral medications?
Adding insulin in Type 2 DM: ADA treatment algorithm

- Basal Insulin: ex. Insulin glargine 10 units SQ q HS
  - Check fasting BS, increase insulin until controlled; ex. Add 2 units glargine q 3 days for BS >130
  - If A1c >7%, check BS before lunch, dinner and bedtime
  - If hypoglycemia develops decrease insulin dose
  - Add short acting insulin with preceding meal: ex. Insulin lispro 4 units before lunch

Case

She calls into clinic a few days later, she hasn’t started her insulin because she read that it’ll lead to weight gain. “I want to try Byetta.”

What do you think?
Incretin based injxn therapies

- Glucagon like peptide-1 agonists (exenatide/Byetta, liraglutide/Victoza):
  - Mechanism: augments glucose mediated insulin secretion (no hypoglycemia), slows gastric emptying (n/v, weight loss)
  - SE: GI, increased risk of pancreatitis, $$$
  - Indications: Type 2 DM, use with oral agents, modest A1c lowering (0.5-1%)
Incretin based injxn therapies

- Amylin agonist (pramlinitide/Symlin):
  - Mechanism: slows gastric emptying, promotes satiety, suppresses abnl post-prandial increase in glucagon seen in pt’s with DM
  - Modest A1c lowering (0.5-0.7%) and weight loss
  - Approved for use with insulin in type 1 and 2 DM
  - SE: GI, hypogycemia
HCM for the Diabetic

• Microvascular complications:
  • Nephropathy: microalbuminuria screening
    • Spot Alb:Cr ratio: nl <30 mg/g, if elevated start an ACE I or ARB
    • If nl screen annually, if Alb:Cr elevated test more frequently
  • Retinopathy: comprehensive eye exam by ophthalmology
    • Get at time of dx of type 2 DM, 5 yrs after dx of type 1
    • Follow up interval to be determined by ophtho
  • Neuropathy: monofilament testing
    • Monofilament testing: with eyes closed pt indicates if they feel the monofilament, pressure applied until it buckles; typically tested at 5 sites (1st, 4th toe, 1st, 3rd, 5th metatarsal heads)
    • If abnl do foot check at every visit, if nl repeat annually

HCM for the Diabetic Patient

• Macrovascular complications:
  • CAD:
    • Statin tx: LDL goal <100, DM is a CAD risk equivalent
    • ASA for 1º prevention: Framingham 10 yr risk >10%, generally M >50 yo, F > 60 yo with additional risk factor
      • JPAD and POPADAD showed no CV benefit of low dose ASA for primary prevention in diabetic patients
    • Stop smoking!
  • BP: goal <130/80 (ADA), <135/80 (USPSTF and ACP),
    • RAS inhibitors: ACE I or ARB
HCM for the Diabetic Patient

- Other:
  - Vaccinations: Influenza, Pneumococcal, Hep B
  - Hypoglycemia mgmt