Diabetes update - Diagnosis and Treatment

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Disclosures - None
Case 1 - Screening for Diabetes

45-year-old Caucasian male seen for his medical visit

- Mother (deceased) had type II diabetes
- His BMI is 29 kg/m2
- He has mild hypertension (on HCTZ)
- No diabetes related symptoms
Question 1 - should you screen for diabetes and how

1. Measure hemoglobin A1C
2. Measure fasting glucose
3. Perform a two hour glucose tolerance test
4. No testing required this year
Testing for Type 2 Diabetes & Prediabetes in Asymptomatic Individuals

- Type 2 diabetes testing
  - All adults who are overweight or obese (BMI ≥25 or ≥23 in Asian Americans) who have ≥1 diabetes risk factor
  - Test starting at age 45, especially if overweight or obese
  - If normal results: repeat testing in ≥3-yr intervals

- Prediabetes testing
  - A1C, FPG, or 2-h PG after 75-g OGT
  - Identify & treat (if appropriate) other CVD risk factors
  - Consider testing in children and adolescents who are overweight/obese and have ≥2 diabetes risk factors

Diabetes Risk Factors
- Physical inactivity
- First-degree relative with diabetes
- High-risk race/ethnicity
- Women who delivered a baby >9 lb or were diagnosed with GDM
- HDL-C <35 mg/dL ± TG >250 mg/dL
- Hypertension (≥140/90 or on therapy)
- A1C ≥5.7%, IGT, or IFG on previous testing
- Conditions associated with insulin resistance: severe obesity, acanthosis nigricans, PCOS
- CVD history
Case 2-lifestyle and metformin are not enough

60-year-old female with DM 2 (5 yrs), hemoglobin A-1 C 10.4% on metformin 1 g a.m./p.m., obese (BMI 34), dyslipidemia (triglyceride 833, HDL-C 25, LDL-C 115), status-post cholecystectomy. No known cardiac disease. Efforts at weight loss have been unsuccessful. No regular exercise.
Case 2- your treatment goals include everything except?

- A1C < 6%
- Triglyceride below 150 mg/dL
- Blood pressure below 135/85
- Lifestyle change
- Addition of statin
**Individualization of Glycemic Targets for Adults With Diabetes**

Lowering A1C below or around 7.0% shown to reduce:
- Microvascular complications
- Macrovascular disease

More or less stringent targets may be appropriate for individual patients if achieved without significant hypoglycemia or adverse events.

**More stringent (<6.5%)**
- Short diabetes duration
- Long life expectancy
- No significant CVD/vascular complications

**Less stringent (<8%)**
- Severe hypoglycemia history
- Limited life expectancy
- Advanced microvascular or macrovascular complications
- Extensive comorbidities
- Long-term diabetes in whom general A1C target difficult to attain

*If implemented soon after diagnosis
CVD=cardiovascular disease
Case 2- Patient prefers not to take injections. Which of these options would lower A1c the most and act most quickly

- Add a gliptin
- Add a sulphonylurea
- Add a TZD
- Add a bile acid binding resin
- Add SGLT-2 inhibitor
- Add alpha-glucosidase inhibitor
Pharmacologic Therapy for Type 2 Diabetes Management

Lifestyle changes

Metformin*: preferred initial therapy when lifestyle changes alone have not achieved or maintained glycemic goals

Consider insulin therapy with or without other agents

At outset in newly diagnosed patients with markedly symptomatic and/or elevated blood glucose levels or A1C

Add 2nd oral agent, GLP-1 receptor agonist, or insulin

If noninsulin monotherapy at maximal tolerated dose does not achieve or maintain A1C target over 3 mos

Choice of pharmacologic therapy based on patient-centered approach

<table>
<thead>
<tr>
<th>Consider</th>
<th>Efficacy</th>
<th>Cost</th>
<th>Potential side effects</th>
<th>Effects on weight</th>
<th>Comorbidities</th>
<th>Hypoglycemia risk</th>
<th>Patient preferences</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin</td>
<td>Insulin</td>
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<td>Comorbidities</td>
<td>Hypoglycemia risk</td>
<td>Patient preferences</td>
</tr>
</tbody>
</table>

Insulin eventually needed for many patients due to progressive nature of type 2 diabetes

*If tolerated and not contraindicated
# Therapeutic Efficacy

## Anticipated A1c Decrease

<table>
<thead>
<tr>
<th>Insulin</th>
<th>GLP-1 RAs, metformin, SUs, TZDs, glinides, pramlintide, SGLT2 inhibitor</th>
<th>DPP-4 inhibitors, α-GIs, bromocriptine, colesevelam</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 1.5%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.8%-1.5%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.5%-0.8%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
# Anti-hyperglycemic Therapy

## Lifestyle

- Metformin
- Insulin
- Insulin analogs
- Sulfonylureas
- TZDs
- Meglitinides
- α-glucosidase inhibitors

- Bile acid sequestrants
- Amylin mimetics
- GLP-1 receptor agonists
- DPP-4 inhibitors
- Dopamine-2 agonists
- SGLT2 inhibitors
Normal Renal Glucose Physiology

90% of glucose is reabsorbed by SGLT2

10% of glucose is reabsorbed by SGLT1

Minimal to no glucose excretion

Glucose filtration (180 g/day)

References:
Dapagliflozin: Changes in HbA$_1c$ at Week 24

**Baseline HbA$_1c$: 7-9%**

### Monotherapy
- Dapagliflozin (10 mg): $-0.89^*$
- Placebo: $-0.23$
- $p<0.0001$

### Add-on to metformin
- Dapagliflozin (10 mg): $-0.84^*$
- Placebo: $-0.30$
- $p<0.0001$

### Add-on to a SU
- Dapagliflozin (10 mg): $-0.82^*$
- Placebo: $-0.13$
- $p<0.0001$

### Add-on to insulin
- Dapagliflozin (10 mg): $-0.96^*$
- Placebo: $-0.39$
- $p<0.001$

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1. Ferrannini E *et al.* *Diabetes Care* 2010;**33**:2217–2224.
The Incretin Effect in Subjects ± T2DM

Control (n=8)

T2DM (n=14)

Oral glucose load

Intravenous (IV) glucose infusion

Add-on to metformin

Add-on to pioglitazone

Mean Baseline A1c: ~ 8.0%

## Anti-hyperglycemic Therapy: Cost for 90 d supply

<table>
<thead>
<tr>
<th>Lifestyle</th>
<th>free?</th>
<th>Cost ($)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin</td>
<td></td>
<td>$10</td>
</tr>
<tr>
<td>Insulin R or N</td>
<td></td>
<td>$400</td>
</tr>
<tr>
<td>Insulin analogs</td>
<td></td>
<td>$1200</td>
</tr>
<tr>
<td>Sulfonylureas</td>
<td></td>
<td>$10</td>
</tr>
<tr>
<td>TZDs</td>
<td></td>
<td>$48</td>
</tr>
<tr>
<td>Meglitinides</td>
<td></td>
<td>$70</td>
</tr>
<tr>
<td>α-glucosidase inhibitors</td>
<td></td>
<td>$130</td>
</tr>
</tbody>
</table>

- **Bile acid sequestrants**: $690
- **Amylin mimetics**: $700
- **GLP-1 receptor agonists**: $1800
- **DPP-4 inhibitors**: $980
- **Dopamine-2 agonists**: $240
- **SGLT2 inhibitors**: $930
New Classes in Development

- Long-acting GLP-1R agonists
- Ranolazine
- Dual & pan PPAR agonists
- 11 Hydroxysteroid dehydrogenase-1 inhibitors
- Fructose 1,6-bisphosphatase inhibitors
- Glucokinase activators
- G protein-coupled receptor-40 & -119 agonists
- Protein tyrosine phosphatase-1b inhibitors
- Canitine-palmitoyltransferase-1 inhibitors
- Acetyl COA carboxylase-1 & -2 inhibitors
- Glucagon receptor antagonists
- Salicylate derivatives
- Immunomodulatory drugs
Case 3- A 35 y.o. caucasian male, obese since childhood, BMI 38, NASH, hypertensive, A1c-12.2, on metformin, SU

All the following are reasonable except:

- Vegan diet
- Add TZD
- Add insulin
- Add SGLT-2 inhibitor
- Add GLP1-R agonist
- Refer to bariatric surgery
Change in body weight with long-acting GLP-1R agonists

**P < 0.001; ***P < 0.0001

Garber AJ. Diabetes Care 2011; 34(Suppl 2):S279-84
Efficacy of GLP-1R Agonists

*P < 0.01 vs. comparator; **P < 0.001; ***P < 0.0001; ###P < 0.0001 vs. placebo

Garber AJ. Diabetes Care 2011; 34(Suppl 2):S279-84
## Candidates for Bariatric Surgery

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>NHLBII Grade</th>
<th>ACC/AHA/COR</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Appropriate option for patients with a BMI ≥40 or BMI ≥35 with obesity-related comorbid conditions, and who: a) Are not motivated to lose weight b) Have not attained sufficient weight loss with behavioral treatment with or without pharmacotherapy</td>
<td>A (Strong)</td>
<td>IIa</td>
<td>A</td>
</tr>
<tr>
<td>2. No recommendation on bariatric surgery for patients with BMI &lt;35*</td>
<td>N (No Recommendation)</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>3. Choice of bariatric surgery procedure affected by patient factors: age, obesity severity, comorbidities, risk of complications, behavioral and psychosocial factors</td>
<td>E (Expert Opinion)</td>
<td>IIb</td>
<td>C</td>
</tr>
</tbody>
</table>

*Benefits of bariatric surgery inconclusive for patients with BMI <35
ACC=American College of Cardiology; AHA=American Heart Association; BMI=body mass index; COR=class of recommendation; LOE=level of evidence; NHLBI=National Heart, Lung and Blood Institute; TOS=The Obesity Society
Summary

- Non-insulin hypoglycemics can be used effectively to control T2DM
- Drug selection should be individualized, based on:
  - age, cost, weight, risk of hypoglycemia
  - Efficacy/Extent of hyperglycemia
  - Pathophysiology/mechanism
  - Disease duration
- Combination of agents with different mechanisms of action

ADD, DO NOT SWITCH