Type 2 Diabetes Prevention: Lifestyle Change and Coverage Considerations

Making the Case for Type 2 Diabetes Prevention and Delay

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Disclosures

• Consultant:
  • Heartland Food Products Group, manufacturer of SPLENDA® Sweeteners
  • Insulet Corporation
  • Johnson and Johnson Diabetes Institute (JJDI)
  • WellDoc, developer of BlueStar mobile medical app
• Book royalties
  • American Diabetes Association

Outline

• Latest Stats
• Disease Onset, Continuum
• Diagnostic numbers, recommendations
• Research – clinical
• Research – translational
• Management – nutrition
• Management – glucose lowering medications
WHY T2 Diabetes Prevention Matters?

Da Qing Diabetes Prevention Study in China:
- Longest (30 yrs) study
- 23 yrs follow up: development of T2D associated with a 73% higher risk of death
  - 79% (428 of 542) developed T2D (174 died)
  - 70% higher death rate than age, sex matched with normal glucose tolerance

Meet M.W.

- Annual physical
  - 2016: FPG 113, Didn’t get A1c
  - 2017: FPG 100, A1c 6.4%
- Wt: 230 (Ht: 5’10”)
- Family hx: Father, grandmother
- Work: Non-profit Quaker org, retired, consulting
- Family: Married 37 yrs, two sons married, 1 grandson
- Hobbies: gardener, “old-fashioned foodie”
- 4/17 Enrolled NDPP within DSMES, Chester County Hospital

U.S. Diabetes Prevention Timeline (~20 years)

From Research at NIH/NIDDK:
- DPP/DPPOS: 1998 start, continuing 2026

To Translation of DPP:
- Real-World Studies: Early 2000s – Present
- CDC National DPP: 2002*, 2012 program inception
- Work to scale, evaluate and improve NDPP continues

To Medicare Service:
- CMS grants study NDPP in & Medicare: Results in improved care, cost savings for Medicare beneficiaries: 2011–2016
- MDPP 1st preventive service model studied by CMMI, certified for expansion in Medicare: 2017 – 2018, Implement 4/2018

*2002 Congress authorized CDC to establish and manage National DPP

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The Latest Stats - Prediabetes

- Estimated Population (U.S.)
  - 84 million, 1 in 3 people\(^1\)
  - 38% adults\(^2\)
  - >60% over 65 yrs\(^2\)
  - Majority overweight
- Awareness: 11%\(^3\)
  - 9 out of 10 people are unaware
- Progression from PreD to T2D
  - Yearly incidence of T2D is 5%–10% in people with prediabetes\(^4\)
  - Overtime 74% estimated progress to T2D\(^5\)
- Future:
  - By 2050, 25–28% in US estimated to have diabetes (T1D, T2D)\(^5\)

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Average Per Person Annual Costs of Care in U.S.

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Progression of Dysglycemia to T2 Diabetes

Egregious Eleven Explains Pathophysiology of Disease Progression

Prediabetes IS a Cardiometabolic Risk Factor

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Diagnostic Criteria$^{1,2}$

<table>
<thead>
<tr>
<th></th>
<th>Nondiabetes</th>
<th>Prediabetes</th>
<th>Diabetes (T1 or T2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting (FPG)</td>
<td>&lt; 100</td>
<td>100 - 125</td>
<td>≥ 126</td>
</tr>
<tr>
<td>Random/casual (PPG)</td>
<td>&lt; 140</td>
<td>140 - 199</td>
<td>≥ 200</td>
</tr>
<tr>
<td>A1c (added 2010)</td>
<td>5.7%</td>
<td>5.7 – 6.4%</td>
<td>≥ 6.5%</td>
</tr>
</tbody>
</table>

Notes:
- Not for diagnosis of GDM
- If results from one test are not convincingly indicative of the diagnosis, then a repeat test should be done on a different day
- Risk is continuous and becomes disproportionately greater at the higher end of range

Testing for Diabetes or Prediabetes in Asymptomatic Adults

- If tests are normal, repeat testing carried out at a minimum of 3-year intervals is reasonable. C
- To test for prediabetes, fasting plasma glucose, 2-h plasma glucose during 75-g oral glucose tolerance test, and A1C are equally appropriate. B
- In patients with prediabetes, identify and, if appropriate, treat other cardiovascular disease risk factors. B

Prediabetes: Recommendations (2)

- If tests are normal, repeat testing carried out at a minimum of 3-year intervals is reasonable. C
- To test for prediabetes, fasting plasma glucose, 2-h plasma glucose during 75-g oral glucose tolerance test, and A1C are equally appropriate. B
- In patients with prediabetes, identify and, if appropriate, treat other cardiovascular disease risk factors. B

Risk-Based Screening in Asymptomatic Children and Adolescents

- Overweight (BMI ≥ 85th percentile for age and sex, weight for height ≥ 85th percentile, or weight > 120% of ideal for height) A
- Plus one or more additional risk factors based on the strength of their association with diabetes as indicated by evidence grades:
  - Maternal history of diabetes or GDM during the child’s gestation A
  - Family history of type 2 diabetes in first- or second-degree relative A
  - Race/ethnicity (Native American, African American, Latino, Asian American, Pacific Islander) A
  - Signs of insulin resistance or conditions associated with insulin resistance (acanthosis nigricans, hypertension, dyslipidemia, polyvastic syndromes, or small for gestational-age birth weight) B

*Persons aged <13 years.
Prevention or Delay of T2DM: Recommendations

- At least annual monitoring for the development of diabetes in those with prediabetes is suggested.
- Patients with prediabetes should be referred to an intensive behavioral lifestyle intervention program modeled on the Diabetes Prevention Program to achieve and maintain 7% loss of initial body weight and increase moderate-intensity physical activity (such as brisk walking) to at least 150 min/week.
- Technology-assisted tools including Internet-based social networks, distance learning, and mobile applications that incorporate bidirectional communication may be useful elements of effective lifestyle modification to prevent diabetes.

Words We Use in Diabetes Prevention and Prediabetes

- Prediabetes is not a diagnosis, T2 Diabetes is a diagnosis
  - Different? Or a continuum?
  - Research-based “line in the sand”?
  - Pluses, minuses of diagnosis
- Do we “prevent” or delay?
  - For how long?
- Right word(s) to use?¹
  - Cure, reverse or remission
    - Metabolic surgery?

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### Global Diabetes Prevention Research

<table>
<thead>
<tr>
<th>Name/Area</th>
<th>Years</th>
<th>Study Basics</th>
<th>Results</th>
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<tbody>
<tr>
<td>Su Dong/China Intervention FA</td>
<td>1988-1989; 1992-1994</td>
<td>3000 participants with IGT or high risk (CAD, CVD, CHF, diabetes family history) randomized to usual care and a lifestyle intervention group</td>
<td>At 1 yr: 30% 4-year incidence reduction</td>
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#### Notes:

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<td>1980-1981</td>
<td>600 participants with IGT or high risk</td>
<td>At 1 yr: 10% in the intervention group reduced to 75%</td>
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#### Notes:

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<td>600 participants with IGT or high risk</td>
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#### Notes:

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<td>1998-2000; 2002-2005; 2013-2016</td>
<td>600 participants with IGT or high risk (CAD, CHD, diabetes family history) randomized to usual care and a lifestyle intervention group</td>
<td>At 1 yr: 10% reduction in diabetes incidence</td>
</tr>
</tbody>
</table>

#### Notes:
Diabetes Prevention Program (DPP): Trial Details

- RCT, multi-site in U.S.
  - ~3000 subjects
- 3 arms:
  - Intensive Lifestyle Intervention (ILI)
  - Metformin w/ standard care
  - Placebo w/ standard care

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Core Goals of DPP ILI

- Attain weight loss of at least 5-7%
  - Maintain maximal weight loss long term
- Promote/consume healthy eating pattern (similar to the U.S. Dietary Guidelines for Americans)
- Engage in regular physical activity (at least 150 minutes of aerobic activity/week)
- Frequent individual counseling with behaviorist
  - Weekly 1st 16 wks, less frequency over time

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Reduction in Risk for Diabetes by Percent Weight Loss in the Intensive Lifestyle Intervention Arm of DPP

DPP: Weight Loss or Physical Activity?

- Wt loss = dominant predictor of reduced T2D incidence and return to normoglycemia\(^1\)
  - For each kg weight loss = 16% reduction in risk for T2\(^2\)
  - Subjects who lost > 5 – 7% reduced T2 risk > 90%\(^3\)
- Physical activity helps sustains weight loss
  - It plays a “supporting role” doesn’t get “best actor/actress”

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Transition: DPP to DPP Outcomes Study (1)

- Study Q: Does further reduction (delay) in development of T2D and development and/or progression of complications?
  - Measured annually by ADA criteria, confirmed by repeat testing
- Timeline:
  - DPP ends July 2001
  - DPPOS began Sept 2002
- Weight status by group: b/w end DPP, start DPPOS (~1 yr)
  - ILI: gained ~1 kg on average (had lost most in DPP)
  - Metformin: lost ~1.5 kg (then weight regain began)
  - Placebo: lost ~2 kg (had lost least in DPP)

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Transition: DPP to DPP Outcomes Study (1)

- All participants offered quarterly ILI, modified for groups
  - Additional group classes offered to ILI
  - 57% placebo, 58% metformin, and 40% ILI attended some sessions
  - Metformin participants given unmasked drug (850 mg twice a day, as tolerated)
- At DPPOS start: 72% not diagnosed with T2D
  - Higher proportion of ILI entered DPPOS:
    - Without T2D (81.2%)
    - Lower fasting insulin levels, better insulin secretion
    - Lower BMI, waist circumference, fewer daily calories
    - Higher physical activity (minutes)
    - Met more DPP goals than other groups
  - Participants observed continually thru DPPOS or until T2D developed (then withdrawn)

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Results Reduction of Incidence of T2D

<table>
<thead>
<tr>
<th></th>
<th>IUI*</th>
<th>Metformin/Std Care*</th>
</tr>
</thead>
<tbody>
<tr>
<td>DPP***</td>
<td>58%**</td>
<td>31%</td>
</tr>
<tr>
<td>DPP at 10 yrs</td>
<td>34%</td>
<td>18%</td>
</tr>
<tr>
<td>DPP at 15 yrs</td>
<td>27%</td>
<td>17%</td>
</tr>
</tbody>
</table>

*Compared to placebo arms. All DPP participants offered lifestyle intervention post-DPP, leading to reduction in cardiovascular risk.
**Non-significant reduction.
***TOPS is an ongoing VEDERE study to 2025.

DPPOS – 15 yr F/U

- Conclusions:
  - Can prevent/delay T2D with IUI or metformin over long term
  - Regardless of DPP treatment type, participants w/ out T2D at 15 yrs had 28% lower occurrence of microvascular disease
  - Minimal incidence of CVD (HA, stroke) (still relatively young, healthy population)
  - Metformin: DPPOS largest, longest trial using drug, safe and well-tolerated; small increase in B-12 deficiency
  - Summary: Weight loss key factor in preventing progression of prediabetes to type 2 and in restoring normoglycemia to some.

DPPOS – Predictors of Achieving Normoglycemia

- Diagnosis of T2 diabetes:
  - 56% lower for participants who had achieved normoglycemia sometime during DPP vs. consistent hyperglycemia (unaffected by DPP group assignment)
- Factors predicting normoglycemia:
  - Previous achievement of normoglycemia (even if transient)
  - "Legacy or memory" effect?
  - Increased β-cell function and insulin sensitivity
  - Diagnosis at younger age
  - Maximum pounds lost

Risk Stratification for Type 2 Diabetes Prevention Interventions1,2

<table>
<thead>
<tr>
<th>Risk Level</th>
<th>Adult Prevalence (%)</th>
<th>10 Years Diabetes Risk (%)</th>
<th>Risk Indicators</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very High</td>
<td>&gt;10%</td>
<td>&gt;30%</td>
<td>A1c &gt; 5.7%</td>
<td>Structured Lifestyle Intervention in Community Setting (NDPP)</td>
</tr>
<tr>
<td>High</td>
<td>20%</td>
<td>20 to 30</td>
<td>FPG &gt; 110</td>
<td>Structured Lifestyle Intervention in Community Setting (NDPP)</td>
</tr>
<tr>
<td>Moderate</td>
<td>30%</td>
<td>10 to 20</td>
<td>Many risk factors</td>
<td>Risk Counseling</td>
</tr>
<tr>
<td>Low</td>
<td>35%</td>
<td>0 to 10</td>
<td>0-1 risk factors</td>
<td>Build Healthy Communities</td>
</tr>
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Translating DPP to Real-World Settings to Test Models, Scale Delivery
- Timeline: Began “early 2000s
- > 50 studies
- Variety of:
  - Models
  - Settings
  - Providers
  - In-person, virtual delivery
Comparison Weight Loss in Several Translational Studies to DPP: 6, 12 Months

ICER Report Conclusions Focus: Cost Effectiveness

- In-person DPP delivered in a group was most cost effective
- In-person DPP delivered individually is cost effective
- DPP adapted to a digital platform with a human coach is cost effective but conclusion based on fewer studies
- Unable to calculate cost effectiveness of fully digital programs due to insufficient research at this point

Conclusion of Community Preventive Services Task Force

- U.S.-based Community Preventive Services Task Force (CPSTF) conducted systematic review of 53 studies and 66 ILI programs published through 2015
- Results showed:
  - Healthier eating patterns and regular physical activity reduced T2D incidence by 41% vs. usual care
  - Average reduction in BW: 2.2%
  - Average reduction in FPG: 2.2 mg/dL
  - More intensive programs with higher frequency of visits, individual sessions and use of additional personnel resulted in
    - Greater weight loss
    - Less likelihood of developing T2D

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Conclusion of Community Preventive Services Task Force

Strong evidence of effectiveness for participation in combined diet and PA promotion programs, such as NDPP, to reduce new-onset T2D in those at risk.


NDPP at 4 Years: At-a-Glance

- From 2/12 – 1/16 (data from 435 CDC-recognized programs)
- Populations studied:
  - 13K attended 4 or > sessions (threshold) 87% completed ≥ 4
  - 87% completed (1st 6 months)
  - 43% completed 16 or > sessions
  - 2K participants did not meet, both populations studied.
- Median sessions attended: 14, most in first 6 months
- Demographics:
  - 80% women
  - 56% 45-64yo
  - 45% non-Hispanic white
  - 75% obese, 23% overweight

NDPP at 4 Years: At-a-Glance

- Average weight loss: 4.2%, 36% achieving ≥ 5% (goal)
  - Greater weight loss > with number of sessions attended (5% generally achieved by people who attended ≥ 17 sessions
  - Per session attended 0.31% wt loss
  - Every 30 min more PA resulted in 0.3% wt loss
- Physical Activity 88% reported
  - Average 152 weekly minutes
  - 42% achieved goal of 150 min/week
  - PA increased with increased number of sessions attended

Conclusion: Engagement, Attendance = Weight loss, Prevent/delay PD

NDPP at 4 Years: At-a-Glance1

- 46 and DC offer NDPP in various venues
- Virtual: since 2/15
- Coverage increasing:
  - Commercial insurance: > 70
  - Millions state employees (15 state plans)
  - Medicaid (few states including PA, PA start 1/1/18; demo projects)
- Current study in > 100 sites:
  - Why attrition?
  - Program implementation strategies
  - Enrollment drivers
  - Engagement activities
  - Program retention (early, late in program)

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Nutrition Management1

- DPP ILI focus: initial low-fat, calorie counting, person ID/set behavior change goals2
  - ADA: Recent evidence suggests that the quality of fats consumed in the diet is more important than the total quantity of dietary fat and may help reduce T2D (Ex: Mediterranean diet)
  - Promote/consume healthy eating pattern (similar to the U.S. Dietary Guidelines for Americans)
    - Eating pattern one can adopt, manage and implement over time (not a "diet")
    - Least disturbance to a person’s current dietary pattern
    - Consideration and respect for food and cultural preferences
- NDPP curriculum3

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2. ADA: Prevention or Delay of Type 2 Diabetes. Standards of Medical Care in Diabetes. 2018. Diabetes Care 2018; 41(Suppl. 1): S10-S114.
4. ADA: Prevention or Delay of Type 2 Diabetes. Standards of Medical Care in Diabetes. 2018. Diabetes Care 2018; 41(Suppl. 1): S10-S114.
Nutrition Management

- Within overall healthy low-calorie eating pattern(s)\(^1\)
- Evidence for reduced T2D:
  - Nuts
  - Berries
  - Yogurt
  - Coffee and Tea
- Evidence for increased T2D:
  - Red meats
  - Sugar-sweetened beverages

- Studies in T2D prevention span from vegan to ketogenic
- Consumer and clinician confusion ensues
- Media headlines, over promises

**BIG Q:** What can people reasonably follow long term?

1. ADA. Prevention or Delay of Type 2 Diabetes. Standards of Medical Care in Diabetes—2018. Diabetes Care 2018; 41 (Suppl. 1): S51-S54

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Recent “Diet” Weight Loss Study

- 2/18 JAMA: DIETFITS RCT\(^1\)
- Q: What is the effect of a healthy low-fat (HLF) diet vs a healthy low-carbohydrate (HLC) diet on weight change at 12 months and are these effects related to genotype pattern or insulin secretion?
- Subjects: 609 adults, 18 to 50 yo without T2D, BMI: 28 and 40
- Intervention:
  - “RD/health educators” delivered the behavior modification intervention in 22 diet-specific small group sessions over 12 months
  - Sessions focused on achieving the lowest fat or carbohydrate intake that could be maintained long-term and emphasized diet quality
- Mean 12-month macronutrient distributions (end): 48% vs 30% for carbohydrates, 29% vs 45% for fat, and 21% vs 23% for protein
- Conclusions:
  - Weight change (12 mos) not significantly different for HLF vs. HLC diet group
  - No significant diet-genotype interaction
  - No significant diet-insulin interaction


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Services for NDPP and MNT

- Strongest evidence for diabetes prevention comes from DPP delivered as NDPP\(^1\)
  - Year-long lifestyle change, structured program (wt loss/maintenance, healthy food choices, healthy eating behaviors, physical activity)
  - Cost-effective, scaleable
  - Increasingly covered by Medicare (4/18), Medicaid, private-payers, state employers, others
  - Individualized MNT is effective in lowering A1c in those with prediabetes\(^1\)

Providers for NDPP and MNT

- NDPP/MDPP: Lifestyle coaches must have attended CDC-Recognized Lifestyle Change Program. Maybe HCP, but credentials not required.¹
  - The use of community health workers to support DPP efforts has been shown to be effective with cost savings
  - Lifestyle Coaches: “facilitate don’t educate”
  - MNT provided by RDN effectively improves outcomes, QOL and is cost-effective²
  - Service vs. program?

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U.S. FDA: Approval GL Meds for Prediabetes

- None approved for prediabetes
- No clear FDA pathway
  - 2008 draft industry guidance never finalized
  - States: “FDA’s expectation for safety of prevention-related products likely to be higher than for T2D.”
  - Manufacturer interest, potential ROI?
- Prediabetes is not a disease state (line in the sand?)
- Prescribing any of these meds is “off-label”
- Yes, prescribed, metformin mainly, but barely

Pharmacologic Interventions for Prevention: Recommendations

- Metformin therapy for prevention of type 2 diabetes should be considered in those with prediabetes, especially for those with BMI ≥ 35 kg/m², those aged <60 years, and women with prior GDM. A
- Long-term use of metformin may be associated with biochemical vitamin B12 deficiency, and periodic measurement of vitamin B12 levels should be considered in metformin-treated patients, especially in those with anemia or peripheral neuropathy. B

Successful Use of Metformin in DPP/DPPOS

- Though lifestyle change most successful across all participants metformin was as effective in:
  - Participants with BMI ≥ 35 kg/m²
  - Women with history GDM, remained highly effective during 10-yr follow up
- Adherence to metformin:
  - DPP: 72%
  - DPPOS: 57%
- Metformin may be cost-saving over a 10 yr period (relative low cost of prescribing a low cost med)

Metformin Use for Prediabetes: Remains Low

- Nationwide sample > 17K, 19-58 yo with prediabetes in U.S. from 2010-2012
  - 3.7% prescribed overall
  - 7.8% meet ADA guideline > BMI, GDM history
- Reasons:
  - Lack knowledge of DPP study
  - Reluctance providers, people to “medicalize” prediabetes
  - Lack of FDA approval is hurdle (prescribers? insurance?)
Research on GL Meds in Prediabetes

- Research studies using these FDA approved meds have shown decrease in incident T2D (varying degrees)
  - Metformin
  - α-glucosidase inhibitors
  - Orlistat (weight loss med)
  - GLP-1 receptor agonists
  - Thiazolidinediones
  - Metformin:
    - Strongest, longest evidence base (DPP/OS)
    - Long term safety
    - Low cost
    - Minimal side effects

Prediabetes to T2 Diabetes
IS Progressive, Not Static

- Goal:
  - Achieve, maintain A1c & glucose targets to prevent, delay, and minimize chronic complications
- EARLY, AGGRESSIVE action can prevent/delay transition from prediabetes to T2D
- Can a GL lowering medication assist?
  - Age, years of prediabetes?
  - Risk for T2D development?
  - Ability, success at weight control, healthy eating, physical activity?
- HCP must: Regularly & objectively explain progressive nature T2D

Weight Effects of Common GL Meds

<table>
<thead>
<tr>
<th>Medication Category</th>
<th>Impact on Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>GLP-1 Receptor Agonists</td>
<td>🏅</td>
</tr>
<tr>
<td>SGLT-2 Inhibitors</td>
<td>🏅</td>
</tr>
<tr>
<td>Metformin</td>
<td>neutral or 🏅</td>
</tr>
<tr>
<td>DPP-4 Inhibitor</td>
<td>neutral</td>
</tr>
<tr>
<td>Insulins (all)</td>
<td>neutral or 🏅</td>
</tr>
<tr>
<td>Sulfonylureas</td>
<td>🏅</td>
</tr>
</tbody>
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Repurposing Diabetes Drugs for Prevention
“Evidence-Free Zone”

- SGLT-2 inhibitors:
  - A1c and BW reduction, CV benefits (empag, canag) (in T2D pop) no trials in pred yet
  - "Unlikely to happen in the foreseeable future" (cost large trial, cost med)
- GLP-1 agonists:
  - A1c and BW reduction, β-cell function improves
  - Semaglutide (Ozempic) injectable upcoming study in obesity, high-dose
    liraglutide (Saxenda for obesity) has shown T2D delay over 3 yrs
- DPP-4 inhibitors:
  - β-cell protection (?), more adherence-friendly, lower cost agent (generic
    closer to reality than others) (weight neutral, no CV benefit)
- α-glucosidase inhibitors:
  - Recent study showed 18% delay new-onset T2D
  - Lack of clear regulatory pathway for prediabetes remains an obstacle for
    manufacturers


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