Diabetes Update: Diabetes Management in Primary Care

Jeffrey Unger, MD, FAAFP, FACE

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Jeffrey Unger, MD, FAAFP, FACE

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• Presentation will include non-approved indications for certain therapeutic interventions. Experimental therapies will also be discussed. The audience will be informed about unapproved drug interventions.

Jeffrey Unger, MD, FAAFP, FACE

Director, Unger Primary Care Concierge Medical Group, Rancho Cucamonga, California; Director of Metabolic Studies, Catalina Research Institute, Montclair, California

Dr. Unger’s private practice is devoted to the comprehensive care of patients who have diabetes, addiction, mental illness, migraine, and other chronic disease states. He has published more than 150 peer-reviewed articles on diabetes, migraine, and pain management. In addition, he has written three medical textbooks on diabetes, including Diabetes Management in Primary Care, 2nd Edition, which was published in December 2012. Dr. Unger is board certified in family medicine and has served as a consulting physician for the Los Angeles Angels of Anaheim baseball club and the World Wrestling Federation.

Learning Objectives

1. Critically evaluate the evidence emerging within diabetes research as it applies to recommendations for physician change.
2. Evaluate current standards of care (screening, prevention, diagnosis, treatment, management) for patients with diabetes, or who are at risk for developing diabetes, for opportunities to update standards in accordance to current research and evidence-based guidelines.
3. Assess new and novel treatments for diabetes in terms of efficacy, safety, contraindications and cost/benefit relative to existing treatments.
4. Apply a patient-centered approach to incorporate guideline recommendations for intensifying therapy to achieve glycemic control.

Associated Session

• Diabetes Update: PBL
The Diabetes Epidemic

**Globally**
- 1 in 11 adults has diabetes
- 1 in 2 adults with diabetes is undiagnosed
- 542,000 children have type 1 diabetes
- 12% of health expenditures is spent on diabetes
- 1 in 7 births is affected by diabetes

**The U.S.**
- 3 in 10 people have diabetes
- 1 in 4 people with diabetes is undiagnosed
- >200,000 children have diabetes
- Medical expenditures are 2.3 times higher than without diabetes
- 2 in 5 cases of kidney failure is due to diabetes

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**Diabetes-related complications in the US**

![Graph showing diabetes-related complications](image)

**Good News! Low Risk of All Cause Mortality For Patients With T1DM**

![Graph showing mortality reduction](image)
Normal Diabetes Prediabetes Impaired Glucose Tolerance

Fasting Plasma Glucose
ULN= 99 mg/dL

2-hour Plasma Glucose On OGTT
ULN= 140 mg/dL

A1C

- 8.0-10.0 mg/dL = normal glycemic range
- Normal A1C = 5.1%

Any abnormality must be repeated and confirmed on a separate day

The diagnosis of diabetes can also be made based on unequivocal symptoms and a random glucose >200 mg/dL

Prediabetes is NOT a benign condition. Patients may progress to diabetes or develop macrovascular/microvascular disease

In 2009-2012, based on fasting glucose or A1C levels, prediabetes was detected in

- 37% of adults ages 20 years and older
- 51% of adults ages 65 years and older
- An estimated 86 million adults ages 20 years and older

People with prediabetes have an increased risk of developing type 2 diabetes, heart disease, and stroke

1/3 billion people in China have prediabetes!

Prediabetes Constitutes Inherent Disease Risk

IGT progression to diabetes is 6-10 % per year
- 50 % of patients with IGT have metabolic syndrome
- IGT doubles the risk of CVD
- DECODE study: All-cause mortality doubled as 2 hr postchallenge OGTT values increased from 95-200 mg/dL. (FBG is not correlated with increased mortality)
- 15 % increased risk of cancer (stomach, colon, liver, pancreas)
- Associated with increased risk of Alzheimer’s disease, Parkinson’s disease and major depression

Baseline A1C Predicts Diabetes Progression Over 5 Years

<table>
<thead>
<tr>
<th>A1C (%)</th>
<th>Risk of Disease Progression (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;5.0</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td>5.0-5.5%</td>
<td>&lt;= 9</td>
</tr>
<tr>
<td>5.5-6%</td>
<td>9–25</td>
</tr>
<tr>
<td>6.5-7%</td>
<td>25–50</td>
</tr>
</tbody>
</table>


Screening Children for Prediabetes and Diabetes

Consider for all children who are overweight and have 2 of any of the following risk factors

- Family history of type 2 diabetes in first- or second-degree relative
- High-risk race/ethnicity
- Early-onset obesity or conditions associated with insulin resistance
- Maternal history of diabetes of GDM during child’s gestation

Begin screening at age 10 years or onset of puberty
Screen every 3 years

A1C test is recommended for diagnosis in children

High Risk Patients For Prediabetes*

Prediabetes High Risk Patients
- PCOS
- 1st degree relative
- GDM by history
- Abdominal obesity (WC > 35 inches female, 40 inches men)

Who to Screen for Prediabetes

- + F H
- History of CVD
- Obesity (BMI < 25 kg/m2)
- Sedentary life style
- Hypertriglyceridemia
- Previous diagnosis of IGT or IFG
- History of HTN
- Elevated TG, low HDL, or both
- PCOS
- Delivered baby weighing > 9 lbs
- Pts with schizophrenia or bipolar disorder

*If NO risk factors begin screening at age 45 then every 2-3 years + risk screen at any time

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Begin screening at age 10 years or onset of puberty
Screen every 3 years

A1C test is recommended for diagnosis in children
Overview Of Lifestyle Recommendations for Prediabetes

- Weight loss: 7% of baseline weight
- Exercise: 150 min/week of moderate exercise
- Diet: No specific recommendations, refer to intensive behavioral management to achieve the 7% weight loss goal
- Among persons in a prediabetic state, the incidence of type 2 diabetes is reduced by approximately 40 to 45% with effective lifestyle changes or drug treatment

Relative risk of progression of diabetic complications

ADA/EASD Position Statement: Management of Hyperglycemia in T2DM

- Target A1C for MOST patients is <7%
- Age: Older adults
  - Reduced life expectancy
  - Higher CVD burden
  - Reduced GFR
  - At risk for adverse events from polypharmacy
  - More likely to be compromised from hypoglycemia

- Less ambitious targets
  - HbA1c <7.5-8.0% if tighter targets not easily achieved
  - Focus on drug safety
At 5.3 years, significantly increased risk of:
- MI 67% (CI 39–101%)
- Stroke 51% (CI 25–83%)
- HF 64% (CI 40–91%)
- Composite CVE 62% (CI 46–80%)

Consequences of delayed intervention


Goals Of Diabetes Management

- Define and achieve metabolic targets (A1C, Fasting and Post prandial glycemia), blood pressure and lipids
- Intensify pharmacologic interventions within 2 years of diagnosis to reduce risk of macrovascular complications
- Preserve beta cell function
- Use medications that do not increase weight or result in hypoglycemia (metformin, SGLT2-inhibitors, DPP-4 inhibitors, GLP-1 RAG)
- In high risk patients, prescribe medications which show cardiovascular protective benefits (SGLT2s and GLP-1RAs)
- Early referral to CDE or RD within 1 year of diagnosis
- Remember, diabetes results in discord between 2 hormones: insulin and glucagon

Why Is Hypoglycemia Associated With Increase Cardiovascular Mortality In High Risk Patients?

Frequency of Adverse Outcomes Among Patients With T2DM Experiencing Severe Hypoglycemia

The median time from an episode of severe hypoglycemia until death is T2DM is < 1.6 years!

Conclusions – severe hypoglycemia is associated with a higher risk of mortality
Hurdles to Intensive Therapy

Rates of Severe Hypoglycemia

Abnormal QT prolongation and T-wave morphology during hypoglycaemia in a single patient

Severe hypoglycaemia is associated with more complications

Hypoglycaemia with antidiabetes therapies

ACCORD All Cause Mortality

Effects of Hypoglycemia on Thrombosis in T2DM

Adapted from: how


aExenatide twice daily; bIncludes liraglutide, exenatide once weekly, albiglutide, and dulaglutide; cIncludes saxagliptin, linagliptin, and sitagliptin; dIncludes canagliflozin, dapagliflozin, and empagliflozin; dIncludes neutral protamine Lysine Hurdles to Intensive Therapy

ACCORD, Action to Control Cardiovascular Risk in Diabetes; ADVANCE, Action in Diabetes and Vascular Disease: PreterAx and DiamicroN MR Controlled Evaluation; CON, conventional therapy; GLY, glibenclamide; HR, hazard ratio; INS, insulin; INT, intensive therapy; STD, standard therapy; UKPDS, UK Prospective Diabetes Study; VADT, Veterans Affairs Diabetes Trial.

)...
Mitigating Hypoglycemia In High Risk Patients

- More frequent SBGM
- Avoid mixed insulin in patients who skip meals
- Use analog, not human insulin
- Preferred basal insulins include degludec and glargine U-300
- Use continuous glucose sensors in patients with a history of hypoglycemia unawareness

Rational Pharmacotherapy For T2DM

- Safety and efficacy TRUMP cost
- Hypoglycemia risk increases with duration of disease
- Consider diabetes pathogenesis when prescribing medications
  - GLP-1 RA + SGLT2 inhibitors effectively reverse 7/8 of the ominous octet defects
- Treat early, effectively, rationally, for as long as possible and as safely as possible

Recommended Targets for Patients with T2DM

<table>
<thead>
<tr>
<th>Target</th>
<th>ADA 2016</th>
<th>AACE/ADA</th>
</tr>
</thead>
<tbody>
<tr>
<td>FRS</td>
<td>&lt;7.5%</td>
<td>&lt;6.5%</td>
</tr>
<tr>
<td>Pre-prandial plasma glucose</td>
<td>50–120 mg/dL</td>
<td>&lt;150 mg/dL</td>
</tr>
<tr>
<td>Peak pre-prandial glucose</td>
<td>&lt;180 mg/dL</td>
<td>&lt;140 mg/dL</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>&lt;140/80 mmHg</td>
<td>&lt;130/80 mmHg</td>
</tr>
<tr>
<td>LDL Cholesterol</td>
<td>&lt;100 mg/dL</td>
<td>&lt;100 mg/dL (male), &lt;70 mg/dL (female)</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>&lt;150 mg/dL</td>
<td>&lt;150 mg/dL</td>
</tr>
<tr>
<td>HDL Cholesterol</td>
<td>&gt;40 mg/dL (male), &gt;50 mg/dL (female)</td>
<td>—</td>
</tr>
</tbody>
</table>

*Individualized based on duration of diabetes, age/life expectancy, comorbid conditions, known CVD or advanced microvascular complications, hypoglycemic unawareness, and based on patient preferences. **The target for SBP should be as low as possible consistent with the reduction in cardiovascular events while minimizing the potential for adverse effects. ***Hypoglycemia unawareness should be considered in patients with diabetes and a history of severe hypoglycemia to minimize the risk for severe hypoglycemia.
The Incretin Effect in Healthy Subjects

GLP-1 Secreted From The L-cells of Gut In Response To Carbohydrate Stimulus

GLP-1 Secretion And Receptor Activation Is Reduced In T2DM

DPP-4 Inhibitors and GLP-1 RAs Increase GLP-1 Activity in Different Ways

Comparing Dosage and Administration of Current GLP-1 RAs: Daily GLP-1 RAs

- GLP-1 activity is higher with GLP-1 RAs (≥ 3 × baseline) vs DPP-4 inhibitors (≥ 2 × baseline)
- Both classes mediate glucose-dependent changes
  - Increase insulin
  - Decrease glucagon
- GLP-1 RAs also
  - Slow gastric emptying
  - Increase satiety

DPP-4 inhibitors increase GLP-1 by preventing degradation

Comparing Dosage and Administration of Current GLP-1 RAs:

- Exenatide BID
  - Inject within 60 minutes prior to 2 main meals of the day, at least 6 h apart
  - Initiate at 0.6 mg once daily for 1 week
  - Can increase to 1.8 mg if 1.2 mg does not provide acceptable glycemic control

- Liraglutide QD
  - Inject within 1 hour of the first daily meal
  - Initiate at 0.6 mg once daily
  - Increase to 1.8 mg if 1.2 mg does not provide acceptable glycemic control

- Lixisenatide QD
  - Inject within 1 hour of the first daily meal
  - Initiate at 5 μg per dose twice daily
  - Increase to 10 μg twice daily after 1 month, based on clinical response
  - Can increase to 10 μg if 5 μg does not provide acceptable glycemic control

- GLP-1 RAs also
  - Slow gastric emptying
  - Increase satiety

DPP-4 Inhibitors and GLP-1 RAs: Daily GLP-1 RAs

US FDA. Drugs@FDA. http://www.accessdata.fda.gov/scripts/cder/D rugsatFDA.
Comparing Dosage and Administration of Current GLP-1 RAs: Once-Weekly GLP-1 RAs

<table>
<thead>
<tr>
<th>GLP-1 RA</th>
<th>Dosage / Administration</th>
<th>Needle Size</th>
<th>Availability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exenatide QW</td>
<td>Initiate at 2 mg once weekly</td>
<td>23-G needle (supplied)</td>
<td>Available in a single-use vial and syringe or in a single-dose pen</td>
</tr>
<tr>
<td>Liraglutide QW</td>
<td>Initiate at 1.8 mg once daily</td>
<td>29-G needle (supplied)</td>
<td>Available in a single-dose pen</td>
</tr>
<tr>
<td>Dulaglutide QW</td>
<td>Initiate at 0.75 mg once weekly</td>
<td>29-G needle (supplied)</td>
<td>Available in a single-dose pen</td>
</tr>
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</table>

GLP-1 Receptor Agonists Demonstrate a Low Risk of Hypoglycemia

<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td>EXN 10 µg BID</td>
<td>35.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LIXI 20 µg QD</td>
<td>28.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LIRA 1.8 mg QD</td>
<td>24.8</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ITCA 650 – Exenatide –Not FDA Approved

- Continuous delivery of exenatide through a matchstick-size, osmotic mini-pump device
- Simple subcutaneously placement
- Continuous and consistent drug therapy using 3- or 6-month pumps with potential for device lasting up to 1 yr

Continuous Delivery of Exenatide

GLP-1 Receptor Agonist + Basal Insulin Analogs

- Simple to initiate
- Can control FPG and PPG
- Do not impair α-cell response to hypoglycemia (reduce severe hypoglycemia)
- Reduce weight
- Achieve HbA1c target in ~60%
Approved Fixed-Ratio Combinations of Basal Insulin and GLP-1 RAs

- GLP-1 RA: Lixisenatide
- Insulin: Glargine
  - IGlarLixi (Soliqua 100/33)

- GLP-1 RA: Liraglutide
- Insulin: Degludec
  - IDegLira (Xultophy 100/3.6)

Check-list For Patients Using GLP-1RAs

- Do not use in patients with hx of pancreatitis
- Do not use in patients with personal or family hx of medullary thyroid carcinoma
- Most common AE= nausea and vomiting. Transient. Educate about satiety
- Injections using 32 g needles or self injectors
- Liraglutide can be used when eGFR is < 30 ml/Min
- Do NOT use with DPP-4s
- When used with insulin in patients with A1C < 8 % reduce dose of insulin by 20 %.

Normal Glucose Homeostasis

Glucose uptake ~250 g/day:
- Dietary intake ~180 g/day
- Glucose production ~70 g/day
- Gluconeogenesis
- Glycogenolysis

Glucose input ~250 g/day:
The kidney filters circulating glucose

Glucose filtered ~180 g/day
Glucose reabsorbed ~180 g/day
The kidney reabsorbs and recirculates glucose

How is Glucose Reabsorbed in the Kidney (Renal Medulla)?

- Glucose reabsorption is mediated in the proximal tubules of the kidney
  - Actively through sodium-coupled glucose cotransporters (SGLT)
  - Passively through glucose transporters (GLUT)
- ~90% of glucose is reabsorbed by SGLT-2 and GLUT-2 in the S1 and S2 segments
- ~10% of glucose is reabsorbed by SGLT-1 and GLUT-1 in the S3 segment

SGLT-2 Inhibitors: Mechanism of Action (cont)

Glucose uptake ~250 g/day:
- Dietary intake ~180 g/day
- Glucose production ~70 g/day
- Gluconeogenesis
- Glycogenolysis

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Increased Glucose Transporter Activity in T2DM

SGLT-2 and GLUT-2 Protein Expression in Healthy Controls and Patients with T2DM

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>T2DM</th>
</tr>
</thead>
<tbody>
<tr>
<td>P&lt;0.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SGLT2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GLUT2</td>
<td></td>
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</tbody>
</table>
Information on diabetes type (i.e. type 1 or 2) was generally not available, although participants' age suggests that the large majority with diabetes would have type 2. In high-income countries, up to 91% of adults with diabetes have type 2.

CVD, cardiovascular disease; CI, confidence interval; T2D, type 2 diabetes


? Amputation Risk With SGLT2s

- CANVAS-R 4.5 year interim analysis:
  - Risk of amputations were 7.5/1000 patient years in patients taking canagliflozin vs. 3/1000 pt years for those taking PBO
- European Medical Association concludes that the risk of amputations should be included in labels for ALL SGLT2 inhibitors

![SGLT2 Inhibition Lowers Tmax, Allowing Elimination of Excess Glucose](image)

- Overexpression of SGLT2 shifts Tmax to the left, eliminating excess glucose
- SGLT2 inhibition shifts Tmax to the right, allowing excess glucose to be reabsorbed
- All CVOTs: Oral hypoglycemia, UUT, GMI, amputation in high risk patients
- Dosing based on eGFR, results in reduced EFG, GMI, and amputation

![Conclusions Regarding Amputation Risk](image)

- High risk patients and those with longer duration diabetes (CV and peripheral vascular disease) have a slightly higher risk of amputations
- Mechanism may be volume depletion
- Higher risk of amputations has also been noted with diuretic use
- Consider DC drugs in patients who develop foot infections or ulcers
- Stop meds if patients have known PVD

![CVD is the leading cause of death in people with T2D](image)

The value of CVOTs

<table>
<thead>
<tr>
<th>Pros</th>
<th>Cons</th>
</tr>
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<tbody>
<tr>
<td>- Trials include patients with high CV risk</td>
<td>- Generalizability of results to all populations may be limited</td>
</tr>
<tr>
<td>- The trials will generate large volumes of long-term data for analysis</td>
<td>- Efficacy data may be of limited value</td>
</tr>
<tr>
<td>- CV safety data are important for diabetes therapies</td>
<td>- Trials are not designed to document efficacy with treat to similar targets</td>
</tr>
<tr>
<td>- Long-term efficacy data from blinded, randomised trials</td>
<td>- Wide range of concomitant medications</td>
</tr>
<tr>
<td>- Non-CV safety data</td>
<td>- Developmental costs increase</td>
</tr>
<tr>
<td>- Identifying rare events</td>
<td>- Larger and longer phase 3 programmes</td>
</tr>
<tr>
<td>- Reduced incentive for development of new drugs</td>
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</tr>
<tr>
<td></td>
<td>- Development limited to larger companies</td>
</tr>
<tr>
<td></td>
<td>- Reduced incentive for development of new drugs</td>
</tr>
</tbody>
</table>

![SGLT2 Label Comparisons](image)
Diabetes Is A Complex Disease State!

- A1C
- Exercise
- Timing of medications in relation to meals
- Blood pressure control
- Lipid control
- Reduce carbs
- Stop smoking
- Reduce alcohol
- Blood glucose monitoring
- Refills

Is This Patient “Non-Compliant?”

- 66 y/o social worker, vet
- T2DM x 17 years
- A1c= 9.1%
- Taking NPH 200 u/d + metformin 1 gram/d + pioglitazone 45 mg/d + glipizide 10 mg/d
- Taking meds as directed

The 5 Strategies Which Guarantee Successful Diabetes Self-Management

- Know your metabolic targets
- Know how to achieve your metabolic targets
- Take your medicines
- Don’t smoke
- Receive care from clinicians who are knowledgeable about diabetes pathogenesis and management

Practice Recommendations

- Timely, intensive intervention in patients with diabetes can reduce the incidence of long-term diabetes-related complications and all-cause mortality. (SOR A).
- Several SGLT2-inhibitors and GLP-1 RAs have been shown to reduce the risk of cardiovascular mortality in “high risk” patients with type 2 diabetes. (SOR A)
- Drugs which reduce the risk of weight gain and hypoglycemia (SGLT2 inhibitors and GLP-1 RAs) should be used as 2nd line therapy in patients threatened with metformin. (SOR A)

Questions