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New Thinking and Approaches in the Management of Type 2 Diabetes

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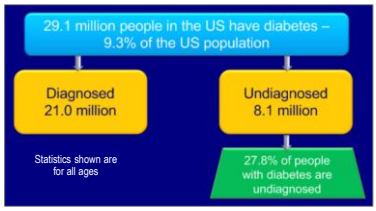
Diabetes and the National Quality Strategy

Diabetes Prevalence in the US, 2012

National Diabetes Statistics Report, 2014



CDC. National Diabetes Statistics Report: Estimates of Diabetes and its Burden in the United States. Atlanta, GA: US Department of Health and Human Services, 2014.

Obesity and T2D: A Common Burden

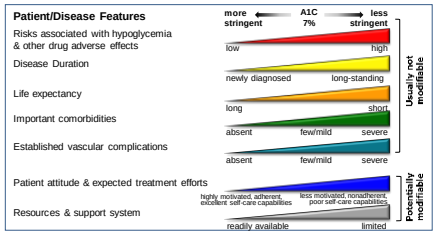
Obesity Prevalence Among US Adults, 2013

County-level Estimates of Diagnosed T2D Among US Adults, 2011

Obesity = BMI ≥30 kg/m² or ~30 lbs. overweight for 5'4" person

CDC Behavioral Risk Factor Surveillance Systems; CDC Diabetes Public Health Resource Center.

Approach to the Management of Hyperglycemia



American Diabetes Association Standards of Medical Care in Diabetes. Glycemic targets. *Diabetes Care.* 2016;39 (Suppl 1):S39-S46

ADA: Foundations of Care

Self-management Education

Nutrition

- Promote healthful eating patterns, appropriate portion sizes; address personal and cultural preferences
- Achieve and maintain body weight goals and individualized glycemic, blood pressure, and lipid goals

Physical Activity

- Adults with diabetes: at least 150 min/wk of moderate-intensity aerobic activity over at least 3 days/week; resistance training at least twice weekly

Smoking Cessation

- Advise all patients not to use cigarettes, other tobacco products, or e-cigarettes; diabetes care should include routine smoking cessation counseling

Adapted from American Diabetes Association Standards of Medical Care in Diabetes. Cardiovascular disease and risk management. *Diabetes Care.* 2016;39(Suppl 1):S60-S71.

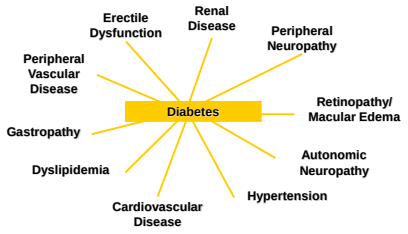
ADA: Foundations of Care

Immunizations in Diabetes

Vaccine frequency of administration	Patient age
Influenza annually	≥6 months
PPSV23, 1 injection before age 65	19-64 years
PVC13 plus PPSV23, 1 injection each, in series ≥1 year apart	≥65 years
Hepatitis B, 3 injection series	20-59 years consider in ≥60 years
Td (or Tdap), every 10 years	≥19 years
Zoster vaccine	≥60 years

Adapted from American Diabetes Association Standards of Medical Care in Diabetes. Cardiovascular disease and risk management. *Diabetes Care.* 2016;39(Suppl 1):S60-S71.

Diabetes Mellitus: A Constellation of Complications



Looking Beyond Glucose Control

BP Targets

- People with T2DM and hypertension should be treated to a systolic blood pressure goal of <140 mmHg; lower targets may be appropriate for certain individuals

Consider aspirin therapy (75-162 mg/day)

- As a primary prevention strategy in those at increased cardiovascular risk (10-year risk >10%)
- Includes most men or women with DM age ≥50 years who have ≥1 major risk factor

Remember to use moderate or high dose statins in most diabetics >40, depending on risk

Adapted from American Diabetes Association Standards of Medical Care in Diabetes. Cardiovascular disease and risk management. *Diabetes Care.* 2016;39(Suppl 1):S60-S71.

Screening Recommendations

- Nephropathy
  - At least yearly, assess urine albumin excretion and estimated glomerular filtration rate (eGFR)
- Retinopathy
  - Dilated exam by ophthalmologist at diagnosis and Q 1-2 years
- Regular foot care
- Neuropathy, including monofilament testing
  - At time of diagnosis and annually

NQS Priorities

Mandated by the Patient Protection and Affordable Care Act, the National Quality Strategy (NQS) was developed to improve patient health and health care quality. The NQS priorities address the most common health concerns among patients:

1. Patient safety
2. Engaging patients and caregivers
3. Coordinating patient care
4. Disseminating effective prevention and treatment practices for leading causes of mortality
5. Promoting use of best practices to enable healthy living within communities
6. Developing new health care delivery models to provide affordable quality care for individuals, families, employers, and governments

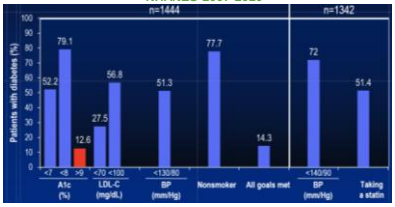
http://www.ahrq.gov/workingforquality/nqs/overview.htm.

CMS National Quality Measures in Diabetes

- Diabetes: Hemoglobin A1C Poor Control
- Diabetes: Low Density Lipoprotein (LDL-C) Control (<100 mg/dL)
- Diabetic Retinopathy: Documentation of Presence or Absence of Macular Edema and Level of Severity of Retinopathy
- Diabetic Retinopathy: Communication with the Physician Managing Ongoing Diabetes Care
- Diabetes: Medical Attention for Nephropathy
- Diabetes Mellitus: Diabetic Foot and Ankle Care, Peripheral Neuropathy – Neurological Evaluation
- Diabetes Mellitus: Diabetic Foot and Ankle Care, Ulcer Prevention – Evaluation of Footwear
- Diabetes: Foot Exam

https://www.cms.gov.

Goal Achievement in Diabetes—How Well Are We Doing?



*Data from separate studies.
BP = blood pressure; LDL-C = low-density lipoprotein cholesterol; NHANES = National Health and Nutrition Examination Survey.
Ali MK et al. *N Engl J Med.* 2013;368:1613-1624. Stark Casagrande S et al. *Diabetes Care.* 2013;36:2271-2279.

Diabetes Management Is Changing...

- New oral agents:
  - DPP-4 inhibitors, SGLT-2 inhibitors, multiple combinations (metformin, SU, TZD)
- Additional injectable options:
  - New insulins: basal, long-acting basal, ultra-rapid
  - New GLP-1 RAs with longer half-life
  - New insulin/GLP-1 RA combinations

Goals of today's discussion:

- Review the most current understanding of T2DM pathophysiology and its implication on treatment options
- Apply treatment strategies to patient scenarios
- Explore patient engagement techniques to help with medication and goal selection, and improve adherence

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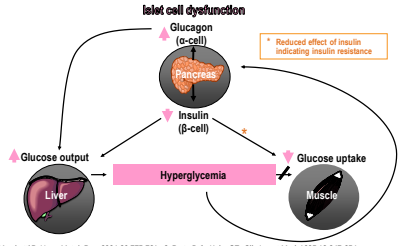
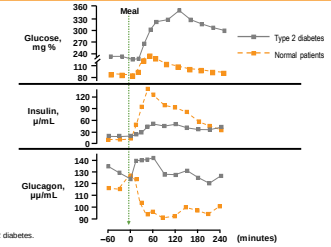
Current Understanding of the Pathophysiology of T2DM and the Targets of Available Anti-Hyperglycemic Agents

The Pathophysiology of Type 2 Diabetes Includes Islet Cell Dysfunction and Insulin Resistance[1,2]



1. Del Prato S, Marchetti P. *Horm Metab Res.* 2004;36:775-781. 2. Porte D Jr, Kahn SE. *Clin Invest Med.* 1995;18:247-254.
Adapted with permission from Kahn CR, Saltiel AR. *Joslin's Diabetes Mellitus.* 14th ed. Lippincott Williams & Wilkins; 2005:145-168.

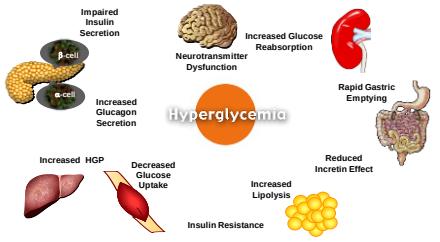
Insulin and Glucagon Dynamics in Response to Meals Are Abnormal in Type 2 Diabetes



n=12 normal; n=12 type 2 diabetes.

Adapted with permission in 2005 from Müller WA et al. *N Engl J Med.* 1970;283:109-115.

Multiple Metabolic Abnormalities Contribute to Hyperglycemia in T2DM



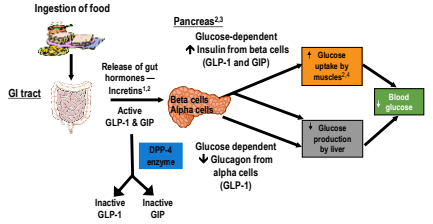
Adapted from DeFronzo RA. *Diabetes.* 2009;58:773-795.

Incretins

- Gut-derived hormones, secreted in response to nutrients, that potentiate insulin secretion and suppress glucagon secretion in a glucose-dependent fashion
  - Many other tissue effects
- Two predominant incretins
  - Glucagon-like peptide-1 (GLP-1)
  - Glucose-dependent insulinotropic peptide (GIP)
- Rapidly inactivated by dipeptidyl peptidase-4
- Incretin effect is impaired in type 2 diabetes

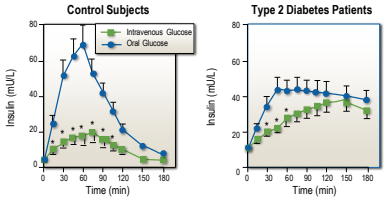
1. Holst JJ et al. *Diabetes*. 2004;53(suppl 3):s197-s204. 2. Meier JJ et al. *Diabetes Metab Res Rev*. 2005;21:91-117.

Role of Incretins in Glucose Homeostasis



DPP-4 = dipeptidyl-peptidase 4
1. Kieffer TJ, Habener JF. *Endocr Rev*. 1999;20:876-913. 2. Ahrén B. *Curr Diab Rep*. 2003;2:365-372.
3. Drucker DJ. *Diabetes Care*. 2003;26:2929-2940. 4. Holst JJ. *Diabetes Metab Res Rev*. 2002;18:430-441.

Reduced Incretin Effect in Type 2 Diabetes Patients



Reprinted with permission from Nauck M et al. *Diabetologia*. 1996;29:46-52.

Incretin Therapies to Treat T2DM

Incretin effect is impaired in T2DM

Natural GLP-1 has extremely short half-life

Add GLP-1 analogues with longer half-life:
Injectables
- Liraglutide
- Lixisenatide
- Albiglutide
- Dulaglutide
- Exenatide
- Exenatide QW

Block DPP-4, the enzyme that degrades GLP-1:
Oral agents
- Sitagliptin
- Saxagliptin
- Linagliptin
- Alogliptin

Drucker. *Curr Pharm Des*. 2001;7:1399-1412. Drucker. *Mol Endocrinol*. 2003;17:161-171.

DPP-4 Inhibitors and GLP-1 RAs: Summary of Efficacy and Other Considerations

	GLP-1 RAs	DPP-4 Inhibitors
Mode of administration	Injectable	Oral
Efficacy: HbA1C reduction	0.5%-2.0%	~0.5%-0.9%
Effect on weight	Potential for loss	Neutral
Hypoglycemia risk	None, unless used with secretagogue or insulin	None, unless used with sulfonylurea
Renal considerations	None	None for linagliptin
Other considerations	CV -, C-cell hyperplasia and medullary cancer in rodents, pancreatitis risk not seen in large databases	CV ?, rare instance of Stevens-Johnson, no proven pancreatitis risk

Glucose Control by the Kidney

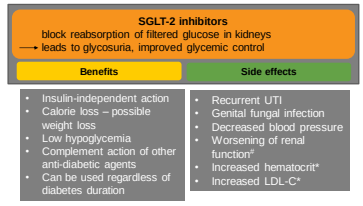
- Gluconeogenesis
  - Proximal tubule
  - Renal contribution more substantial than previously believed
    - ≈ 20% of post-absorptive total-body glucose release
    - ≈ 40% of gluconeogenesis
- Reabsorption of filtered glucose
  - >99% of glucose in glomerular filtrate is reabsorbed in the proximal renal tubule
  - Sodium-coupled glucose co-transporters (SGLTs) transport glucose against gradient from lumen into epithelial cells
  - Facilitated glucose transporters (GLUTs) transport glucose down gradient to plasma

Marsenic O. *Am J Kidney Dis*. 2009;53:875-883. Bakris GL et al. *Kidney Int*. 2009;75:1272-1277.

SGLT-2 Inhibitors: FDA Approved or in Clinical Development

Compounds in development	Development status
Dapagliflozin	FDA APPROVED
Canagliflozin	FDA APPROVED
Empagliflozin	FDA APPROVED
Ipragliflozin	US – Phase III clinical trials Approved for use in Japan
LX4211	Phase II clinical trials

SGLT-2 Inhibitors for Treatment of Type 2 Diabetes



Specific considerations for individuals with existing renal insufficiency, the elderly, and those receiving loop diuretics
* Significance on patient outcomes is unclear at this time

Kim Y et al. *Diabetes Metab Syndr Obes.* 2012;5:313-327.

Pathophysiology and Pharmacologic Targets: Summary

- Several new agents have hit the market in recent years, providing increased ability to tailor treatments based on patient profiles
- Expanded treatment armamentarium allows for more personalized shared decision-making between PCP and patient