Diabetes-Medications
Diabetes Update Class

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UC Irvine Health

Disclosures

NONE

Learning Objectives

- Provide the tools on how to use the medications that are now available for diabetes management.
- Discuss the efficacy of the diabetes-related medications.
- Identify cultural and other health belief barriers to insulin use and other therapies for diabetes.

Diabetes Overview

Type 1 Diabetes

- Autoimmune disease that can develop at any age
- Absolute absence of insulin
- Daily insulin administration is required for life
- ~5-10% of all cases of diabetes
- Most prevalent in those of northern European ancestry

Type 2 Diabetes

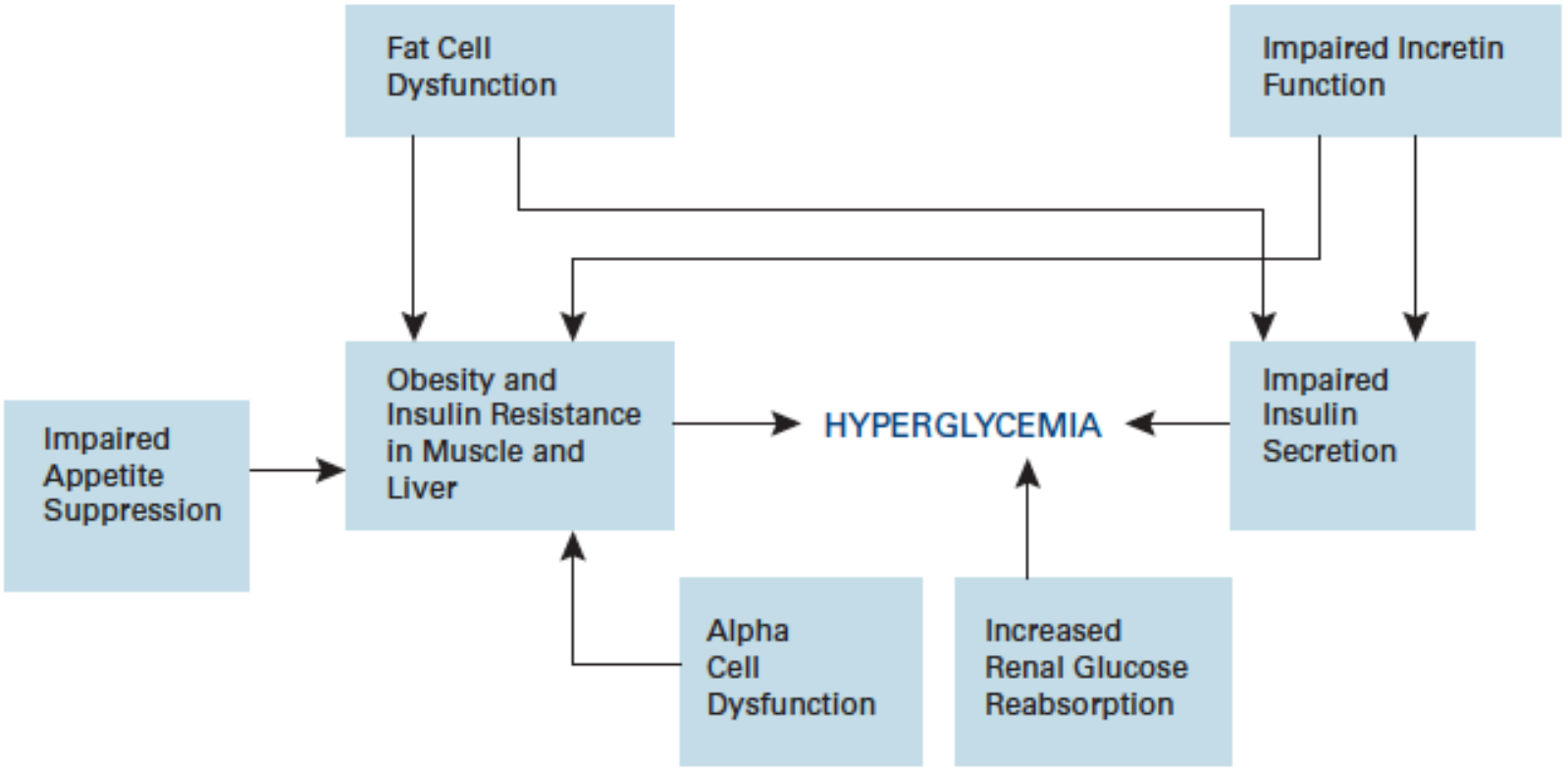
- Progressive disease related to:
  - A decline in insulin production
  - A loss of first phase insulin release
  - Insulin resistance
- ~90% of all cases of diabetes
- At risk populations include:
  - Hispanic-American, Asian-American, Native American, Pacific Islander, African-American

Gestational Diabetes

- Diabetes diagnosed in third trimester (24-28 weeks) using 75g 2 hour OGTT
- Positive for GDM with any of the following results:
- Fasting glucose >92mg/dL
- 1 hour pp >180mg/dL
- 2 hour pp >153mg/dL

Type 2 Diabetes

Figure 1. Metabolic Abnormalities That Contribute to Hyperglycemia



Source: Abdul-Ghani, MA. Type 2 Diabetes and the Evolving Paradigm in Glucose Regulation
Am J Manag Care. 2013;19(3 suppl):S43-S50

Natural History of T2DM and Risk for Complications

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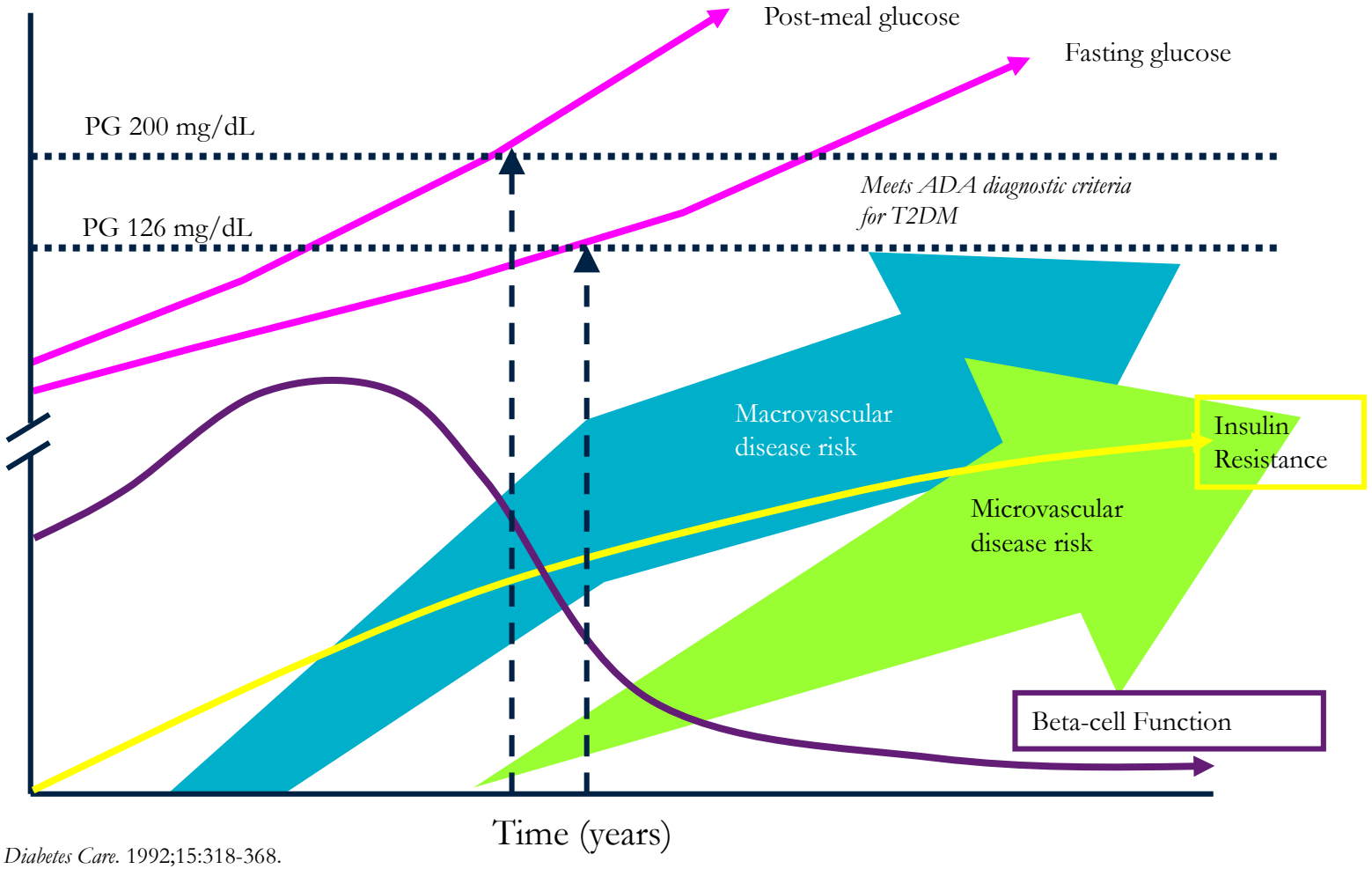

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Haffner S, et al. *Diabetes Care.* 1999;22:562-568.
Haffner S, et al. *N Engl J Med.* 1998;339:229-234.
American Diabetes Association. *Diabetes Care.* 2003;26:S33-S50.

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Diabetes Diagnosis

Symptoms of diabetes plus random plasma glucose	≥200 mg/dL
or	
FPG	≥126 mg/dL
or	
2-h plasma glucose during a 75-g OGTT	≥200 mg/dL
or	
Hemoglobin A1c	>6.5%

Diagnosing Diabetes Type 1 & Latent Autoimmune Diabetes in Adults (LADA): Beyond Glucose

- C-peptide-fasting with BG <250mg/dL
- Glutamic Acid Decarboxylase Autoantibodies (Anti-GAD)
- Insulin Autoantibodies (IAA)
- Insulinoma-Associated-2 Autoantibodies (IA-2A)
- Islet Cell Cytoplasmic Autoantibodies (ICA)-oldest test, not used
- Zinc Transporter 8 (ZnT8Ab)-newest, not widely available yet

IFG and IGT

Intermediate Between Normal and Diabetes

Impaired Fasting Glucose (IFG)

- FPG ≥100 but <126 mg/dL
- Predicts increased risk of diabetes and micro- and macrovascular complications

Impaired Glucose Tolerance (IGT)

- 2-h PG on OGTT ≥140 but <200 mg/dL
- Predicts increased risk of diabetes and cardiovascular disease

Regulation of Fasting Glucose

- Hepatic glucose production is a primary factor determining fasting plasma glucose
- Fasting hepatic glucose production is regulated by
  - Fasting (basal) plasma insulin
  - Hepatic sensitivity to insulin
  - Fasting substrate availability
- In type 2 diabetes
  - Basal insulin secretion is impaired
  - Hepatic sensitivity to insulin is decreased

Regulation of Postprandial Glucose

- A meal contains 6 to 20 times the glucose content of the blood
- Normally, postprandial hyperglycemia is regulated by
  - Clearance of ingested glucose by the liver
  - Suppression of hepatic glucose production
  - Peripheral clearance of glucose

Goals of Therapy

- **A**1c 7% or lower
- **B**lood pressure 140/90 or lower
- **C**holesterol 200mg/dL or lower (LDL <100)
- Maintain a healthy body weight
- Prevent/delay complications of unmanaged diabetes
- Maintain quality of life

Medications in Diabetes

Non-Insulin Medication Options for Type 2 Diabetes

Medication Therapies in Type 2 Diabetes: Orals

- Sulfonylureas (secretagogues)
  - Glyburide* (Diabeta/Glynase), glipizide* (Glucotrol/Glucotrol XL), glimepiride* (Amaryl), nateglinide*, repaglinide*
- Biguanides
  - Metformin*(Glucophage/Glucophage XR/Glumetza/Fortamet, Riomet)
- Thiazolidinedione aka TZDs
  - Pioglitazone* (Actos), rosiglitazone* (Avandia)
- DPP-4 Inhibitors
  - Sitagliptin (Januvia), saxagliptin (Onglyza), linagliptin (Tradjenta), alogliptin*(Nesina)
- SGLT2 Inhibitors
  - Dapagliflozin (Farxiga), canagliflozin*(Invokana), empagliflozin*(Jardiance), ertugliflozin (Steglatro)
- Alpha-glucosidase Inhibitors
  - Acarbose* (Precose), miglitol* (Glyset)
- Bile Acid Sequestrants
  - Cholestyramine*, cholestipol*, colesevelam HCL (Wellchol)
- Dopamine agonist
  - Bromocriptine* (Cycloset)

Sulfonylureas

Widely used oral medication in the U.S.

increased cardiovascular risk related to

weight gain

fluid retention

hypoglycemia

No longer recommended as first agent of choice.

Biguanides (metformin)

Benefits of metformin related to improving insulin resistance

- weight management
- fatty liver disease
- cardiovascular disease
  - endothelial function
  - anti-inflammatory agent
  - anti-oxidant

American Diabetes Association. 9. Pharmacologic approaches to glycemic treatment: Standards of Medical Care-2019. Diabetes Care 2019; 42 (Suppl 1):S90-S102.

Biguanides (metformin)

Benefits in non diabetes related conditions

- HIV treatment side effects (insulin resistance)
- reduces cancer risk
  - liver, pancreas, colon, breast, prostate, cervical, renal cell

Risk associated with metformin

- vitamin B12 deficiency resulting in worsening neuropathy
- should not be used in patients with eGFR <30

Abdelgadir E, et al. Effect of metformin on different non-diabetes related conditions and special focus on malignant conditions:review of the literature. J Clin Med Res 2017; 9 (5):388-395

SGLT2 Inhibitors

Benefits of therapy beyond glycemic management

- Cardiovascular benefits (FDA approval 2018)
  - decreased nonfatal heart attack
  - decreased nonfatal stroke
  - decreased CV death
  - decreased all mortality
  - decreased hospitalizations for HF

FDA label for CV benefit for canagliflozin and empagliflozin only

SGLT2 Inhibitors

Mechanism of action

- osmotic diuresis (modulation of cardio-renal axis)
- weight loss
- decrease arterial stiffness
- decrease left ventricular afterload
- decrease in blood pressure

Renal benefits include

- decrease in renal disease progression
- delaying dialysis

SGLT2 Inhibitors

Adverse effects

genital mycotic infections especially in women and uncircumcised men

increase risk of UTIs

normoglycemic DKA (especially in clinical trials with type 1 DM)

increased amputation risk (canagliflozin)

increased bone fractures (canagliflozin)

Medication Therapies in Type 2 Diabetes : Non-Insulin Injected

- GLP-1 Inhibitors
  - Exenatide*(Byetta), exenatide XR (Bydureon), liraglutide (Victoza), dulaglutide (Trulicity), lixisenatide (Adlyxin), semaglutide (Ozempic)

- Amylin synthetic
  - Pramlintide (Symlin)

Medication Therapies in Type 2 Diabetes : Non-Insulin Injected

Combination Therapies

Xultophy- degludec + liraglutide (Tresiba + Victoza)

iGlarLixi/Soliqua- glargine + lixisenatide (Lantus + Adlyxin)

GLP-1 Agonist

Liraglutide, semaglutide and dulaglutide have been shown to have cardio protective effects.

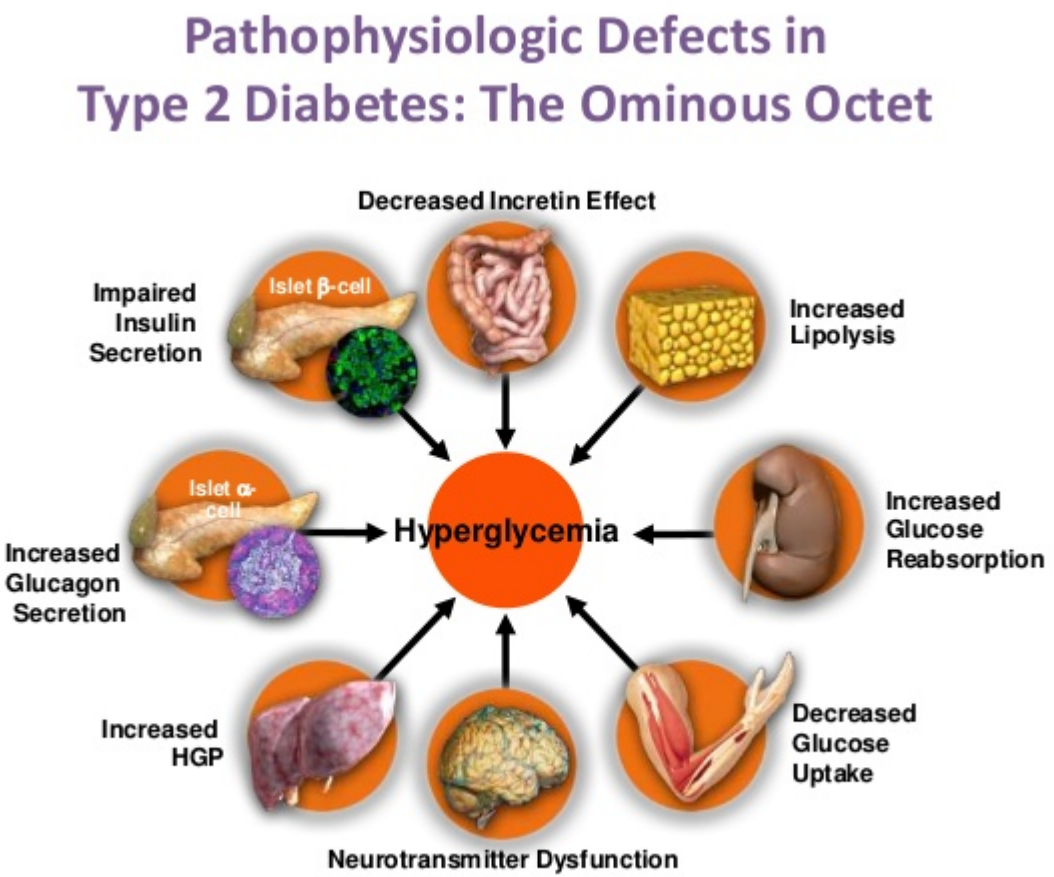
- decrease major CV events
- decrease CV death
- decrease all mortality

Appear to have an anti-atherothrombotic effect

Decrease blood pressure and weight without hypoglycemia risk.

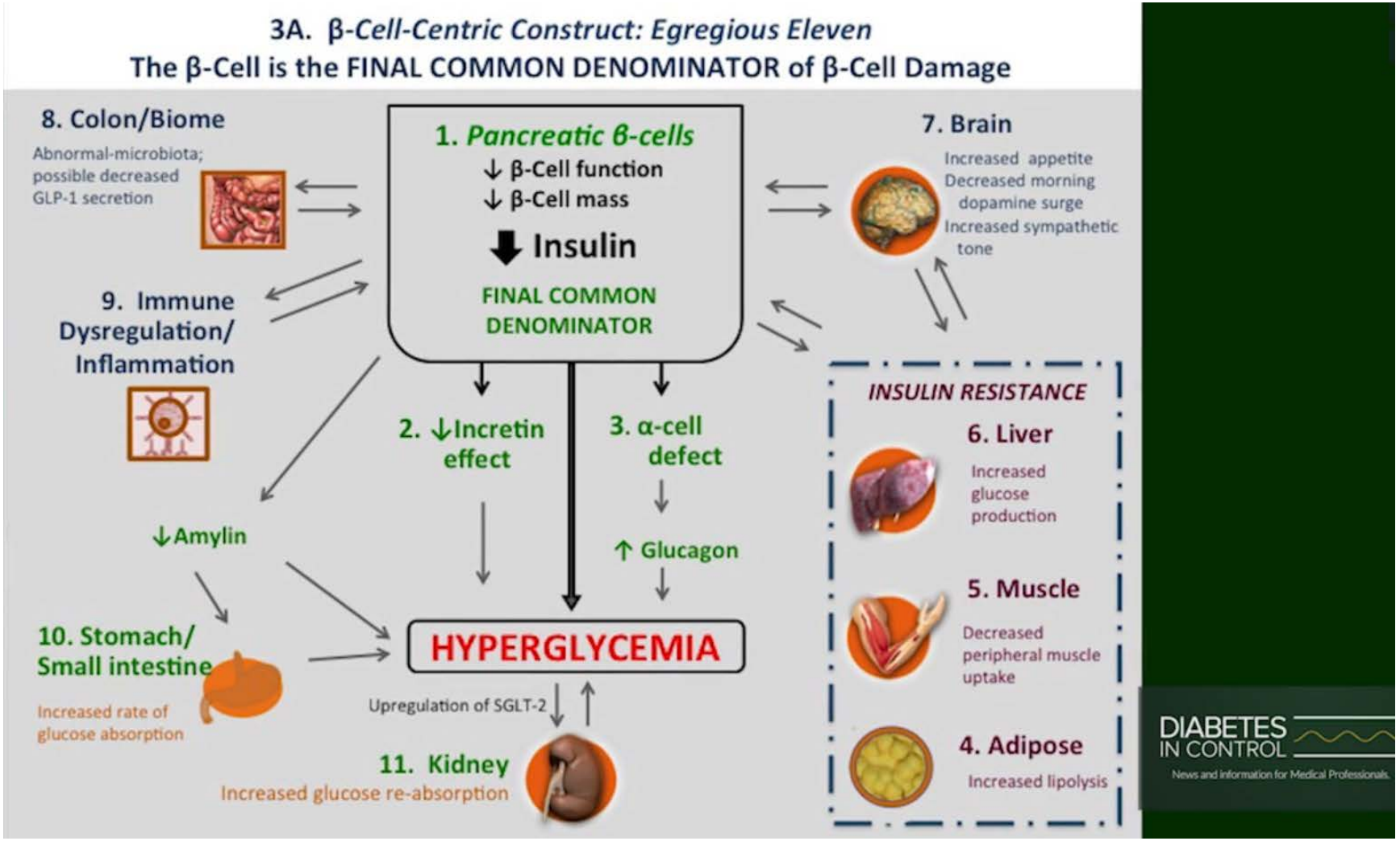
 Acharya, T. Deedwania, P. The role of newer anti-diabetic drugs in cardiovascular disease. American College of Cardiology, May 23, 2018.

Metabolic Defects in Type 2 Diabetes

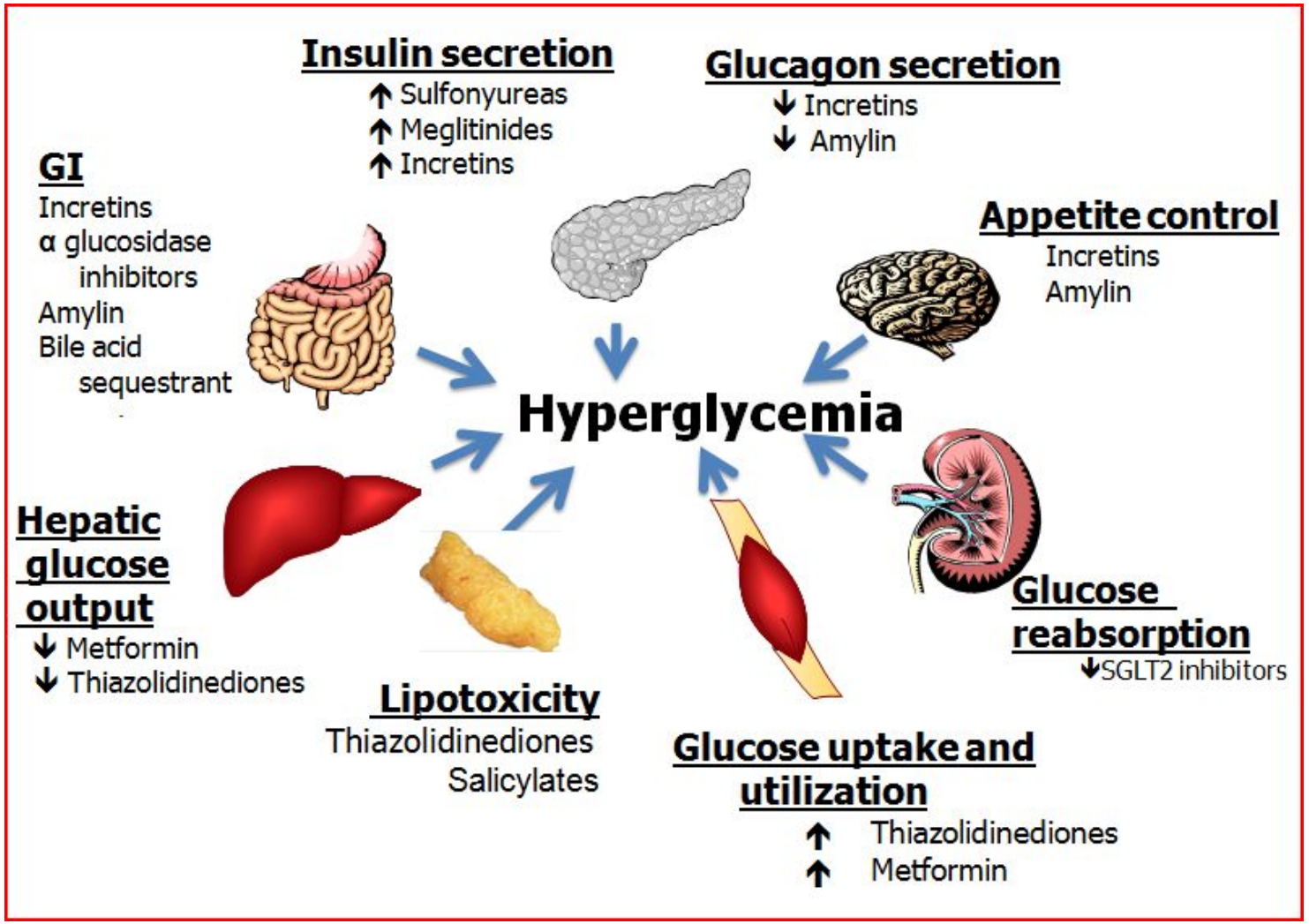


DeFronzo RA. *Diabetes*. 2009;58(4):773-795.

Metabolic Defects in Type 2 Diabetes



Sites of Action in Type 2 Diabetes

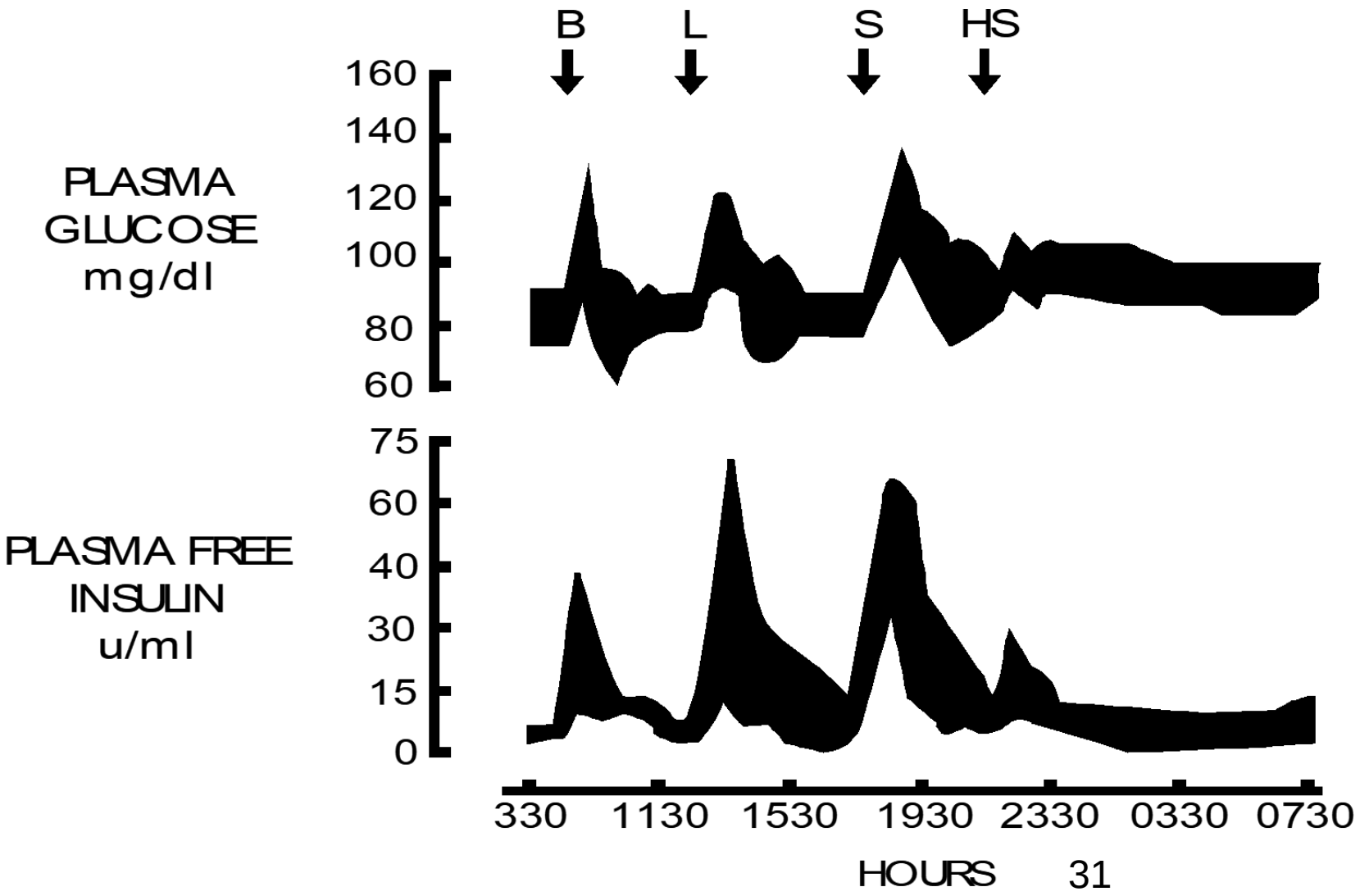


Medications in Diabetes

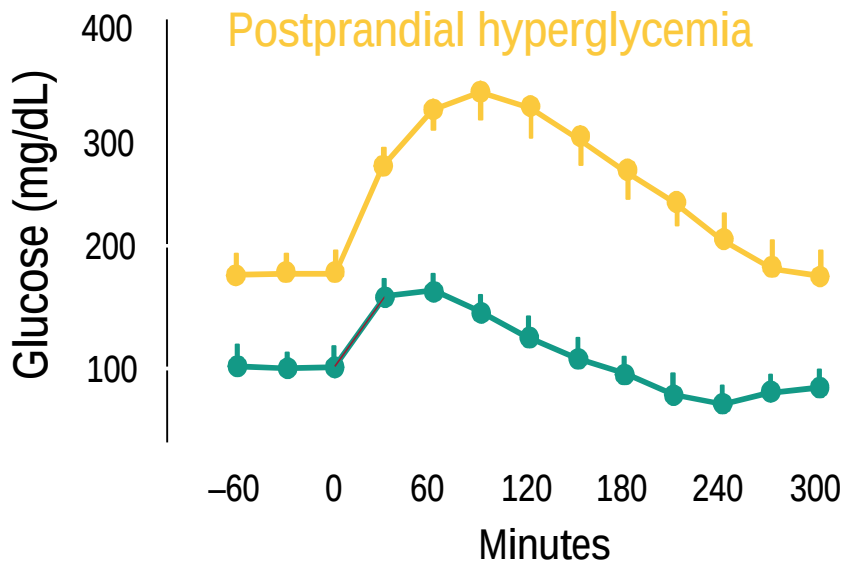
Insulin Options

The Goal of Insulin Therapy:

Attempt to Mimic Normal Pancreatic Function

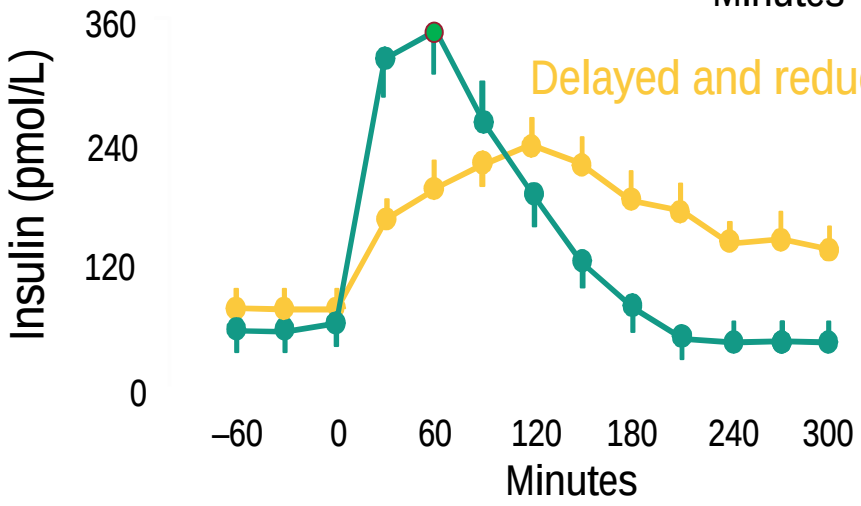


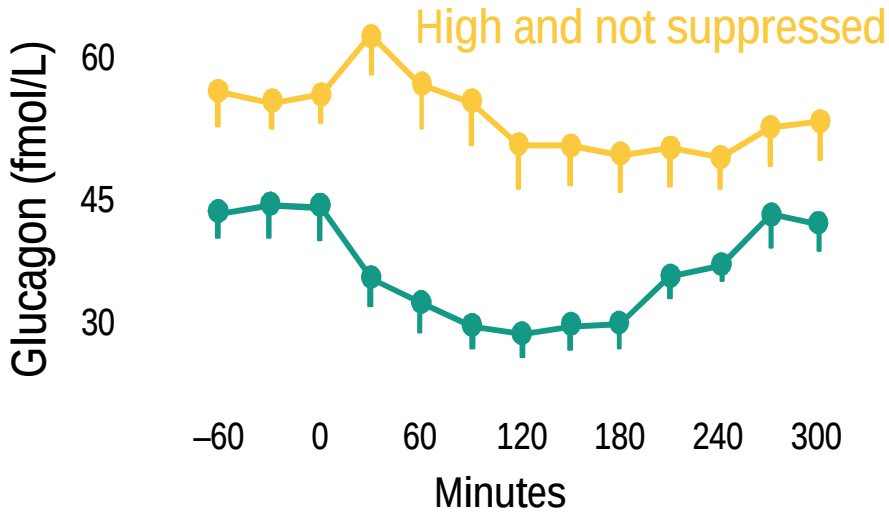
Patterns of Glucose, Insulin, and Glucagon After Oral Glucose in Type 2 Diabetes



Type 2 Diabetes

Normal





Mitrakou A et al. *Diabetes.* 1990;39:1381-1390

Insulin Therapy Options

- Rapid acting- *lispro*(Humalog/Admelog), lispro U200*, aspart* (Novolog), glulisine (Apidra),* inhaled regular(Afrezza) , aspart (Fiasp)*
- Short acting- *regular*, regular U500*
- Intermediate acting- *NPH**
- Long acting- *glargine* (Lantus/Basaglar), glargine U300 (Toujeo), detemir*(Levemir), degludec (Tresiba), degludec U 200 (Trisiba)*

Insulin Therapy Options

Combination insulins

70/30 mix*- 70%NPH and 30%Regular (Humulin/Novolin)

75/25 mix*- 75%NPL and 25% lispro (Humalog)

50/50 mix*- 50% NPL and 50% lispro (Humalog)

70/30* analog mix- 70% insulin aspart (Novolog) protamine and 30% aspart

70/30 mix-70% degludec and 30% aspart (Ryzodeg)

Human Insulins and Analogues Typical Times of Action

Insulin Preparations	Onset of Action	Peak	Duration of Action
Aspart, glulisine, lispro	~15 minutes	1–2 hours	4–6 hours
Afrezza Inhaled regular	0-1 minute	20-30 minutes	90 minutes
Human regular	30–60 minutes	2–4 hours	6–8 hours
Human NPH	2–4 hours	4–10 hours	12–20 hours
Glargine, Detemir, etc	2–4 hours	Flat	12-42 hours

Pharmacokinetics of Insulin Products

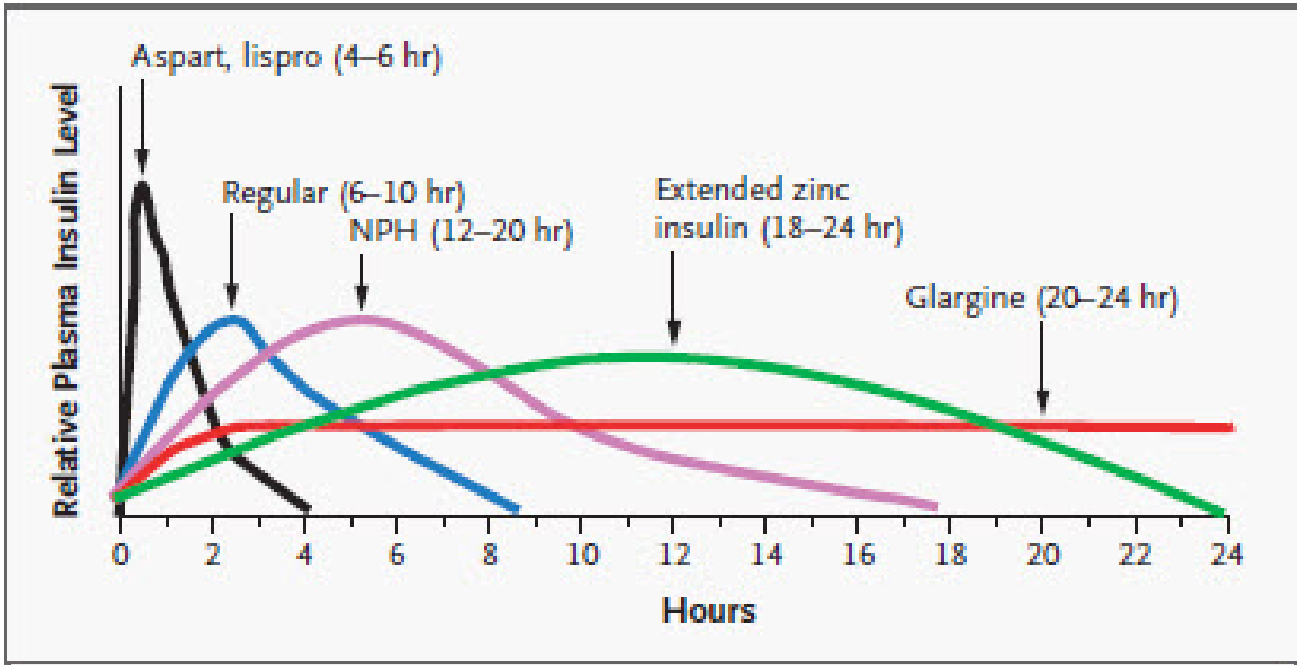
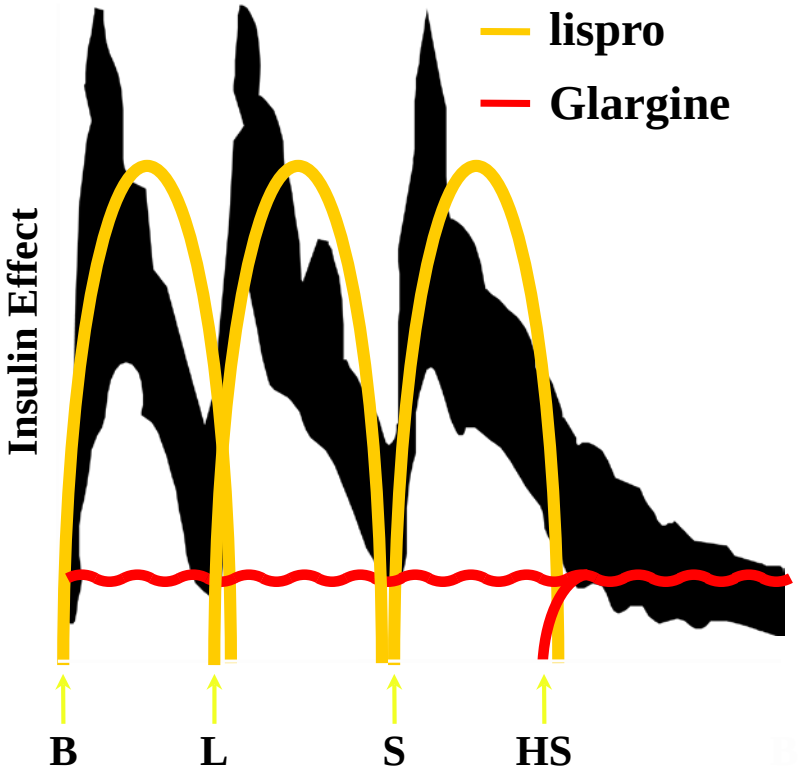


Figure 2. Approximate Pharmacokinetic Profiles of Human Insulin and Insulin Analogues.

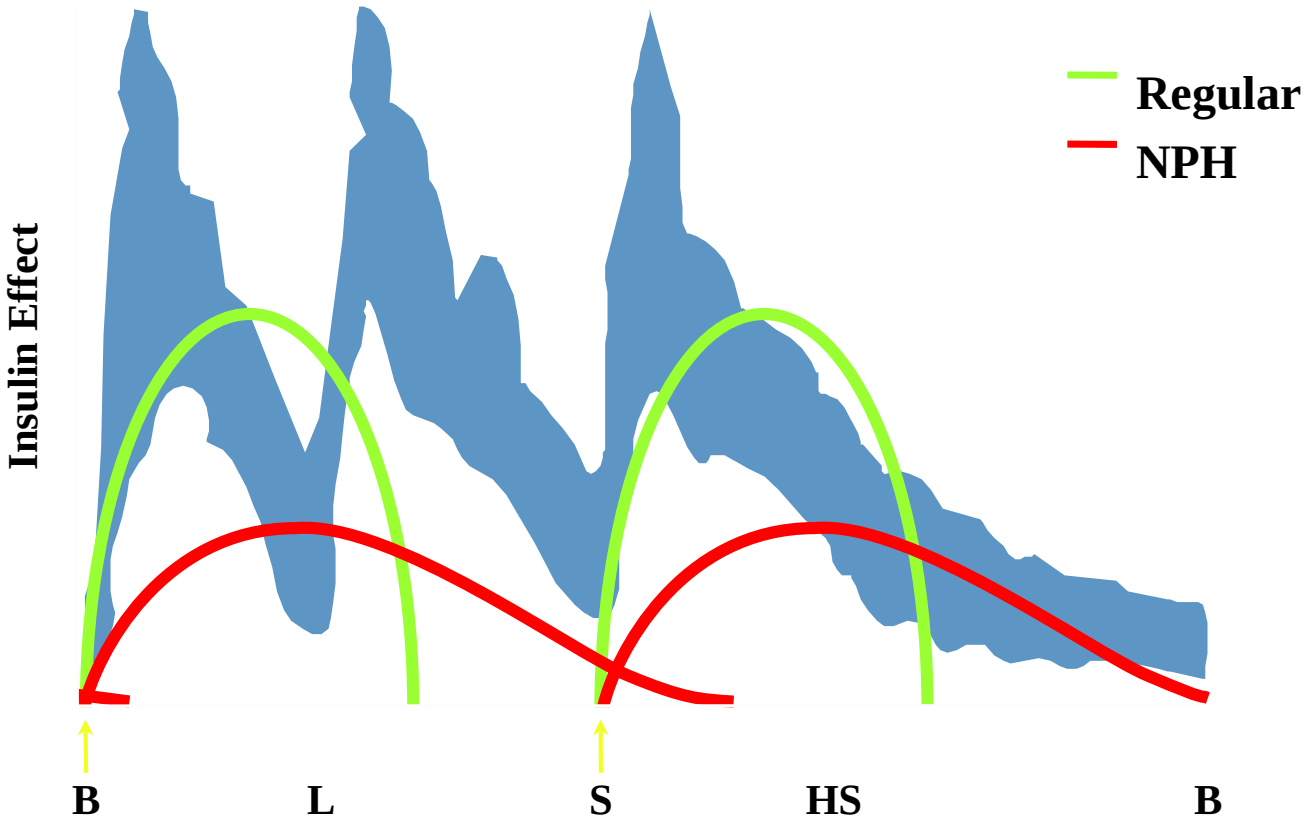
The relative duration of action of the various forms of insulin is shown. The duration will vary widely both between and within persons.

Adapted from Hirsch I. *N Engl J Med*. 2005;352:174–183.

Basal Bolus Regimen with Glargine and Lispro



Twice-daily Split-mixed Regimens



Summary of Pathophysiology

- Type 1 diabetes
  - The main abnormality is insulin deficiency
- Type 2 diabetes
  - Both insulin deficiency and insulin resistance contribute
- Glucotoxicity and lipotoxicity
  - Poor metabolic control worsens insulin deficiency and insulin resistance

Medication & Meal Planning

BASAL MEDICATIONS

Consistent carbohydrate

Calorie control for weight management

Small, frequent meals may be of benefit

Heart healthy foods

Glycemic index/Glycemic load guide

BOLUS MEDICATIONS

Match carbohydrate load to medication action

Calorie control as needed for weight management

Carbohydrate counting

Heart healthy foods

Higher risk for hypoglycemia on oral meds when meals are skipped

Exercise Safety

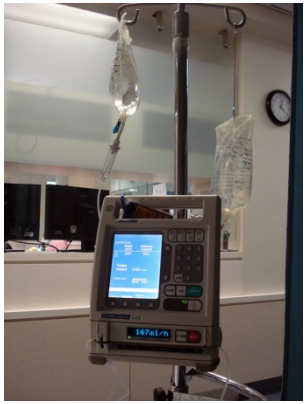
- Obtain medical clearance
- Wear appropriate clothing and footwear
- Monitor blood glucose before, during and after exercise
- BG target is 90-180mg/dL. No exercise if BG >275/300mg/dL
- Wear medical ID
- Know how to adjust insulin(s) for exercise
- Carry a fast-acting carbohydrate source

Insulin Delivery

Syringes, Pens & Pumps

Insulin Delivery Options

- vial and syringe
- inhaled
- insulin pen devices
- insulin pump
- IV insulin



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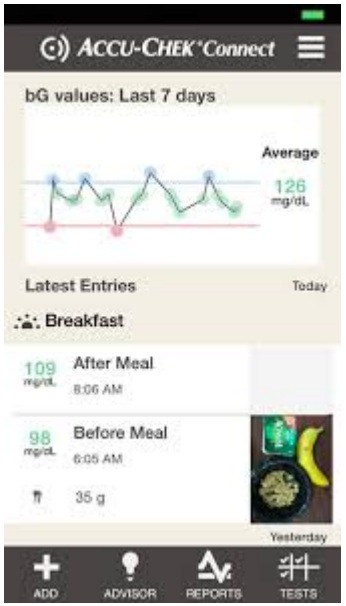
Self-Management Tools

The Apps Store

Chronic Disease Tools



myfitnesspal

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Barriers to Diabetes Self Management

Much more than a patient

Barriers to Diabetes Management

- Clinical inertia by healthcare providers
- Patient's access to transportation, cost of DM supplies/medications/education.
- Lack of healthy food choices in the neighborhood
- Limited literacy/health literacy
- Long standing diabetes with very old lifestyle habits

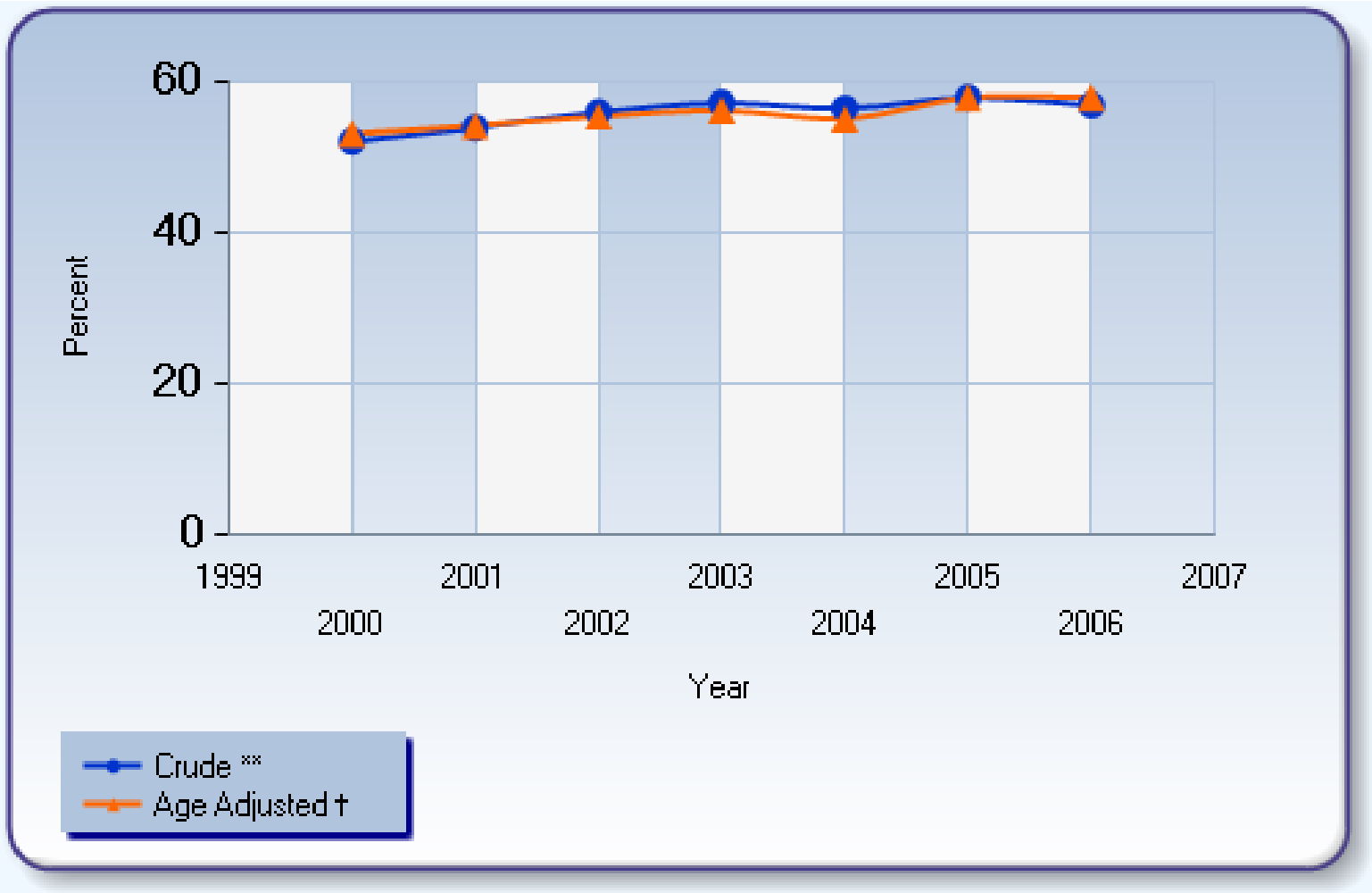
Health Disparities

- Diabetes care is often deficient in minority populations
- Diabetes complications (renal disease, amputation, neuropathy) are higher in minority populations
- Limited access to health care services
- Health myths and misconceptions

Health Disparities

- Fewer medical visits
- Underdiagnosis
- Lower rates of recommended monitoring tests for diabetes
- Decrease in optimal health

Diabetes Education at Least Once



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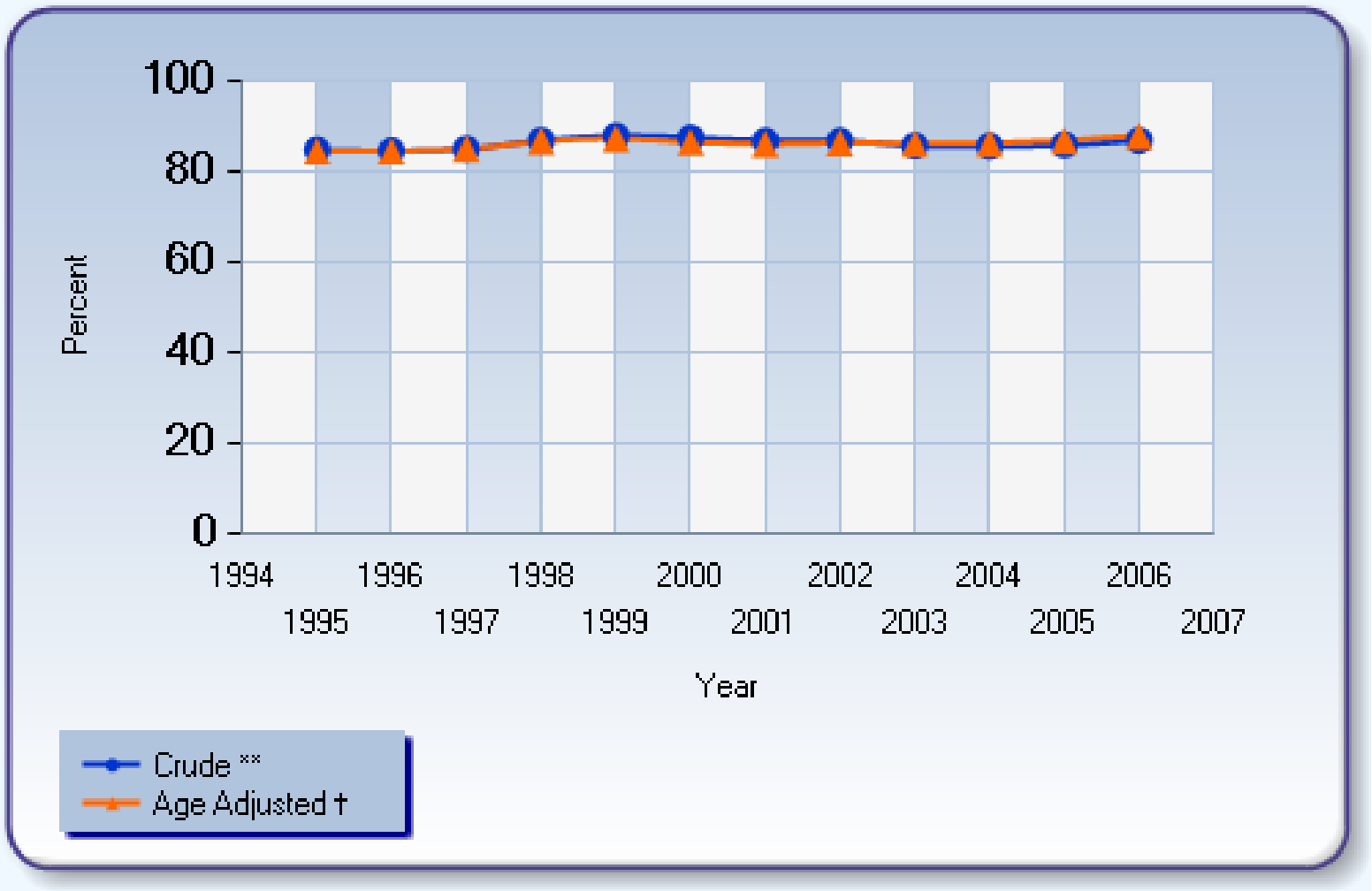
Seen by a Physician at Least Once a Year



Care Indicators for California Guideline Therapy

- Annual dilated eye exam 59.7%
- Annual foot exam 62.9%
- 2 or more A1c tests 63.9%
- Flu vaccine 50.6%
- Pneumococcal vaccine 46.6%
- At least one MD/DO/NP visit/year 79.3%

Self Care Behaviors: California

- Daily blood glucose monitoring 42.7%
- Self foot exam 49%
- Attended at least 1 diabetes self management class 64.5% (6% of Medicare beneficiaries use their DSMT benefit)
- Smoking 13.1%
- Physical Inactivity 28%
- Obese 48.2%
- Cardiovascular risk awareness (HTN=58.9% Chol=56.7%)

Models of Success

2 % reduction in A1c with…

- Adequate health care interventions and diabetes education that is culturally sensitive provided by a multidisciplinary team at the provider's location.

Reimbursement is available for DSME, DPP and MNT. (MediCare, MediCal and commercial)

Resources

Free patient education materials in multiple languages

www.diabetes.org

www.eatright.org

www.nih.gov

www.cdc.gov

www.diabeteseducator.org

Resources

Dietary Guidelines for Americans	www.dietaryguidelines.gov
My Pyramid Tracker	www.mypyramidtracker.gov
Nutrition	www.eatright.org
Food and Nutrition Information Center	http://fnic.nal.usda.gov
Healthy People	www.healthypeople.gov
Aim for a Healthy Weight	www.nhlbi.nih.gov
National Weight Registry	www.nwcr.ws
Calorie, Fat, Carbohydrate Counter	www.calorieking.com
Nutrient Database	www.nal.usda.gov
U.S. National Physical Activity Plan	www.physicalactivityplan.org
Centers for Disease Control and Prevention	www.cdc.gov/obesity
Obesity (Silver Spring). 2011.	Oct;19(10):1957-62. doi: 10.1038/oby.2011.204. Epub 2011 Jul 14
Diagnosis and Management of Obesity. 2013	www.aafp.org

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Gold, Robert, et al, The Diabetes educator, Volume 34, Number 6, November/December 2008, p. 990-1012.

Horton, Edward, et a l, The Diabetes Educator, Volume 34, Supplement 4, July/August 2008.

Metghalchi, Shiva, et al, The Diabetes educator, Volume 34, Number 4, July/August 2008, p. 698-706.

Centers for Disease Control and Prevention, National Diabetes Statistics Report, 2017. Atlanta, GA: Centers for Disease Control and Prevention, U.S. Department of Health and Human Services: 2017

Diabetes Care, Standards of Medical care in Diabetes- 2018. diabetes Care volume 41, Supplement 1, January 2018.

American Association of Clinical Endocrinologists, AACE, www.aace.com

Questions

THANK YOU