Optimizing Diabetes Treatment in a Sea of Options

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Disclosures

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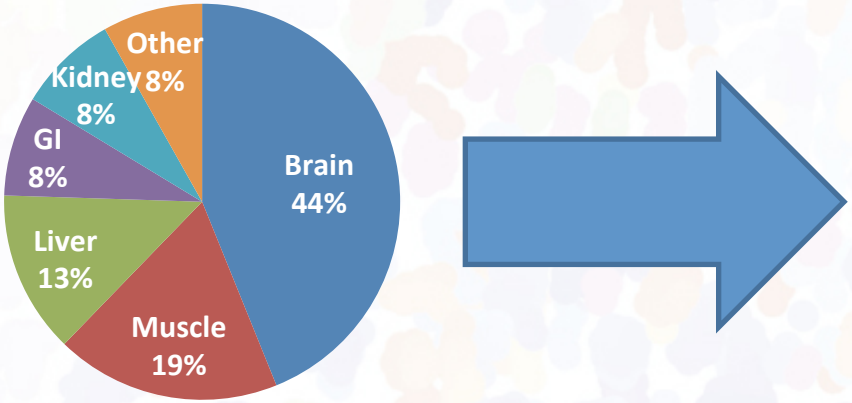
Learning Objectives

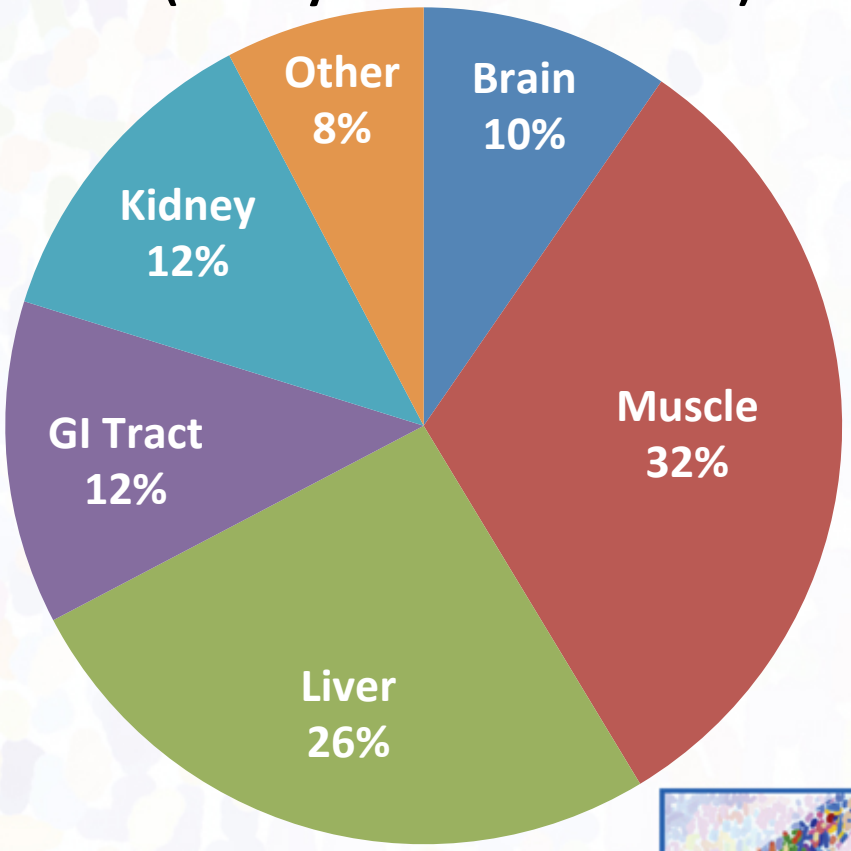
- Explain the incretin and sodium glucose co-transporter pathways and the differences between agents whose mechanisms are based on them.
- Evaluate new safety and efficacy data related to available and emerging agents, in light of recent recommendations.
- Formulate a diabetes management plan that takes into account specific patient characteristics and dosing preferences.
- Explain the considerations and rationale for combination therapy in diabetes.

Glucose Utilization: Role of Various Tissues

Fasting State
2 mg/Kg/min
(mainly insulin independent)



Postprandial State
10 mg/Kg/min
(mainly insulin stimulated)



Gerich JE. *Diabet Med*. 2010;27(2):136-142.

Glucose Utilization: Role of Various Tissues

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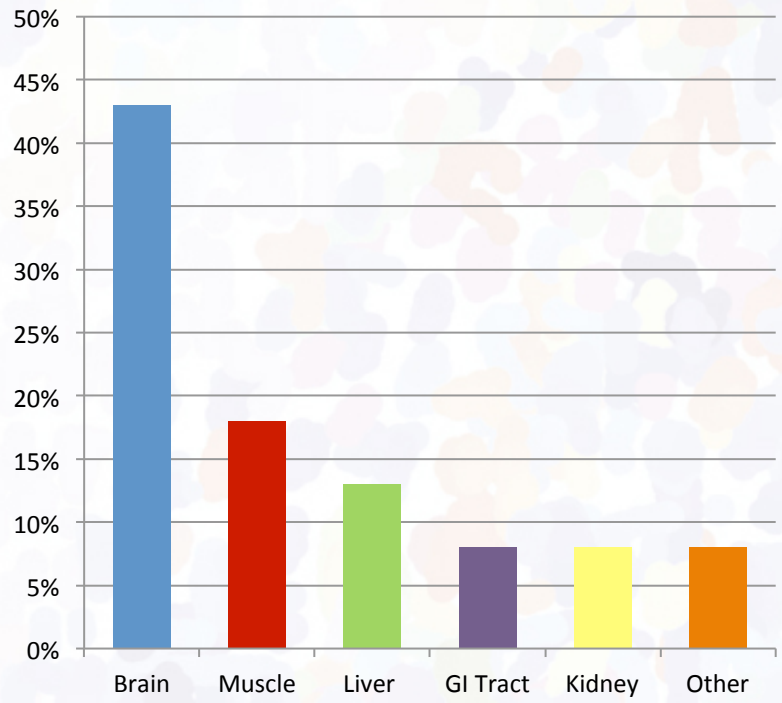

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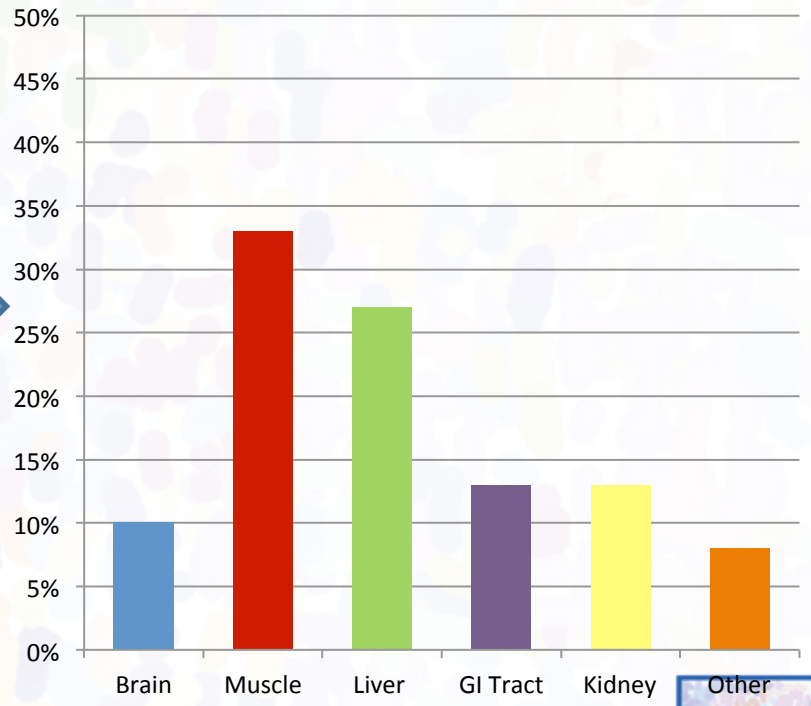
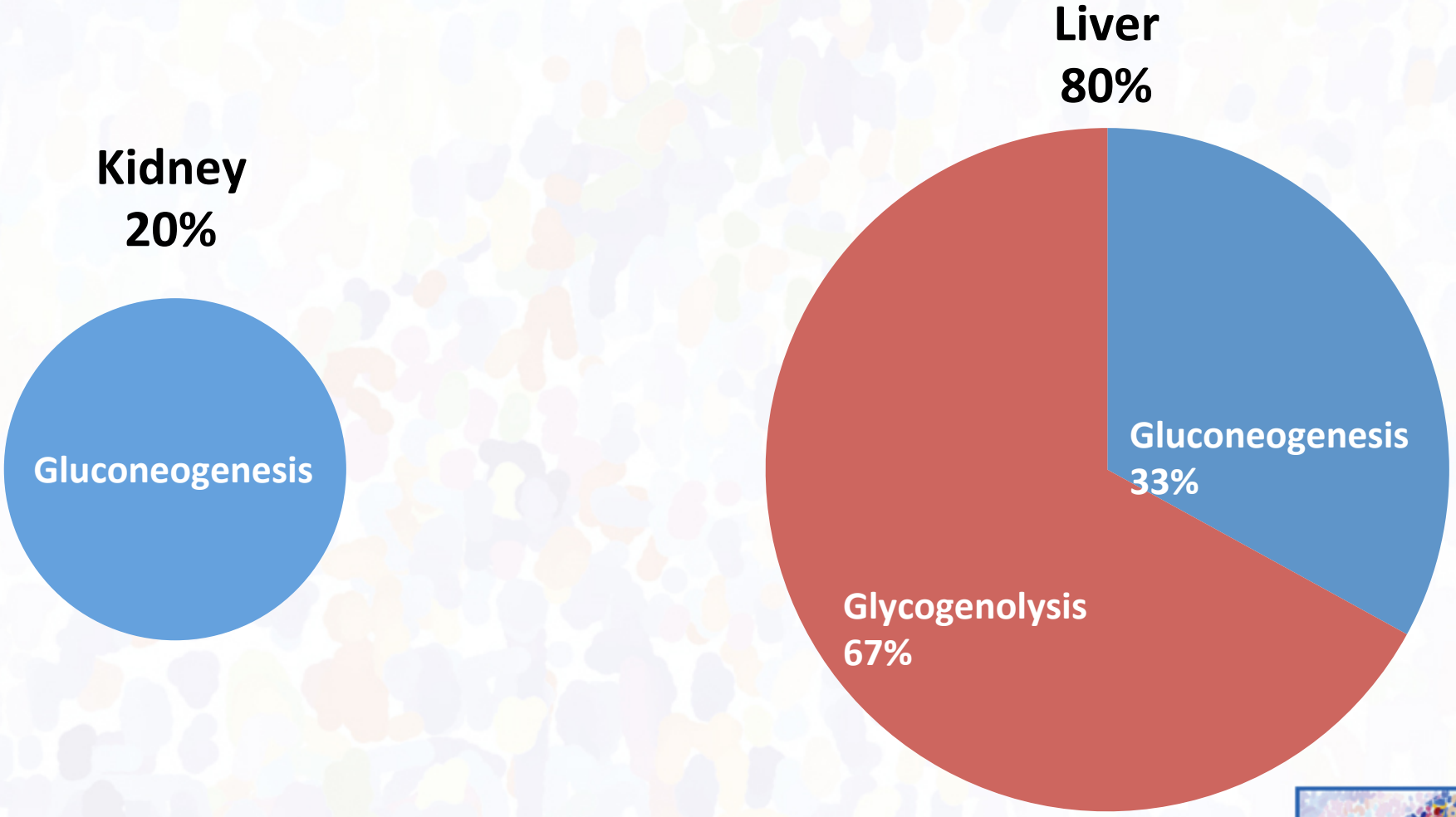


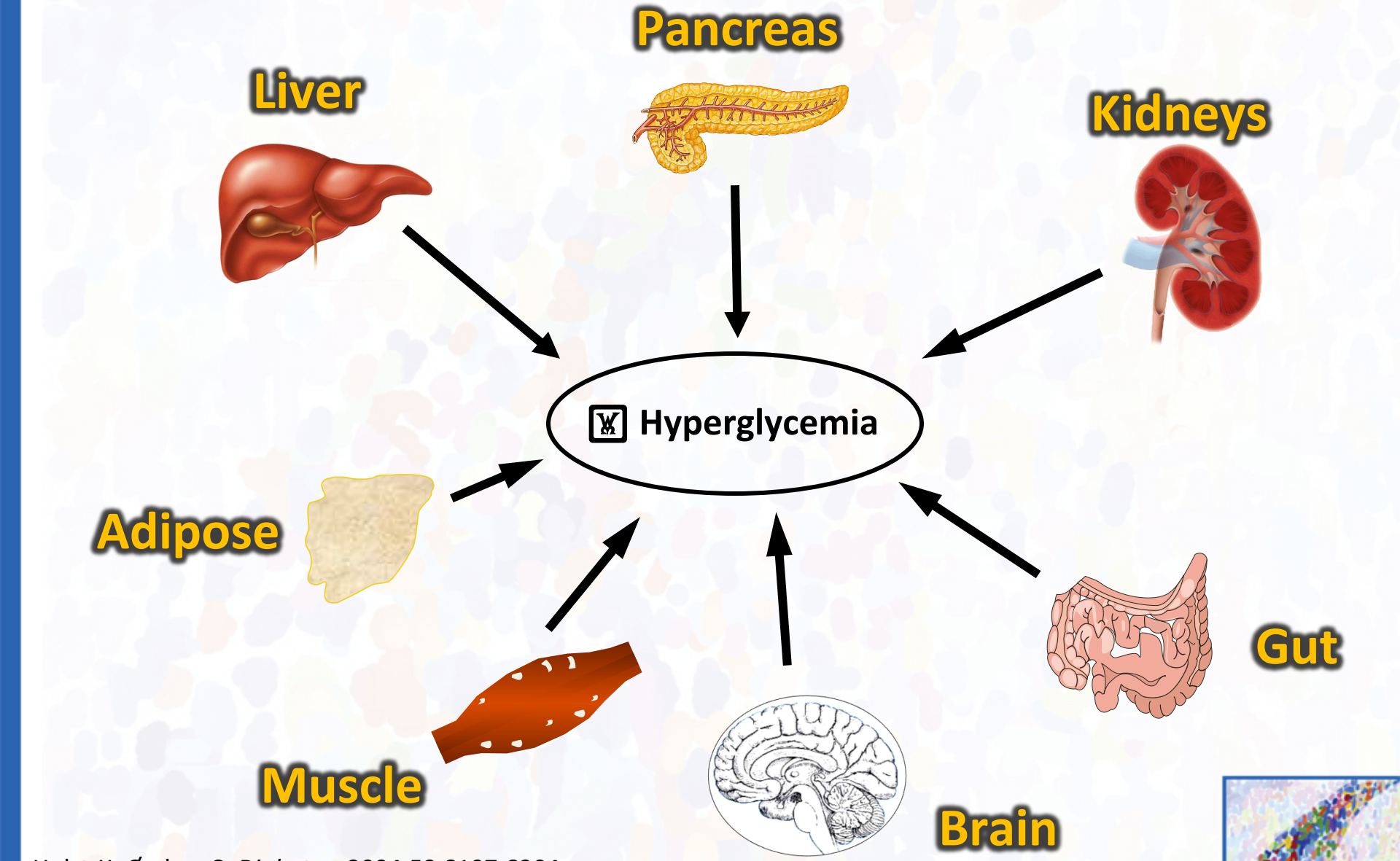
Gerich JE. *Diabet Med*. 2010;27(2):136-142.

Contribution of Tissues to Fasting Plasma Glucose



Gerich JE. *Diabet Med*. 2010;27(2):136-142.

Organs Involved with Glucose Homeostasis



Holst JJ, Ørskov C. *Diabetes.* 2004;53:S197-S204.
Lebovitz HE. *Diabetes Rev.* 1999;7:139-153.

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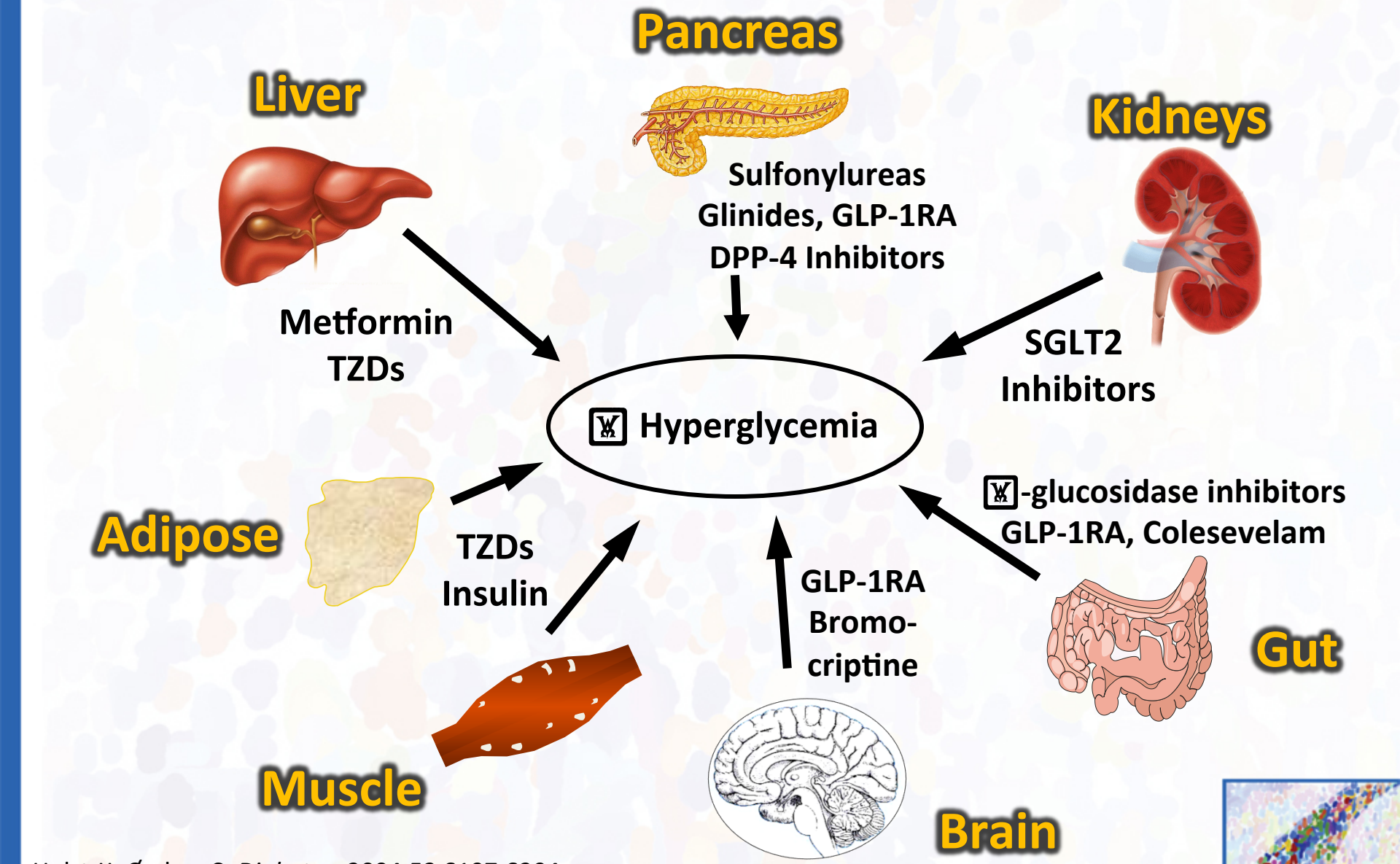


Holst JJ, Ørskov C. *Diabetes.* 2004;53:S197-S204.
Lebovitz HE. *Diabetes Rev.* 1999;7:139-153.

Diabetes Drugs and Associated Risk Factors

Drug	Weight	Blood Pressure	Dyslipidemia	Hypoglycemia Risk
[illegible]-glucosidase inhibitors	Neutral	Improved	Neutral/ Improved	Low
DPP-4 inhibitors	Loss/Neutral	Neutral	Improved	Low
GLP-1 agonists	Loss	Improved	Improved	Low
Insulin	Gain	Neutral*	Improved	High
Meglitinides	Gain	Neutral	Neutral	Moderate
Metformin	Loss/Neutral	Neutral	Improved	Low
SGLT2 inhibitors	Loss	Improved	?	Low
Sulfonylureas-	Gain	Neutral	Variable	Moderate
TZD	Gain	Improved	Mixed	Low

*Hyperinsulinemia is associated with hypertension

Basile JN. *J Diabetes Complications*. 2013;27(3):280-286.

ADA 2015 Recommended A1C Goals

< 8%

- History of severe hypoglycemia
- Limited life expectancy
- Advanced micro- or macrovascular complications
- Extensive comorbid conditions, or
- Long-standing diabetes where the general goal is difficult to attain despite active management

< 7%

< 6.5%

American Diabetes Association. *Diabetes Care.* 2015;38:S1-S93. http://care.diabetesjournals.org/content/suppl/2014/12/23/38.Supplement_1.DC1/January_Supplement_Combined_Final.6-99.pdf. Accessed April/2015.

ADA 2015 Recommended A1C Goals

< 8%

< 7%

- Many non-pregnant adults

< 6.5%

American Diabetes Association. *Diabetes Care.* 2015;38:S1-S93. http://care.diabetesjournals.org/content/suppl/2014/12/23/38.Supplement_1.DC1/January_Supplement_Combined_Final.6-99.pdf. Accessed April/2015.

ADA 2015 Recommended A1C Goals

< 8%

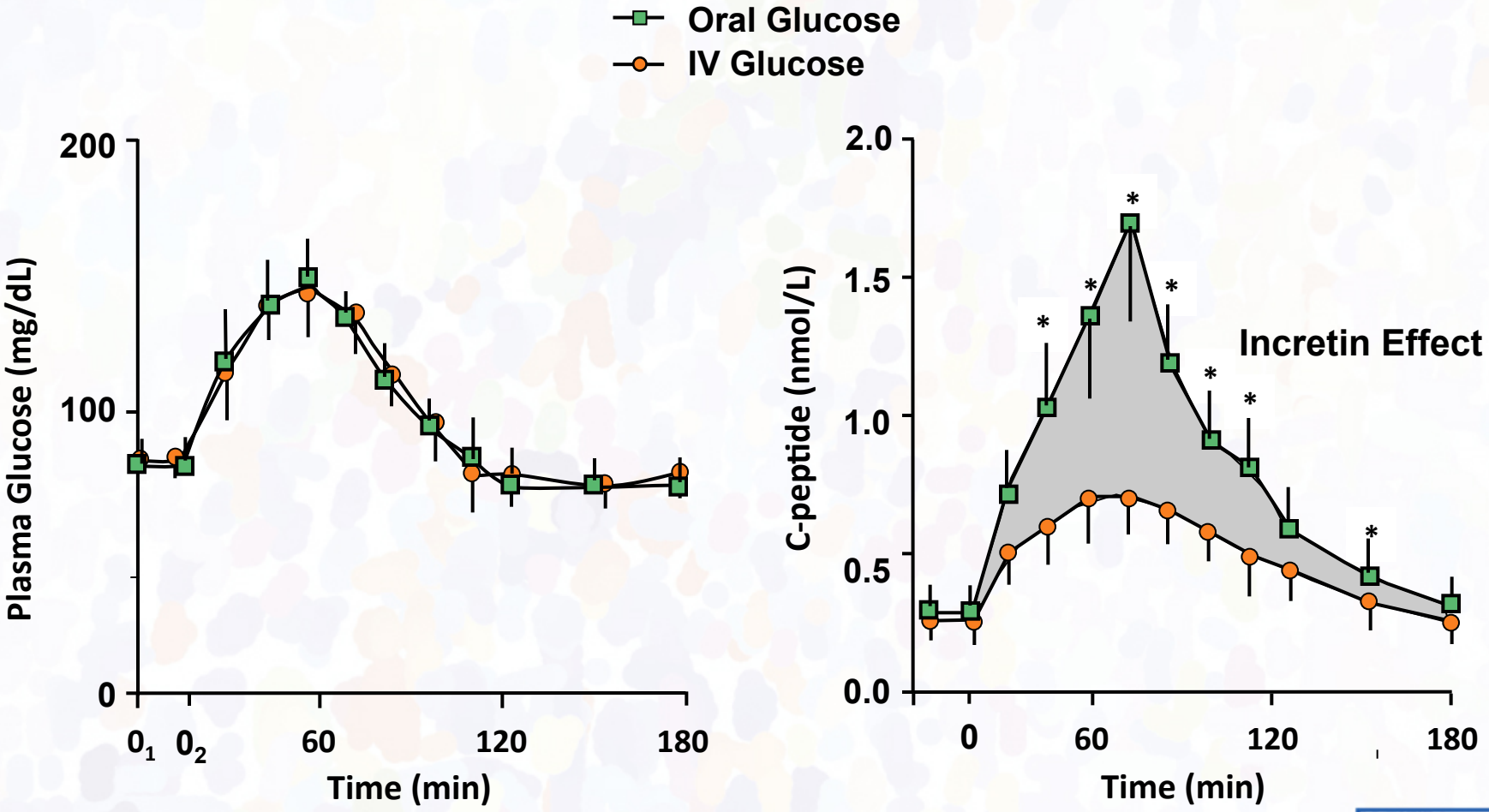
< 7%

< 6.5%

- Without significant hypoglycemia or other adverse effects
- Short duration of diabetes
- T2DM treated with lifestyle or metformin only
- Long life expectancy
- No significant CVD

American Diabetes Association. *Diabetes Care.* 2015;38:S1-S93. http://care.diabetesjournals.org/content/suppl/2014/12/23/38.Supplement_1.DC1/January_Supplement_Combined_Final.6-99.pdf. Accessed April/2015.

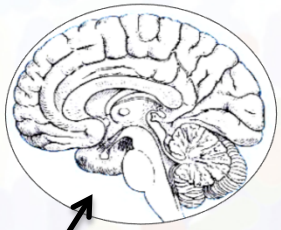
The Incretin Effect in Healthy Subjects



Mean ± SE; N = 6; *p ⊠ .05; 0_1-0_2 = glucose infusion time.

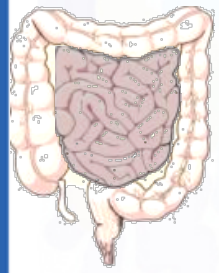
Nauck MA, et al. Incretin effects of increasing glucose loads in man calculated from venous insulin and C-peptide responses. *J Clin Endocrinol Metab.* 1986;63:492-498.

Role of Incretins in Glucose Homeostasis



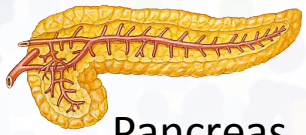
↑ satiety
↓ appetite

↑ glucose uptake by muscles



Release
⇄
↓ gut motility

Active GLP-1 and GIP



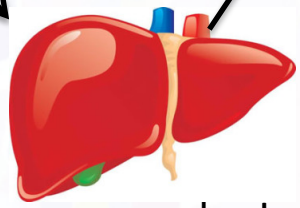
Pancreas

Decreased blood glucose

- ↓ glucose-dependent glucagon release from α-cells (GLP-1)
- ↑ glucose-dependent insulin release, ↑ β-cell regeneration? (GLP-1 & GIP)

DPP-4

Inactive



↓ glucose production

Adapted from Drucker DJ. *Cell Metab*. 2006;3(3):153-165.
Nauck MA. *Am J Med*. 2011;124(1 Suppl):S3-18.

Physiologic Effects of GLP-1

Blunted Glucagon Secretion

- Glucagon stimulates hepatic glucose output
- In T2DM, FASTING glucagon levels are elevated
- In T2DM, glucagon levels RISE after a meal (→ worse hyperglycemia)
- **Glucose effect of GLP-1: Improved FBS and PPG**

Enhanced Glucose Dependent Insulin Secretion

Improved Satiety

Decreased Gastric Motility

Gallwitz B. *Int J Clin Pract.* 2006;60(12):1654-1661.
Del Prato S, et al. *Horm Metab Res.* 2004;36:775–781.

Physiologic Effects of GLP-1

Blunted Glucagon Secretion

Enhanced Glucose Dependent Insulin Secretion

- Healthy beta cells secrete insulin when glucose is elevated
  - 1st-phase insulin release is deficient in T2DM →elevated post prandial glucose
- GLP1 enhances glucose dependent insulin secretion
- **<u>Glucose effect of GLP-1</u>: Improved FBS and PPG**

Improved Satiety

Decreased Gastric Motility

Drucker DJ. *Diabetes Care.* 2003;26:2929-2940.

Physiologic Effects of GLP-1

Blunted Glucagon Secretion

Enhanced Glucose Dependent Insulin Secretion

Improved Satiety

- CNS effect
- Associated with WEIGHT LOSS
  - NOT attributable to nausea
  - Similar weight loss NOT seen with DPP4
- **Effect of GLP-1: Weight loss**

Decreased Gastric Motility

Meier JJ. *Nat Rev Endocrinol*. 2012;8(12):728-742.

Physiologic Effects of GLP-1

Blunted Glucagon Secretion

Enhanced Glucose Dependent Insulin Secretion

Improved Satiety

Decreased Gastric Motility

- Slower absorption of nutrients into blood results in a broader glucose curve with lower amplitude after a meal
- **<u>Glucose effect of GLP-1</u>: Improved PPG**

Nauck MA, et al. *Diabetologia*. 1996;39:1546–1553.
Shah M, et al. *Rev Endocr Metab Disord*. 2014;15(3):181-187.

GLP-1 Receptor Agonist Drugs

	Short-Acting	Long-Acting
FDA Approved Drugs	Exenatide (Byetta)	Liraglutide (Victoza) Exenatide-LAR (Bydureon) Albiglutide (Tanzeum) Dulaglutide (Trulicity)
Half-life	2–5 h	12 h–several days
Fasting BG	Modest reduction	Strong reduction
A1C	Modest reduction	Strong reduction
Postprandial hyperglycemia	Strong reduction	Modest reduction
Gastric emptying rate	Deceleration	No effect
Blood pressure	Reduction	Reduction
Body weight reduction	1–5 kg	2–5 kg

Meier JJ. *Nat Rev Endocrinol*. 2012;8(12):728-742.
Lund A, et al. *Eur J Intern Med*. 2014;25(5):407-414.

DPP-4 Inhibitors
(Daily Dosing)

Inhibitor	Trade Name	FDA Approval
Sitagliptin	Januvia	2006
Saxagliptin	Onglyza	2009
Linagliptin	Tradjenta	2011
Alogliptin	Nesina	2013

GLP-1R Agonists vs DPP-4 Inhibitors

Property/Effect	GLP-1R Agonists	DPP-4 Inhibitors
Mechanism of action	Pharmacologic agonist of GLP-1R	Inhibitor of incretin degradation
Route of administration	Subcutaneous	Oral
A1C lowering (dose dependent)	Up to 1.5%	Up to 1%
Slows gastric emptying	Yes	No
Promotes satiety	Yes	No
Weight	Decreased	Neutral

Drucker DJ. *Cell Metab*. 2006 Mar;3(3):153-165.
Lund A, et al. *Eur J Intern Med*. 2014;25(5):407-414.
Neumiller JJ. *Clin Ther*. 2011;33(5):528-576.

GLP-1R Agonists vs DPP-4 Inhibitors
(continued)

Property/Effect	GLP-1R Agonists		DPP-4 Inhibitors	
Hypoglycemia	Low risk		Low risk	
Side effects	Early nausea, vomiting		Well tolerated	
FDA approved drugs	Exenatide Liraglutide Exenatide LAR Albiglutide Dulaglutide	BID QD QW QW QW	Sitagliptin Saxagliptin Linagliptin Alogliptin	QD

Drucker DJ. *Cell Metab*. 2006 Mar;3(3):153-165.
Lund A, et al. *Eur J Intern Med*. 2014;25(5):407-414.
Neumiller JJ. *Clin Ther*. 2011;33(5):528-576.

Role of the Kidney in Glucose Metabolism

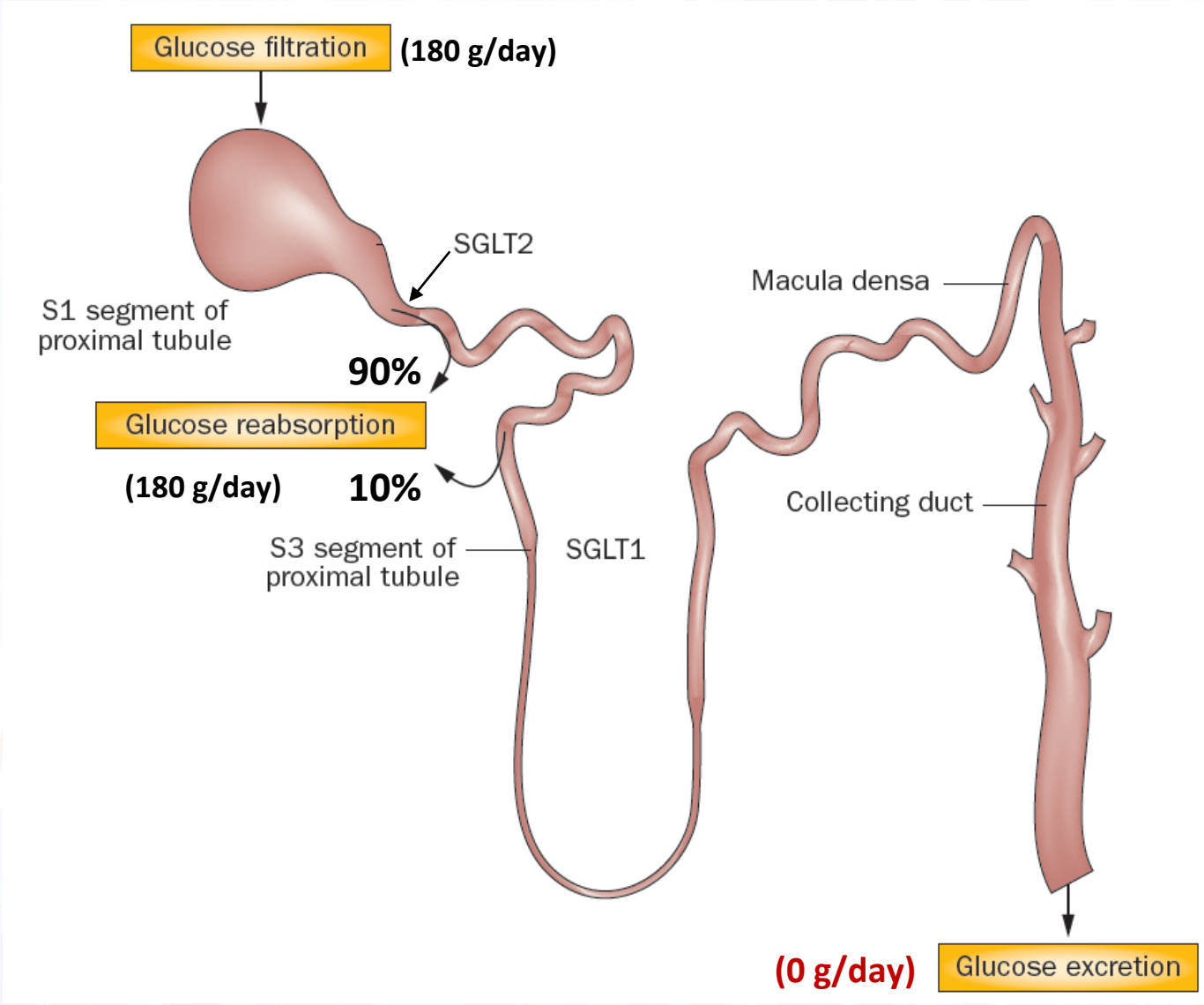
Production

Utilization

Reabsorption

Wright EM, et al. *J Intern Med*. 2007;261(1):32-43.

Glucose: From Blood to Urine

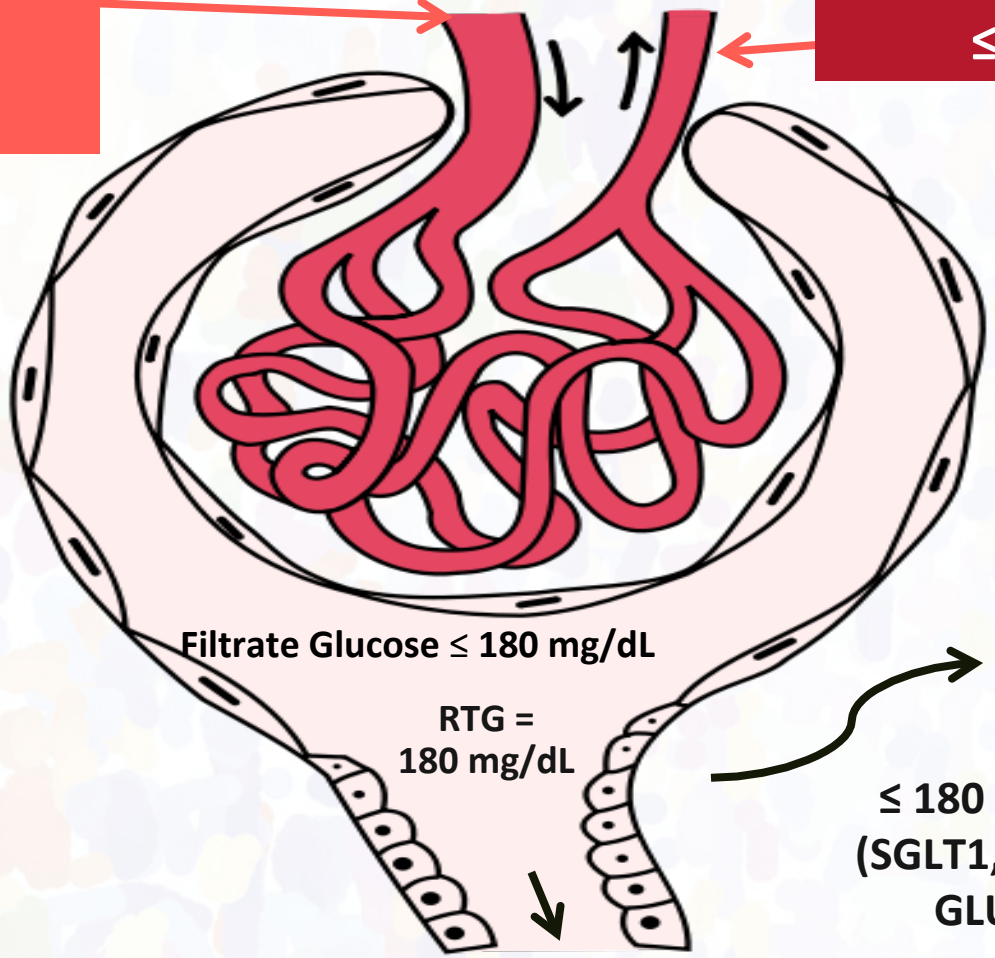


Adapted from Ferrannini E, Solini A. *Nat Rev Endocrinol*. 2012;8:495-502.

Normal Glucose: Normal Threshold

AFFERENT Arteriole
Plasma Glucose
≤ 180 mg/dL

EFFERENT Arteriole
Plasma Glucose
≤ 180 mg/dL

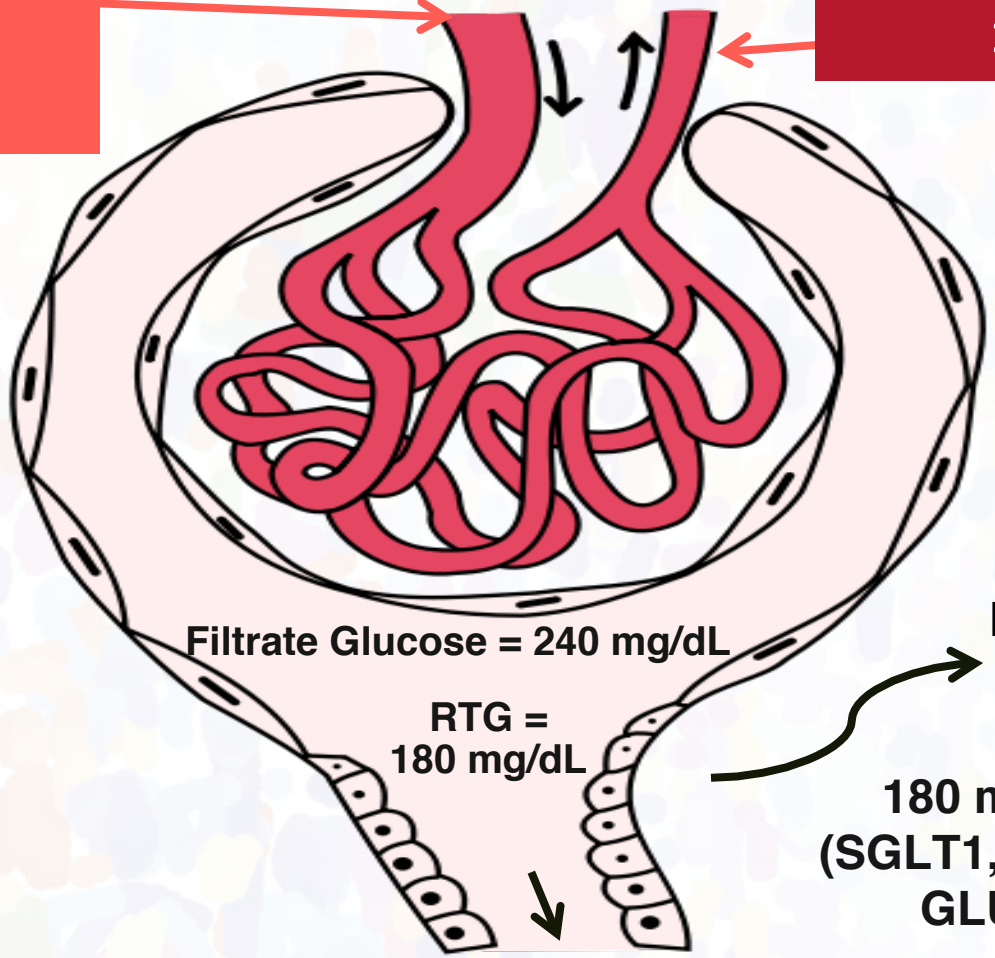


Urinary glucose excretion = 0 mg/dL

Hyperglycemia: Normal RTG

AFFERENT Arteriole
Plasma Glucose = 240 mg/dL

EFFERENT Arteriole
Plasma Glucose 180 mg/dL

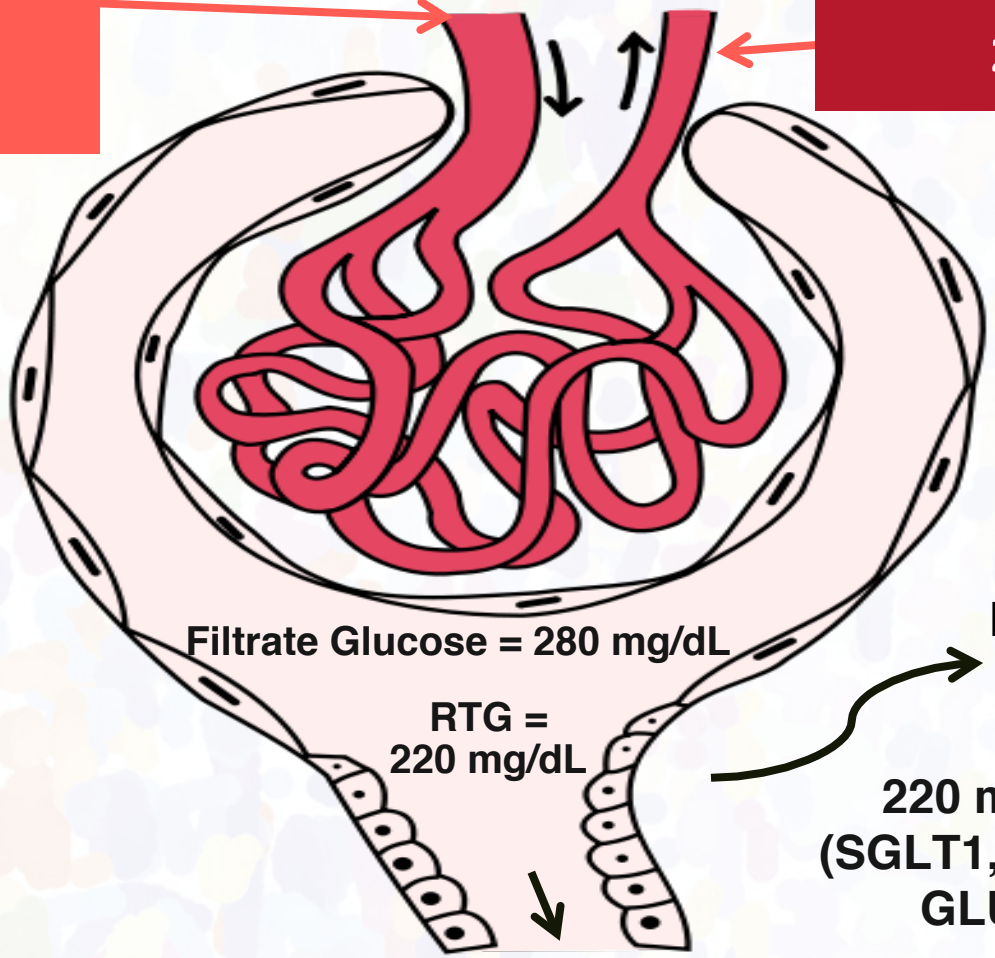


Urinary glucose excretion = 60 mg/dL

Hyperglycemia: T2DM

AFFERENT Arteriole
Plasma Glucose = 280 mg/dL

EFFERENT Arteriole
Plasma Glucose = 220 mg/dL

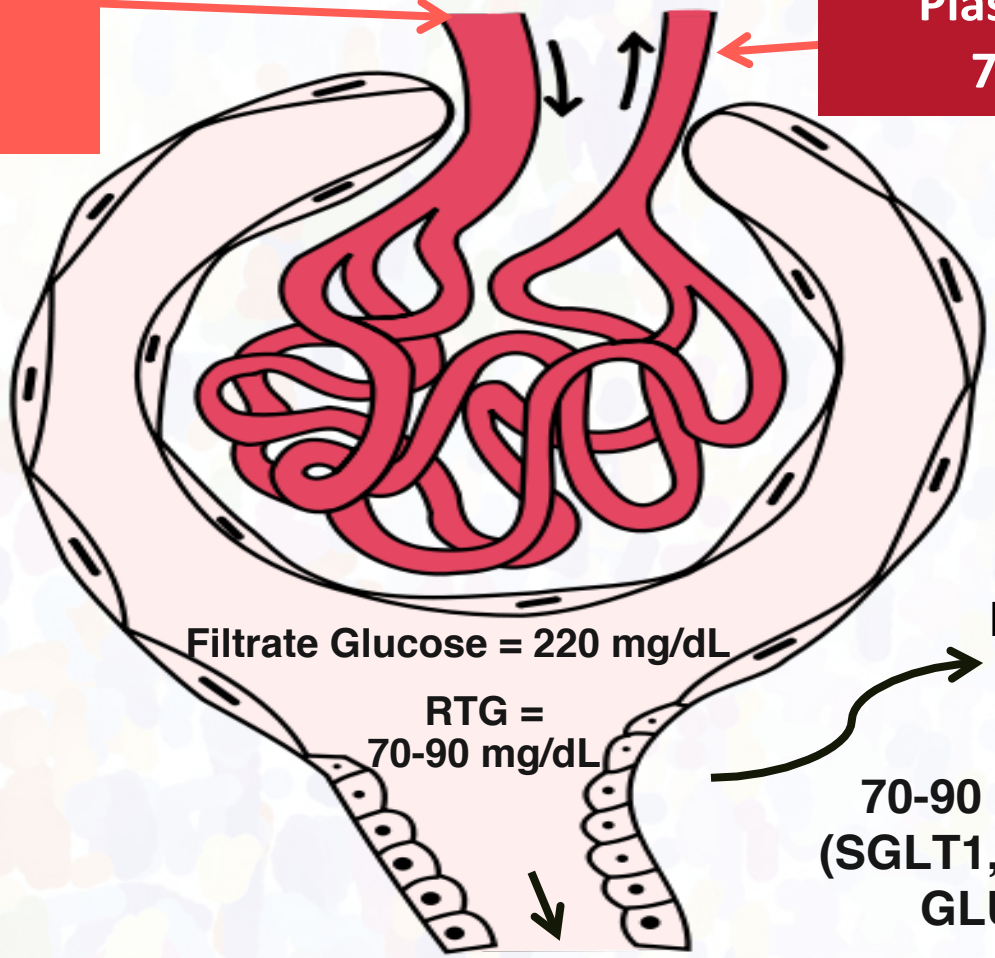


Urinary glucose excretion = 60 mg/dL

Hyperglycemia: T2DM SGLT2 Modulated

AFFERENT Arteriole
Plasma Glucose = 220 mg/dL

EFFERENT Arteriole
Plasma Glucose = 70-90 mg/dL



Urinary glucose excretion = 130-150 mg/dL

Renal Reuptake Summary

- In type 2 diabetes, enhanced renal glucose reabsorption contributes to hyperglycemia
- The glucose transporter SGLT2 is responsible for 90% of this glucose reabsorption
- Inhibition of SGLT2
  - Decreases glucose reabsorption
  - Increases urinary glucose excretion
- Observe weight loss and reduction in blood pressure

SGLT2 Inhibitors

Inhibitor	Trade Name	FDA Approval
Canagliflozin	Invokana	2013
Dapagliflozin	Farxiga	2014
Empagliflozin	Jardiance	2014

Haas B, et al. *Nutr Diabetes*. 2014;4:e143.
https://www.clinicaltrials.gov. Accessed May, 2015.

SGLT2 Inhibitors: Adverse Events

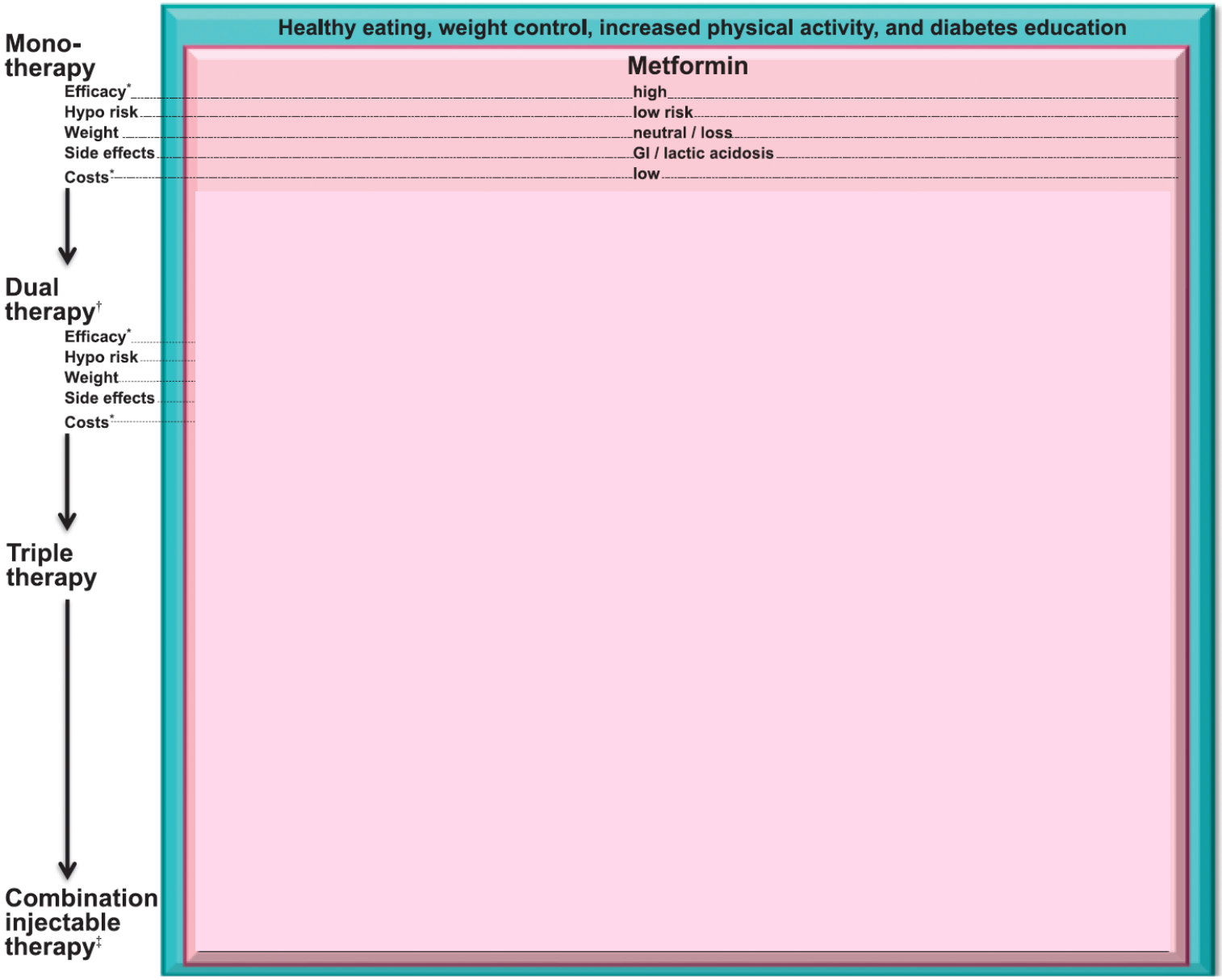
- Increased genital mycotic infection
  - 2% to 8% excess over placebo
  - More frequent in females
  - Circumcision lowers risk in males
- Bacterial urinary tract infections
  - 1% to 12% excess over placebo
  - No observed episodes of pyelonephritis or urosepsis
- Infections were manageable and rarely led to discontinuation of treatment
  - Managed with standard antimycotic creams and hygienic measures

Ferrannini E, et al. *Diabetes Obes Metab*. 2013;15(8):721-728.
Fonseca V, et al. *J Diabetes Complications*. 2013;27:268-273.
Nauck MA, et al. *Diabetes Care*. 2011;34:2015-2022.
Stenlöf K, et al. *Diabetes Obes Metab*. 2013;15:372-382.
Wilding JPH, et al. *Diabetes Obes Metab*. 2013;15:403-409.

SGLT2 Inhibition as a Treatment for Diabetes

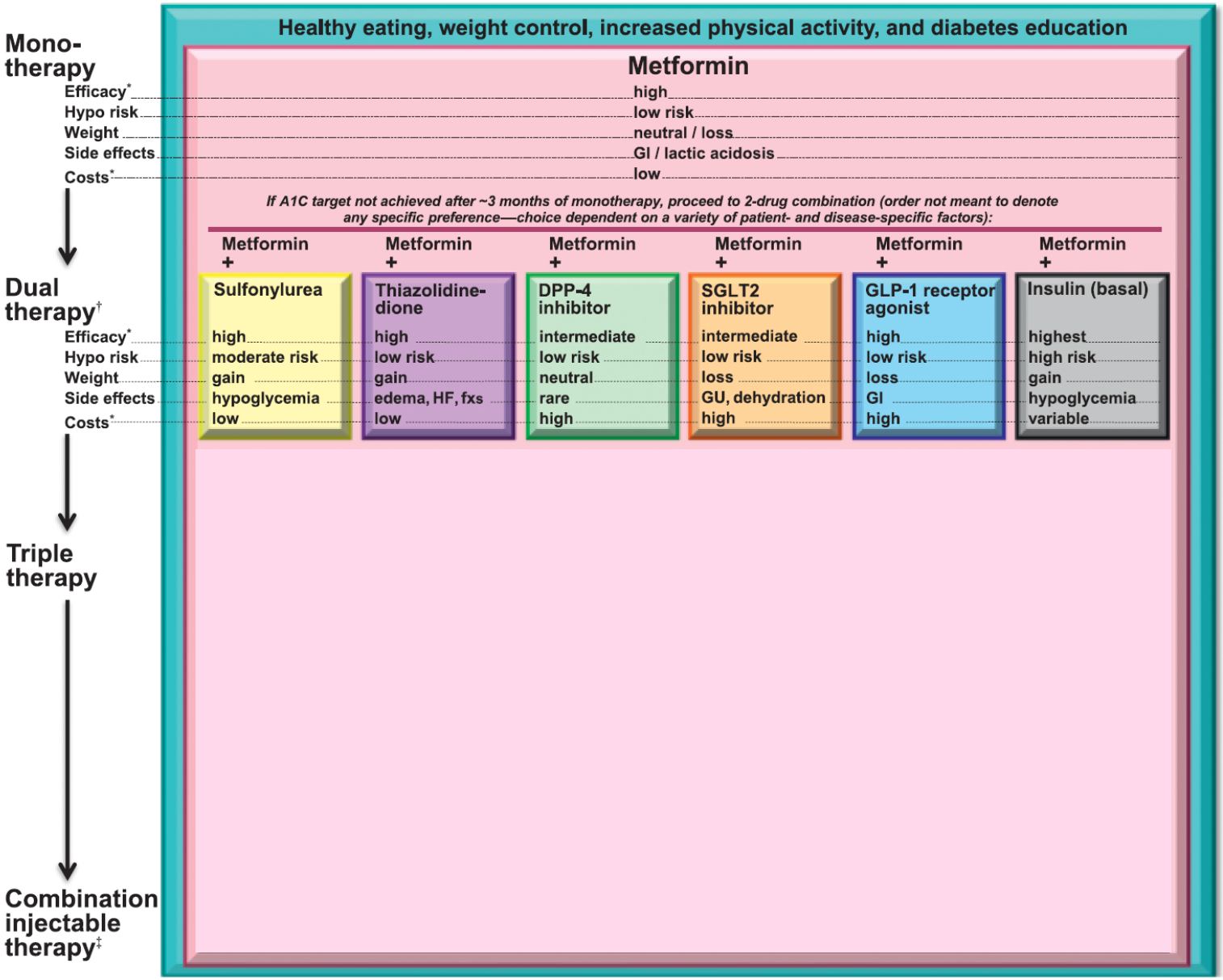
- Efficacy
  - Reduction in A1C of 0.5% to 1.0%
  - Weight reduction of ~3 kg
  - Reduction in systolic BP of 3 to 5 mmHg
  - Effective as monotherapy and in combination
  - Diminished efficacy at GFR < 45
- Safety
  - Little or no risk of hypoglycemia
  - Increased risk of mycotic genital infections
  - Uncommon hyperkalemia in select populations
- Side Effects (typically transient)
  - Increased urination
  - Mild hypotension

ADA Guidelines



Diabetes Care. 2015;38(Suppl. 1):S41–S48.

ADA Guidelines



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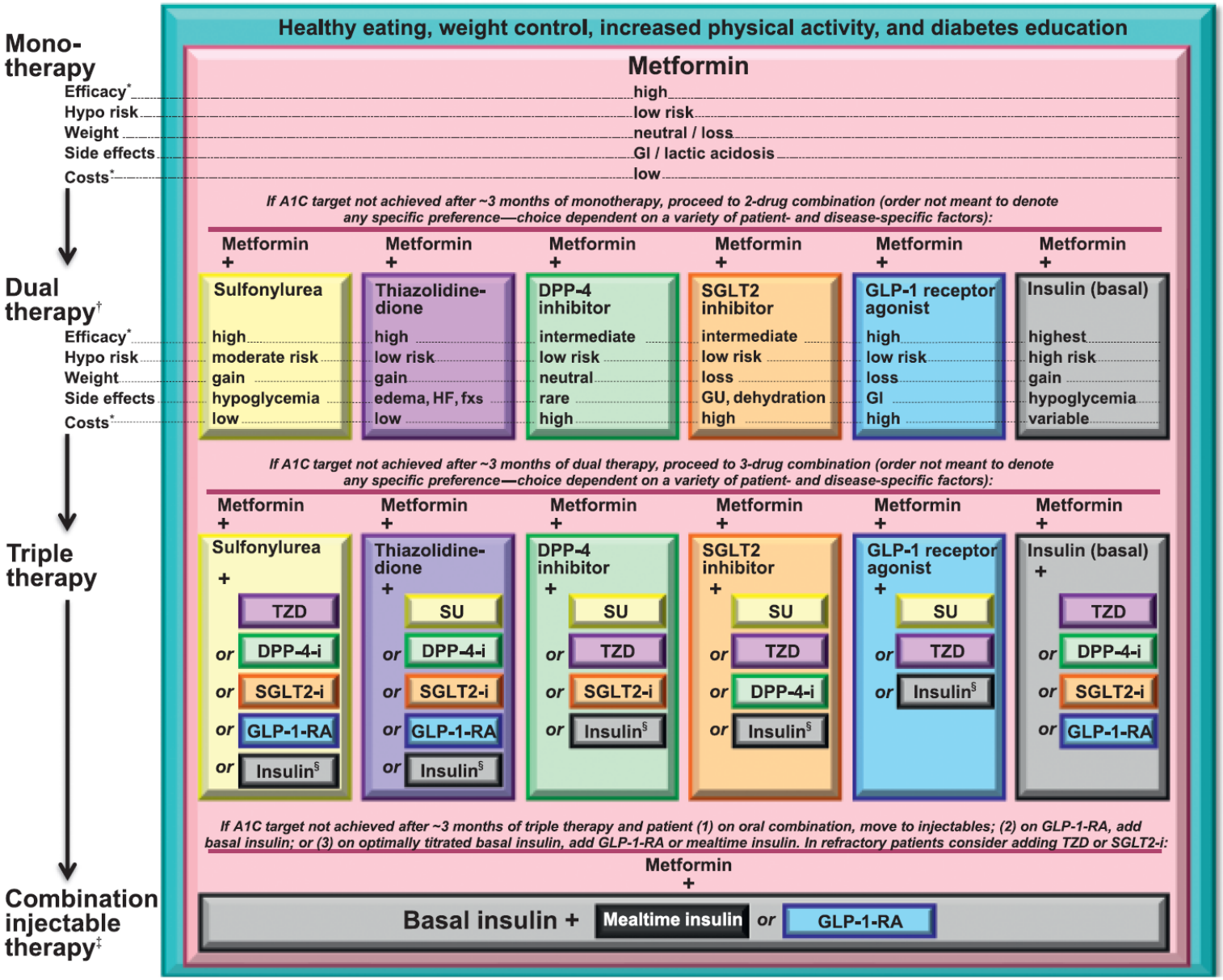


Diabetes Care. 2015;38(Suppl. 1):S41–S48.

Formulating a Management Plan: Collaboration

- People are the experts in their own lives
- Health professionals are the experts in clinical aspects of diabetes
- 99% of diabetes care is *self care*
- Behavior change takes place as health professionals help people make informed decisions about their *self care*.
- Not all patients will be primary decision makers in their own care.

Courtesy of D Hinnen.

Teaching Patients: Promoting Behavior Change

- What part of diabetes is most difficult for you?
- How does that (situation) make you feel?
- How would this have to change to make you feel better about it?
- Are you willing to take action to improve the situation for yourself?
- What are some steps you could take to get you there?
- Is there *one thing* you will do when you leave here to improve things for yourself?

Courtesy of D Hinnen.

For Better Glucose, Consider…

- Health beliefs
- Insufficient financial resources
- Lack of diabetes education
- Multicultural issues
- The diabetes regimen
- Fear of hypoglycemia
- Inadequate Support System
- Prescriptions should provide generous insulin dose to cover increased needs

Courtesy of D Hinnen.

Conclusions

- Multiple organs are involved in glucose homeostasis and many therapies are available
- ADA recommends that treatment goals and plans should be individualized
- Synthetic analogs of GLP-1 and inhibitors of DPP4 have multiple positive effects
- Reduction of renal glucose reuptake by inhibiting SGLT2 has multiple positive effects
- ADA offers a stepwise algorithm for advancing the treatment of T2DM

You Might Like……

- The **Implementation Workshop** is a forum to address practical issues of diabetes management

5 MINUTES

Implementation Workshop
Agenda and Introduction

- 5’ Introduction
- 5’ Reflection on diabetes care in your practice (individual)
- 15’ Small group discussion
- 20’ Facilitated large group discussion
- 10’ Commitment to change (individual)
- 5’ Evaluation

5 MINUTES

STEP 1 – DIABETES CARE SURVEY:
IDENTIFICATION OF BARRIERS (PROVIDERS/PATIENTS)

Reflect on diabetes care in your practice

- Work on your own to think about barriers in your practice that impede optimal T2DM patient care
- Record your thoughts on the **"STEP 1"** handout
  - PROVIDER FACTORS
  - PATIENT FACTORS

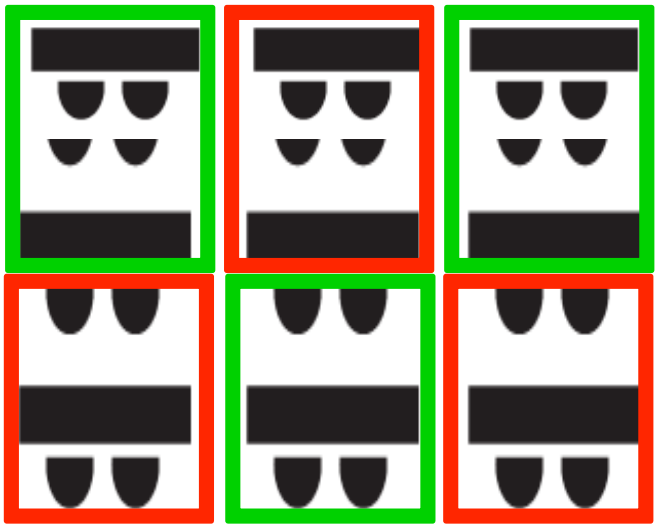
Small Group Discussion

Please Break Into Work Groups

With your neighbor, turn around and form a team of 4 with the two neighbors behind you

If you are not matched up with a group, join a group that is closest to you

Goal is groups of 4-6



15 MINUTES

Small Group Discussion

- What are the group's most common barriers?
  - Patient barriers?
  - Provider barriers?
- Has anyone addressed these barriers?
- What did they do?

Each group needs someone to:

- ✓ Take notes
- ✓ To volunteer to present back to the larger group

Describe your situation
What was your approach?
What difficulties did you face?
What were the results/impact of your effort?

20 MINUTES

Facilitated Large Group Discussion

- Most common barriers – review the options on the STEP 1 handout checklist (show of hands)
- *Which group has a story to share about the barriers discussed?*
- *What about the less commonly cited barriers. Any stories?*
- *How were barriers overcome?*
- *Which barriers can't be changed?*
- *How do we measure success for overcoming each barrier?*
  - Incremental improvements
  - Setting achievable goals

Commitment to Change (Individual)

- Important to understand:
  - By improving our knowledge, understanding, and treatment of T2DM we can gain the confidence of our patient thereby alleviating many of their barriers
- Let's discuss how we can do so:
  - For example, creating a positive atmosphere where the patient can openly discuss the flaws and failures and create positive changes to enhance adherence

10 MINUTES

STEP 2 – DIABETES CARE ACTION PLAN

Individual Commitment to Change

- Which barrier in your practice will you address?
- Use the SMART framework to create your goal
- What are the first steps you will take?

Choose an Accountability Partner From Your Small Group

- Invite a partner who you'll check-in on, to encourage each other to continue to pursue your action plan goal
- Share contact information
- Commit to follow-up with specific date

10 MINUTES

Please Complete and Return

1. STEP 1 handout
2. STEP 2 – Keep the top sheet, return the carbon copy of your action plan
3. Activity evaluation

Tools and Resources

- **Management of Hyperglycemia in Type 2 Diabetes, 2015: A Patient-Centered Approach.**
  - Inzucchi SE, et al. *Diabetes Care.* 2015;38:140–149.
- **American Diabetes Association**
  - www.diabetes.org
- **Strategies for Improving Care**
  - Diabetes Care. 2015;38(Suppl. 1):S5–S7.
- **Patient assistance programs**
  - http://www.rxassist.org/
- **National Certification Board for Diabetes Educators**
  - http://www.ncbde.org/
- **American Association of Diabetes Educators**
  - http://www.diabeteseducator.org/ProfessionalResources/Certification/
- **Diabetic foot exam**
  - http://care.diabetesjournals.org/content/31/8/1679.full
  - http://www.diabetes.org/living-with-diabetes/complications/foot-complications/foot-care.html
  - http://www.jfponline.com/specialty-focus/diabetes/article/how-to-do-a-3-minute-diabetic-foot-exam/1cddff37043a979887747ccfedc96086.html
- **Insulin self-injection**
  - https://www.diabeteseducator.org/export/sites/aade/_resources/pdf/research/AADE_MedEd.pdf

Please visit
www.T2diabetesCME.org
for more education