

# Overview of Diabetes in Renal Disease

Diabetes Management Centre  
Trillium Health Partners

Jacque Tanaka-Sibley, RN, CDE, CPT



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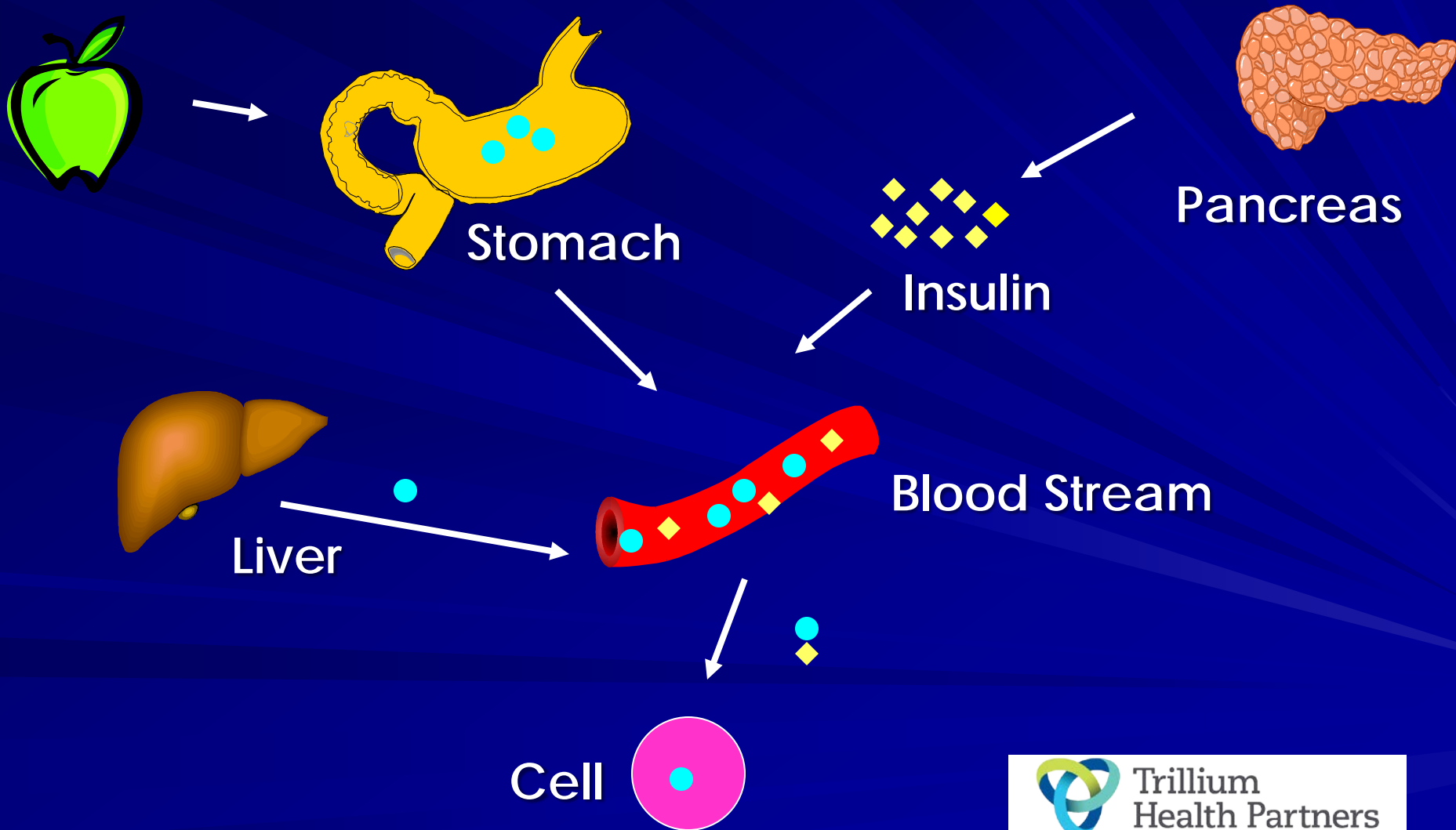
# Learning Objectives

To understand :

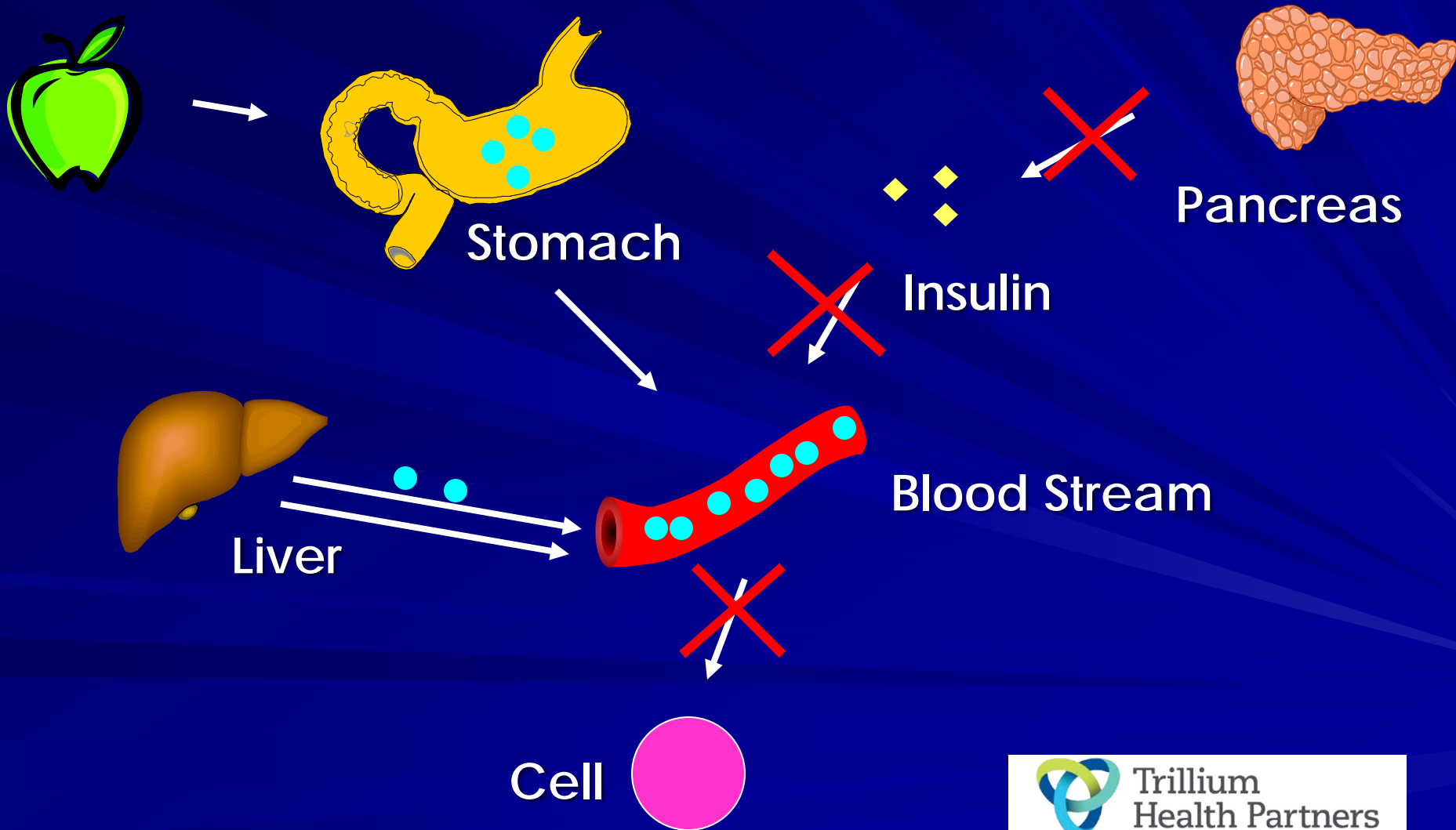
- Causes and progression of diabetes
- Goals and tools of diabetes management
- New treatments for diabetes



# What Happens When you Eat?



# What is Diabetes?



# Types of Diabetes

- Type 1
- Type 2
- Prediabetes
- Gestational Diabetes



# Types of Diabetes – Type 2

- Not enough insulin is being made or the insulin is not working properly – pills or insulin injections
- 90% of all people with diabetes have Type 2 diabetes
- Majority are insulin resistant
- 50% have complications at diagnosis



# Risk Factors for Type 2

- Family history
- High risk populations
- Over 40
- Overweight/obesity
- Sedentary
- Hx of Gestational diabetes or large baby
- others



Diagnosis:

FBS less than 6.1

2 hrs after meals  
under 7.8

**No Diabetes**

**PreDiabetes**

FBS 6.1 – 6.9

2 hrs after meals  
7.8 – 11.0

**Diabetes**

FBS 7.0 or over

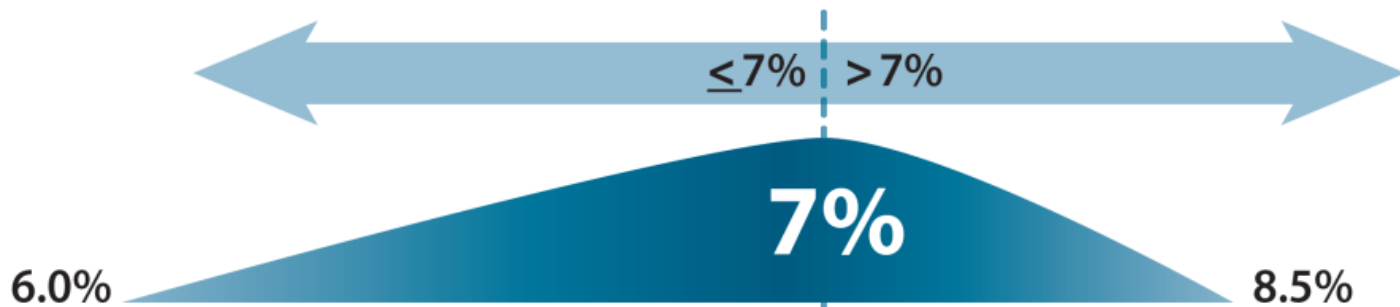
2 hrs after meals  
over 11.0

A1C  $\geq$  6.5%





# Individualized Targets



A target A1C  $\leq 6.5\%$  may be considered in some patients with type 2 diabetes to further lower the risk of nephropathy and retinopathy

**Most patients  
with type 1  
and type 2  
diabetes**

#### Consider if:

- Limited life expectancy
- High level of functional dependency
- Extensive vascular disease
- Multiple co-morbidities
- Recurrent severe hypoglycemia
- Hypoglycemia unawareness
- Long standing diabetes for whom it is difficult to achieve A1C  $\leq 7.0\%$  despite effective doses of multiple antihyperglycemic agents including intensified basal-bolus insulin therapy



# What is the A1C?

- Blood test which shows average blood sugar over past 3 months

What is your A1C (%) ?	Your Average Blood Sugar (mmol/l)
13%	18 - 19
12	16 - 17
11	14 - 15
10	13 - 14
9	11 - 12
8	10 - 11
7	8 - 9
6	7

[Translating the hemoglobin A1c assay into estimated average glucose values](#)

David M. Nathan, Judith Kuenen, Rikke Borg, Hui Zheng, David Schoenfeld, and Robert J. Heine, for the A1c-Derived Average Glucose (ADAG) Study Group. Diabetes Care 2008 . Average Blood Glucose (mmol) =  $1.59 \times \text{A1C} - 2.59$



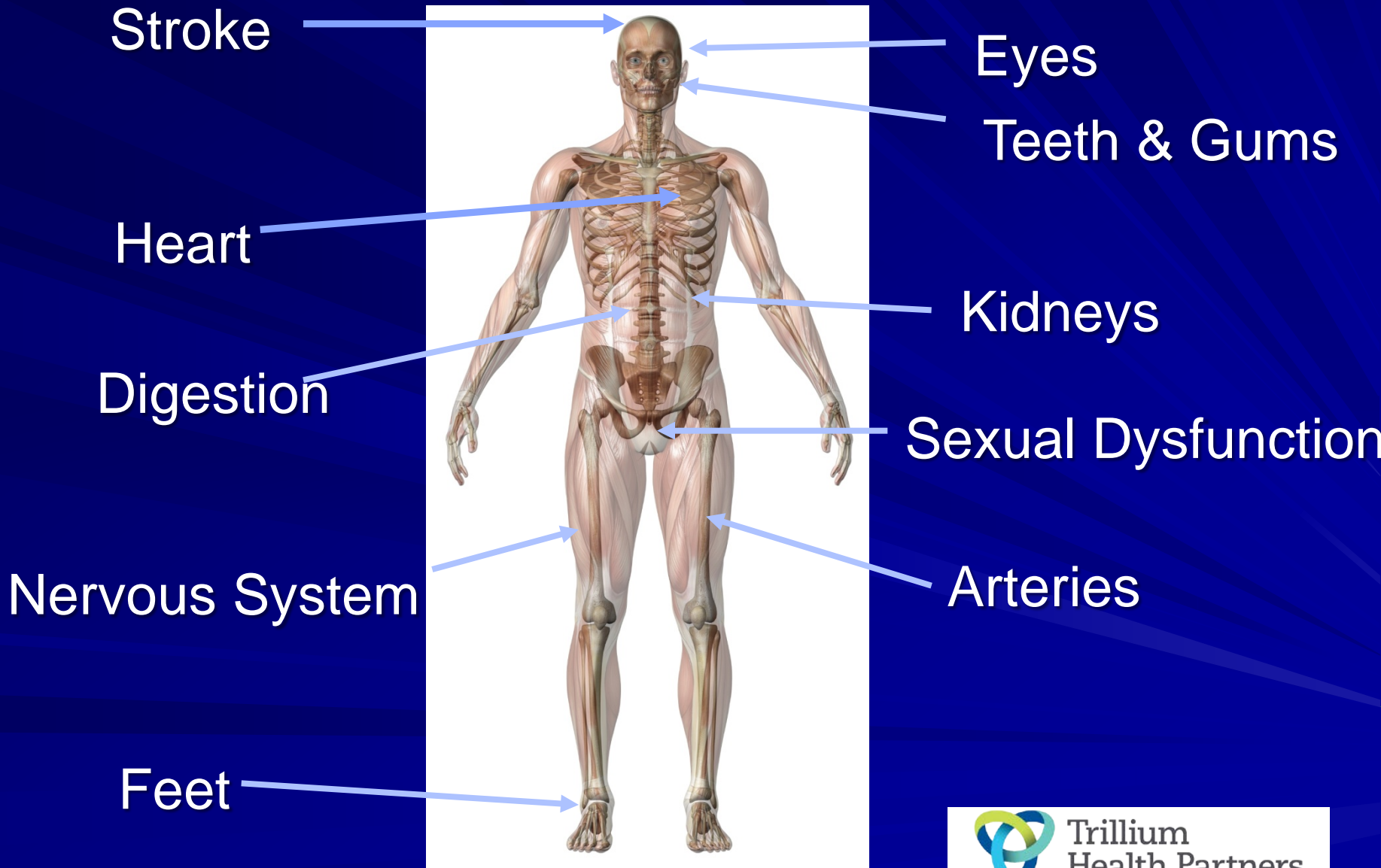
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# Complications

- Prevention of complications is the ultimate goal
- High blood sugar damages the blood vessels
- Complications develop over 10-20 years
- Good blood glucose control is the key



# Complications



# Managing Diabetes

Food



Exercise

Medications



2013

# CDA 2013 Clinical Practice Guidelines

## AT DIAGNOSIS OF TYPE 2 DIABETES

Start lifestyle intervention (nutrition therapy and physical activity) +/- Metformin

A1C <8.5%

A1C ≥8.5%

Symptomatic hyperglycemia with metabolic decompensation

If not at glycemic target (2-3 mos)

Start metformin immediately

Initiate insulin +/- metformin

Start / Increase metformin

Consider initial combination with another antihyperglycemic agent

If not at glycemic targets

Add an agent best suited to the individual:

### Patient Characteristics

Degree of hyperglycemia  
Risk of hypoglycemia  
Overweight or obesity  
Comorbidities (renal, cardiac, hepatic)  
Preferences & access to treatment  
Other

### Agent Characteristics

BG lowering efficacy and durability  
Risk of inducing hypoglycemia  
Effect on weight  
Contraindications & side-effects  
Cost and coverage  
Other

L  
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**Add an agent best suited to the individual** (agents listed in alphabetical order):

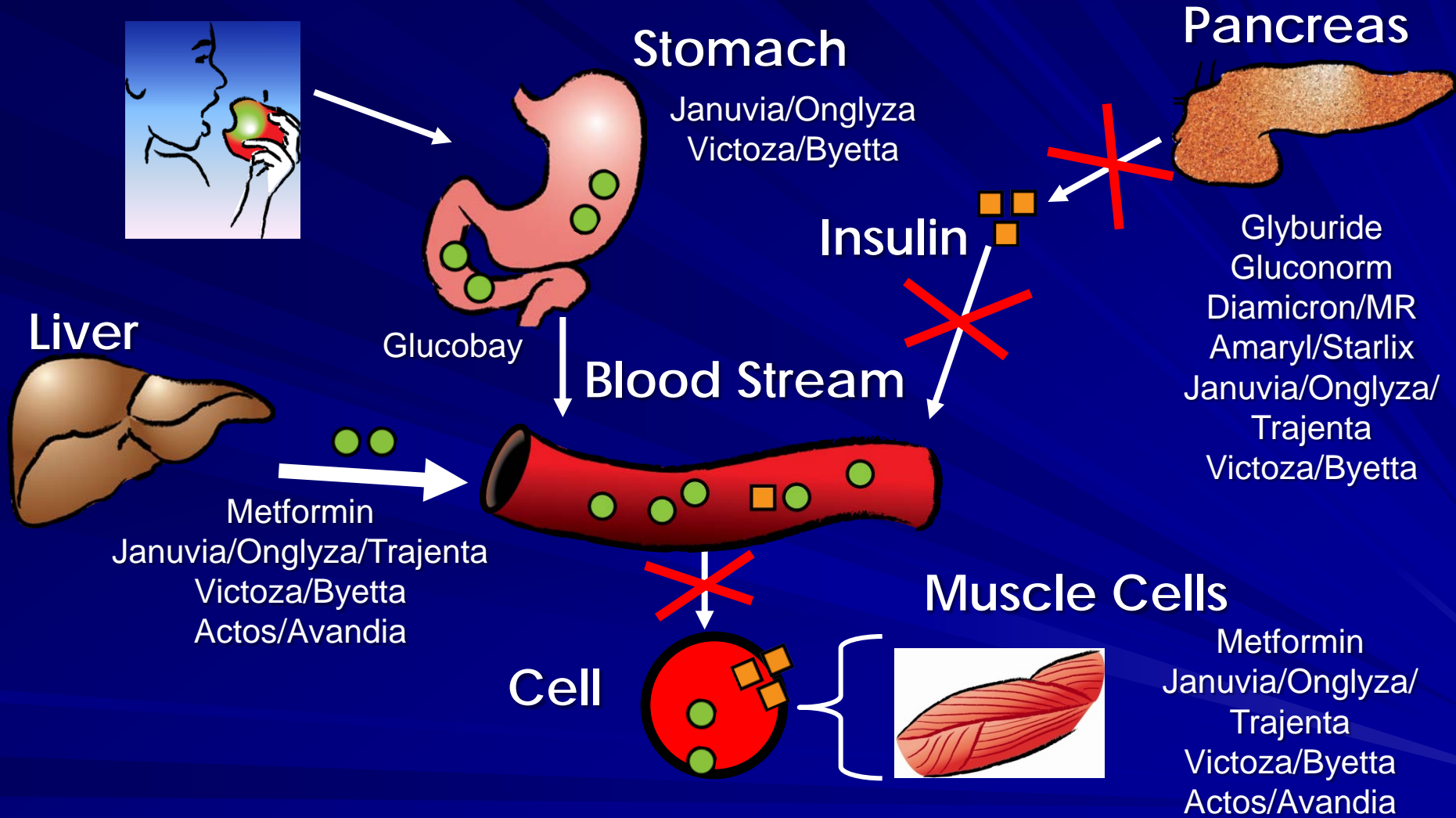
Class	Relative A1C lowering	Hypo-glycemia	Weight	Other therapeutic considerations	Cost
Alpha-glucosidase inhibitor (acarbose)	↓	Rare	neutral to ↓	Improved postprandial control, GI side effects	\$\$
Incretin agents: DPP-4 Inhibitors GLP-1 receptor agonists	↓↓ ↓↓ to ↓↓↓	Rare Rare	neutral to ↓ ↓↓	GI side effects	\$\$\$ \$\$\$\$
Insulin	↓↓↓	Yes	↑↑	No dose ceiling, flexible regimens	\$-\$\$\$\$
Insulin secretagogue: Meglitinide	↓↓	Yes	↑	Less hypoglycemia in context of missed meals but usually requires TID to QID dosing	\$\$
Sulfonylurea	↓↓	Yes	↑	Gliclazide and glimepiride associated with less hypoglycemia than glyburide	\$
TZD	↓↓	Rare	↑↑	CHF, edema, fractures, rare bladder cancer (pioglitazone), cardiovascular controversy (rosiglitazone), 6-12 weeks required for maximal effect	\$\$
Weight loss agent (orlistat)	↓	None	↓	GI side effects	\$\$\$

If not at glycemic target

- Add another agent from a different class
- Add/Intensify insulin regimen

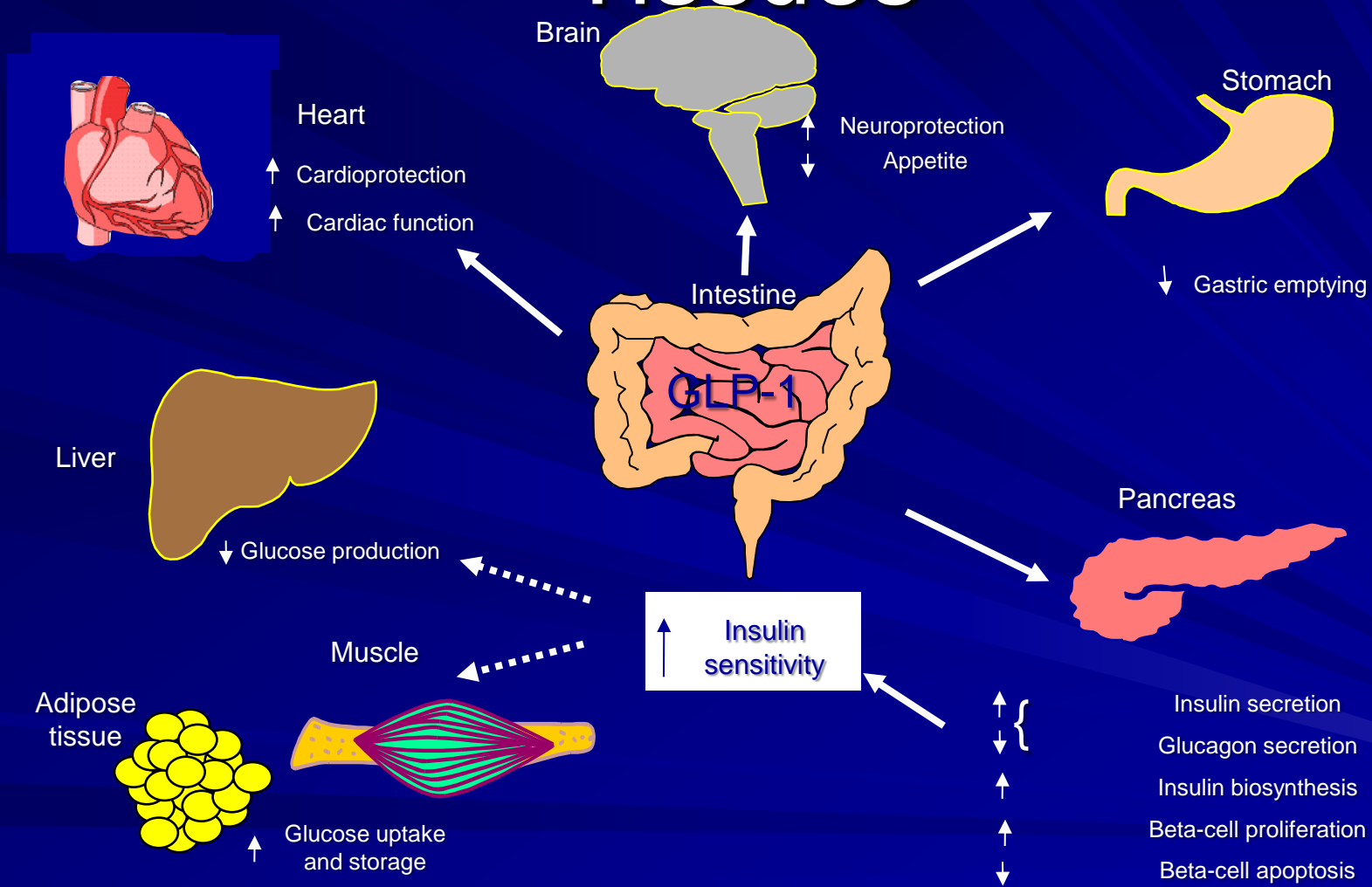
**Make timely adjustments to attain target A1C within 3-6 months**

# Diabetes Medications





# GLP-1 Actions in Peripheral Tissues



Baggio LL, et al. *Gastroenterology*. 2007;132:2131-2157. Reprinted with permission from Elsevier. © 2007

# DPP4 Inhibitors

- Weight neutral
- Prevents breakdown of natural GLP-1
- Indirectly increase insulin release (glucose dependant)
- Do not cause hypoglycemia
- Covered by Ontario Drug Benefits/third party
- Januvia/Onglyza indicated with insulin
- Renal dosing available
- Onglyza, Januvia, Trajenta
- Cost: \$2.64 – 2.97/day

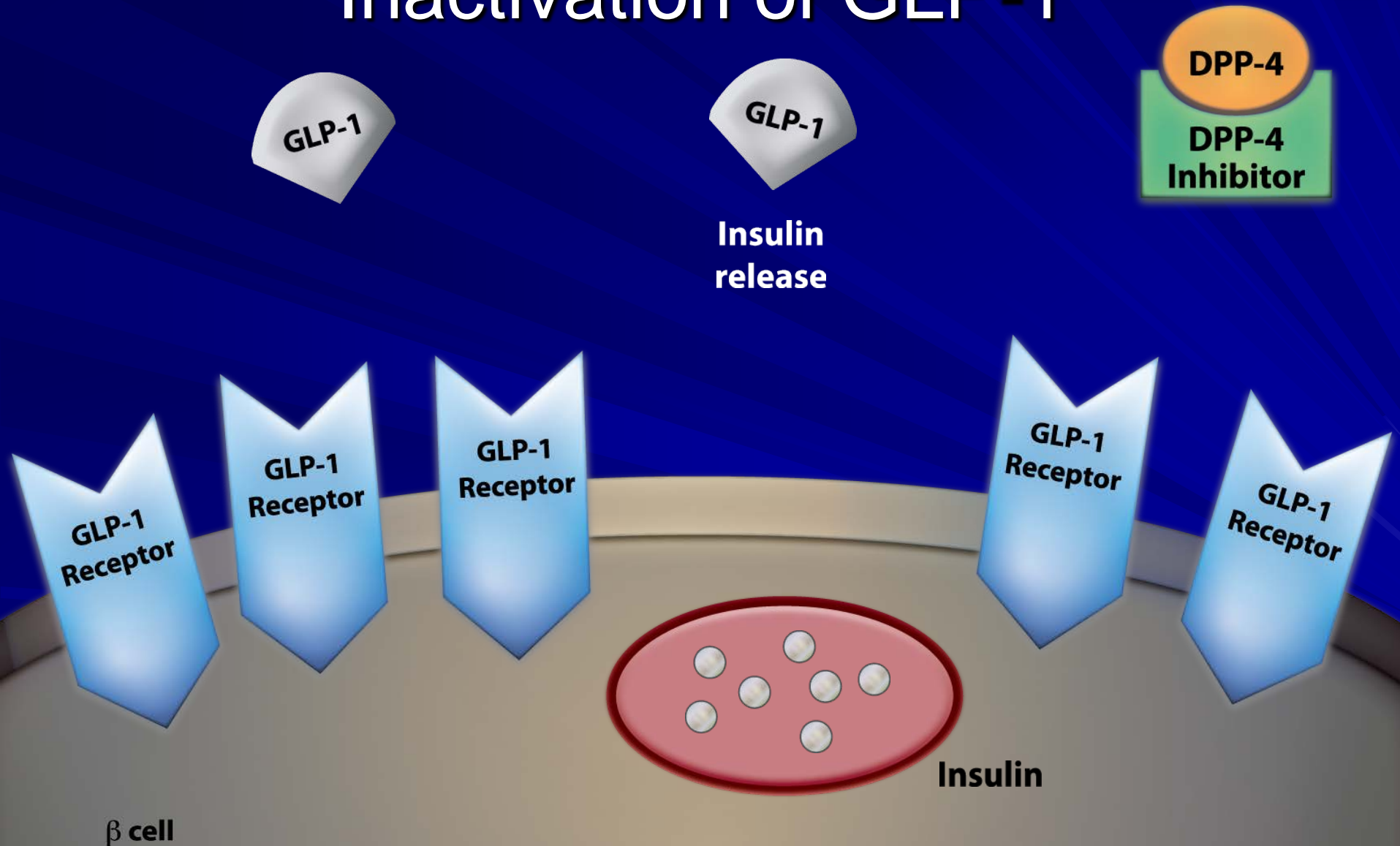


# GLP-1 Agonists

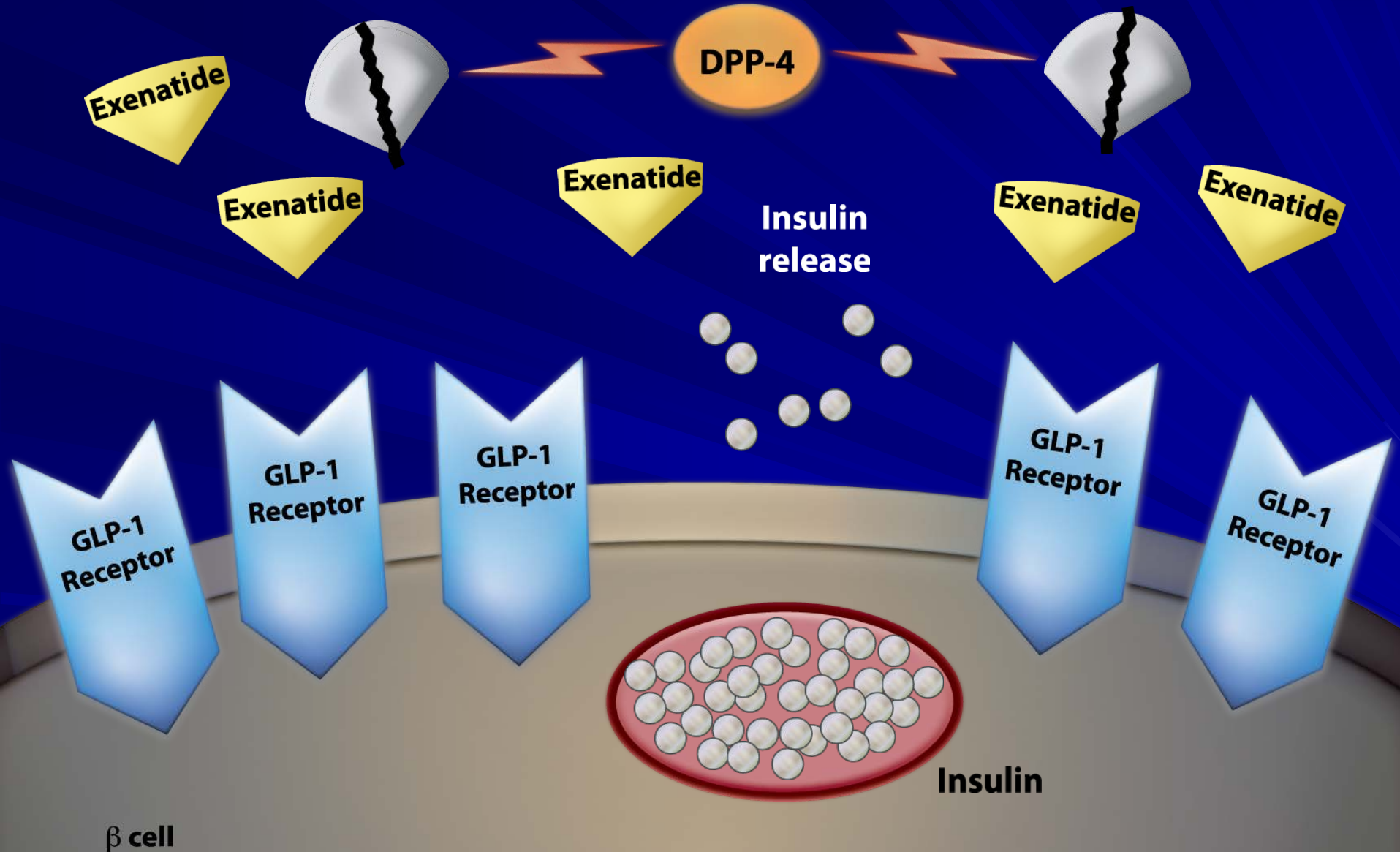
- Weight loss/weight neutral
- Directly increase insulin release (glucose dependant)
- Do not cause hypoglycemia
- Not covered by Ontario Drug Benefits
- Now indicated with insulin
- Injectable
- Victoza (1/day)/Byetta (2/day)
- ~ \$5-\$6/day



# DPP-4 Inhibitors Prevent the Inactivation of GLP-1



# GLP-1 analogues are Not Inactivated by DPP-4



# DPP-4 Inhibitors Increase Endogenous GLP-1 Levels



## Nutrients

Duodenum and  
Small Intestine

GIP

GLP-1

Inactive  
GLP-1  
and GIP

DPP-4

- DPP-4 is the major GLP-1 inactivator<sup>1</sup>
  - GLP-1 and GIP stimulate insulin secretion<sup>2</sup>
  - GLP-1 suppresses glucagon secretion<sup>2</sup>
- DPP-4 inhibitors increases the concentrations of active incretin hormones<sup>3</sup>
  - Stimulate the release of insulin in a glucose-dependent manner<sup>3</sup>
  - Decrease the levels of glucagon in the circulation<sup>3</sup>

1. Rosenstock J, Zinman B. *Curr Opin Endocrinol Diabetes Obes.* 2007;14:98-107.

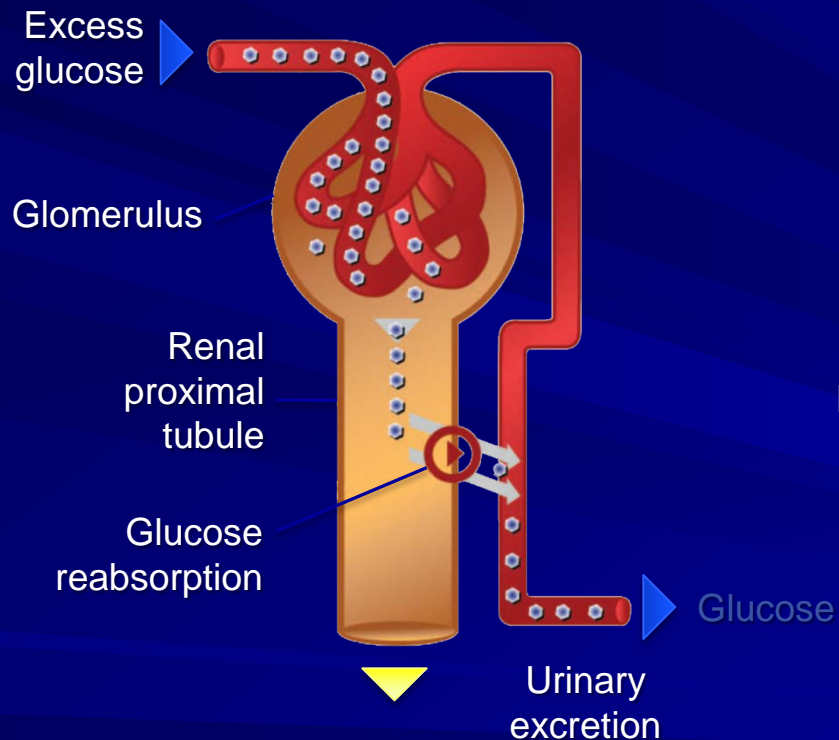
2. Drucker DJ. *Diabetes Care.* 2003;26:2929-2940.

3. Boehringer Ingelheim (Canada) Ltd. *Trajenta Product Monograph.* July 30, 2012.

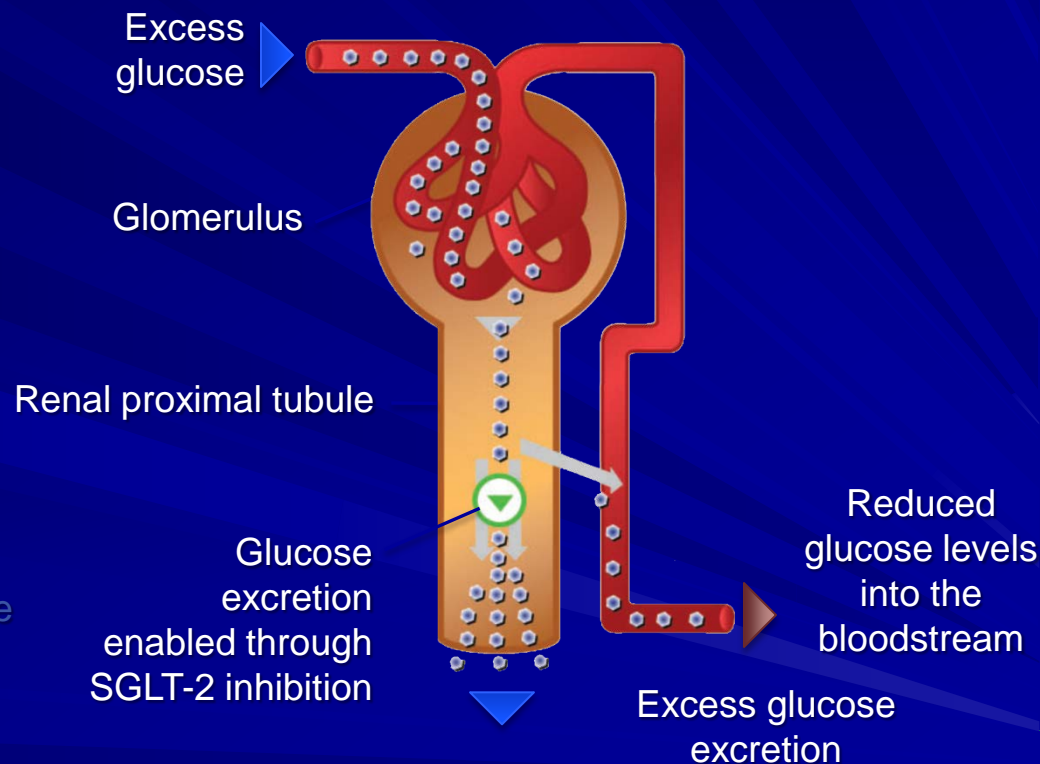


# Renal SGLT-2 Inhibition: A Novel Approach to T2DM

Patients with Type 2 Diabetes



Type 2 Diabetes with SGLT-2 Inhibition



# Summary: SGLT-2 Inhibition

- Inhibition of SGLT-2 in patients with diabetes results in decreased glucose reabsorption and increased glucosuria
- Lowering the renal threshold for glucose provides an insulin-independent mechanism for correction of hyperglycemia
- When blood glucose levels are normalized there is decreased gluconeogenesis and total hepatic glucose production



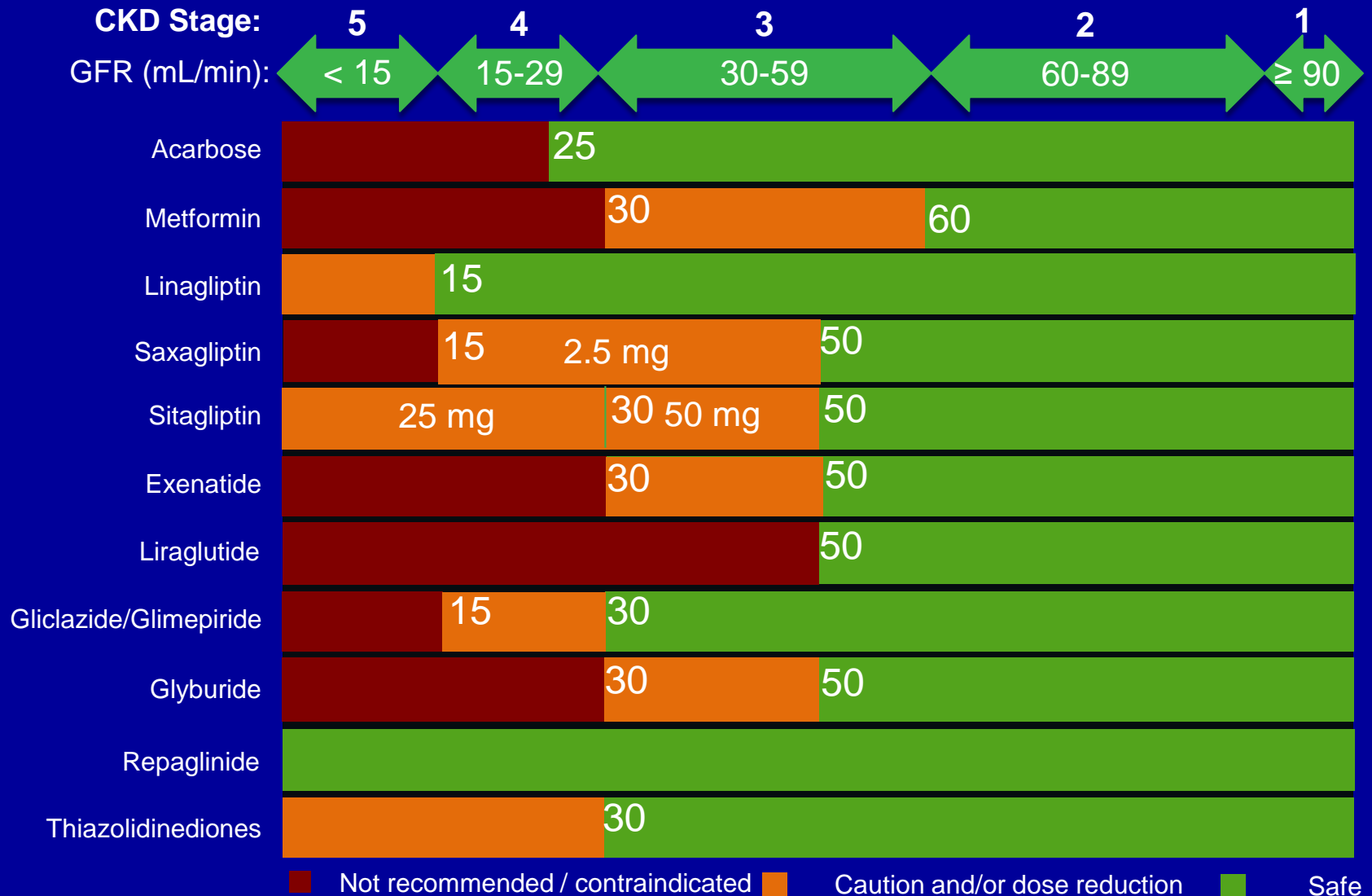


# SGLT-2 Take Away Messages

1. Selective SGLT-2 inhibitors reduce blood glucose levels due to increased renal excretion of glucose
2. SGLT-2 inhibitors have been shown to be effective in lowering glucose levels for a variety of T2DM patients including as an add-on to monotherapy, add-on to metformin or add-on to insulin
3. Potential advantages of SGLT-2 inhibitors include weight loss, low risk of hypoglycemia, and modest blood pressure lowering
4. Based on clinical data to date, there are no signals of major safety concerns
5. Adverse events requiring further study:
  - Increase in fungal genital infections
  - Potential volume depletion in vulnerable patients
6. Results of ongoing studies awaited

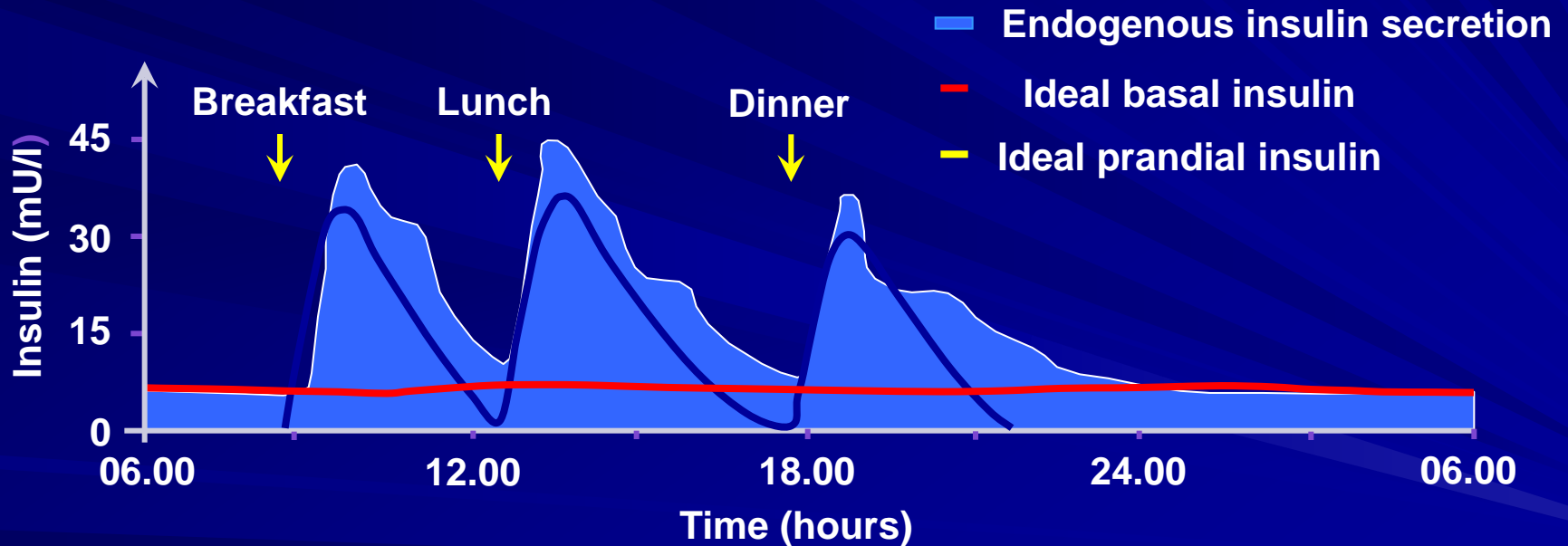


# Antihyperglycemic Agents and Renal Function



Adapted from: Product Monographs as of March 1, 2013; CDA Guidelines 2008; and Yale JF. J Am Soc Nephrol 2005; 16:S7-S10.  
 guidelines.diabetes.ca | 1-800-BANTING (226-8464) | diabetes.ca

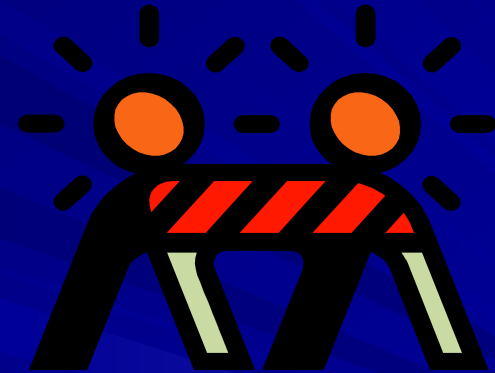
# Physiological Insulin Secretion



Adapted from Kruszynska YT, et al. Diabetologia 1987;30:16–21.

# Patient Barriers to Insulin

- Fear of....
  - Low blood sugar (defensive eating)
- Sense of failure
- Loss of control
- Depression
- Time consuming
- Cost



# Physician Barriers to Care

- Knowledge and understanding of diabetes management may be limited or outdated
- Limited appointment time to offer and teach appropriate insulin therapy.
- Follow-up dose adjustment is complex and time consuming



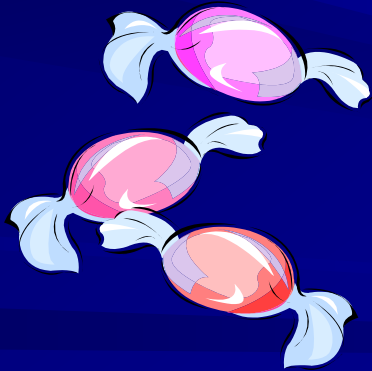
# Insulin Regimens

- Once daily (basal insulin)
- Twice daily (premix insulin)
- Basal Plus (basal plus rapid a largest meal(s))
- Four times daily (basal/bolus)



# Hypoglycemia

- When blood sugar is less than 4.0 mmol/L
- Signs and symptoms
- Treatment
- Causes



Thank You!



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