Learning Objectives

1 Describe and differentiate type 1 and type 2 diabetes

2 Identify the criteria required for diagnosis of diabetes and the analytical methods used in the clinical laboratory

3 Discuss blood glucose monitoring, insulin administration, and medications used in managing diabetes

Outline

Clinical Presentation

- Normal glucose handling

- Diabetes
  - Type 1 vs Type 2
  - Symptoms

Diagnosis

- Blood glucose

- HbA1c

- Oral glucose tolerance test

Treatment/Monitoring

- Glucose monitors

- Insulin therapy

- Oral medications used for T2D

CASE STUDY

Case Study: Patient Presentation

Patient: Cookie

- 59-year-old man
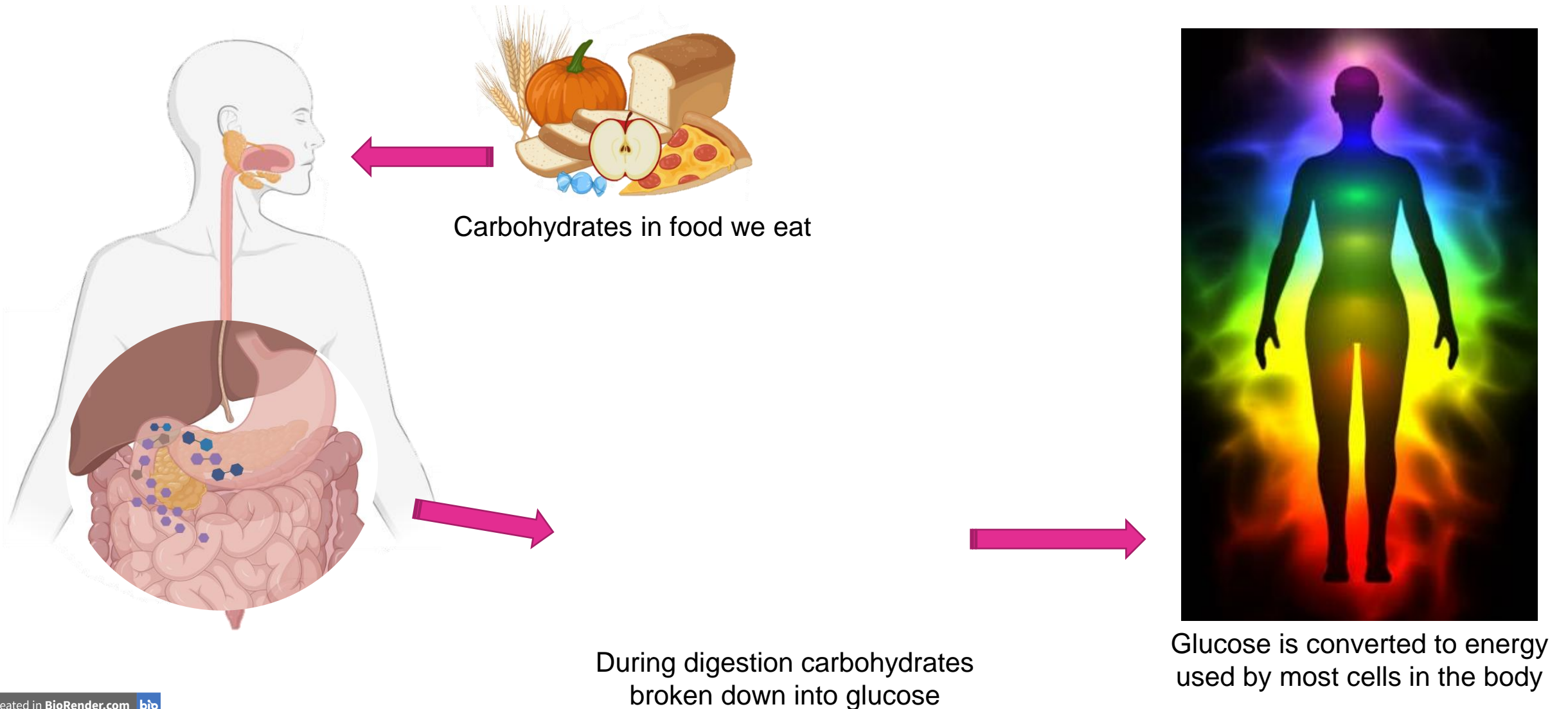- Height: 5'7"
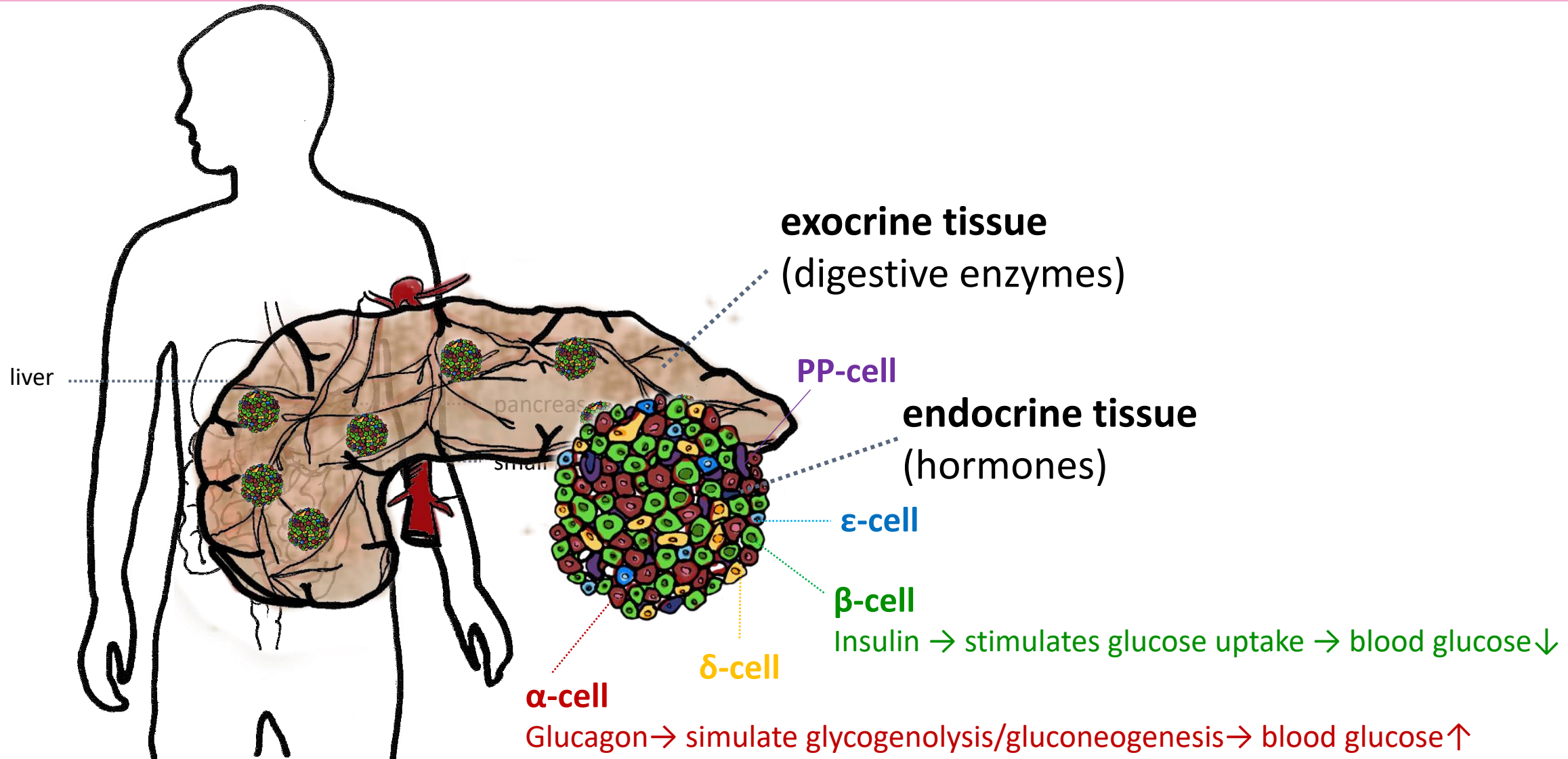- Weight: 220 lbs
- BMI: 34.5 kg/m^2

Patient complaints

Patient history
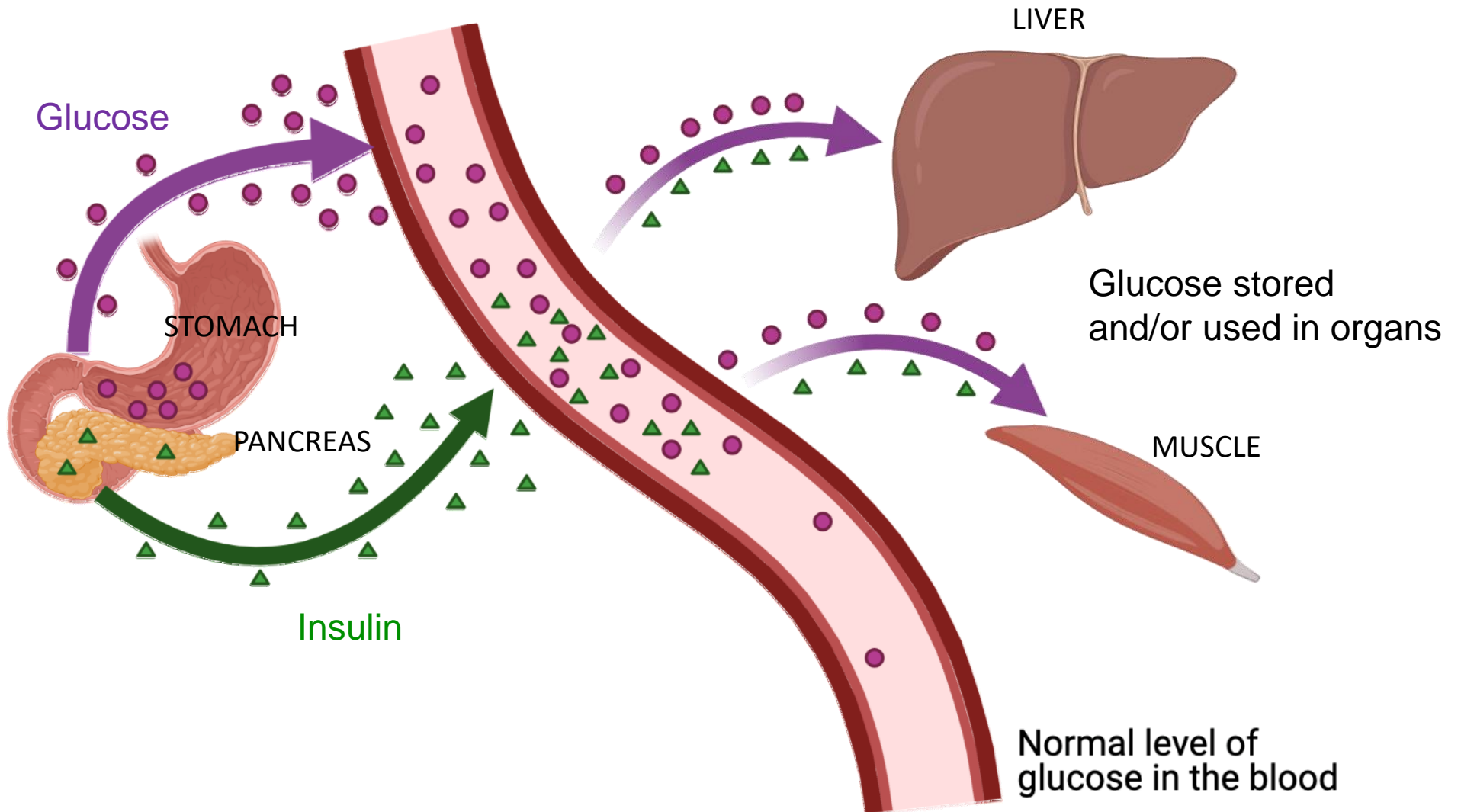
- Poor diet
- Sedentary lifestyle
- Father with Type 2 diabetes

How Our Body Gets Energy

Carbohydrates in food we eat

During digestion carbohydrates broken down into glucose

Glucose is converted to energy used by most cells in the body

Pancreatic Islet Coordinates Glucose Homeostasis

liver

exocrine tissue
(digestive enzymes)

pancreas

small

PP-cell

endocrine tissue
(hormones)

ε-cell

β-cell
Insulin → stimulates glucose uptake → blood glucose↓

δ-cell

α-cell
Glucagon→ simulate glycogenolysis/gluconeogenesis→ blood glucose↑

Glucose Regulation

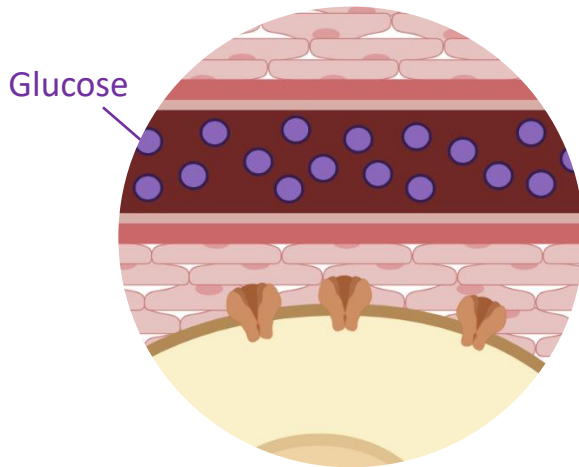# Dysfunctional Glucose Regulation
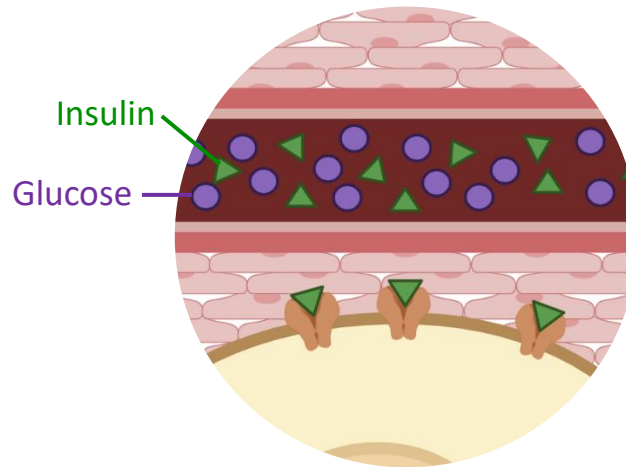
Glucose

STOMACH

PANCREAS

Insulin

LIVER

MUSCLE
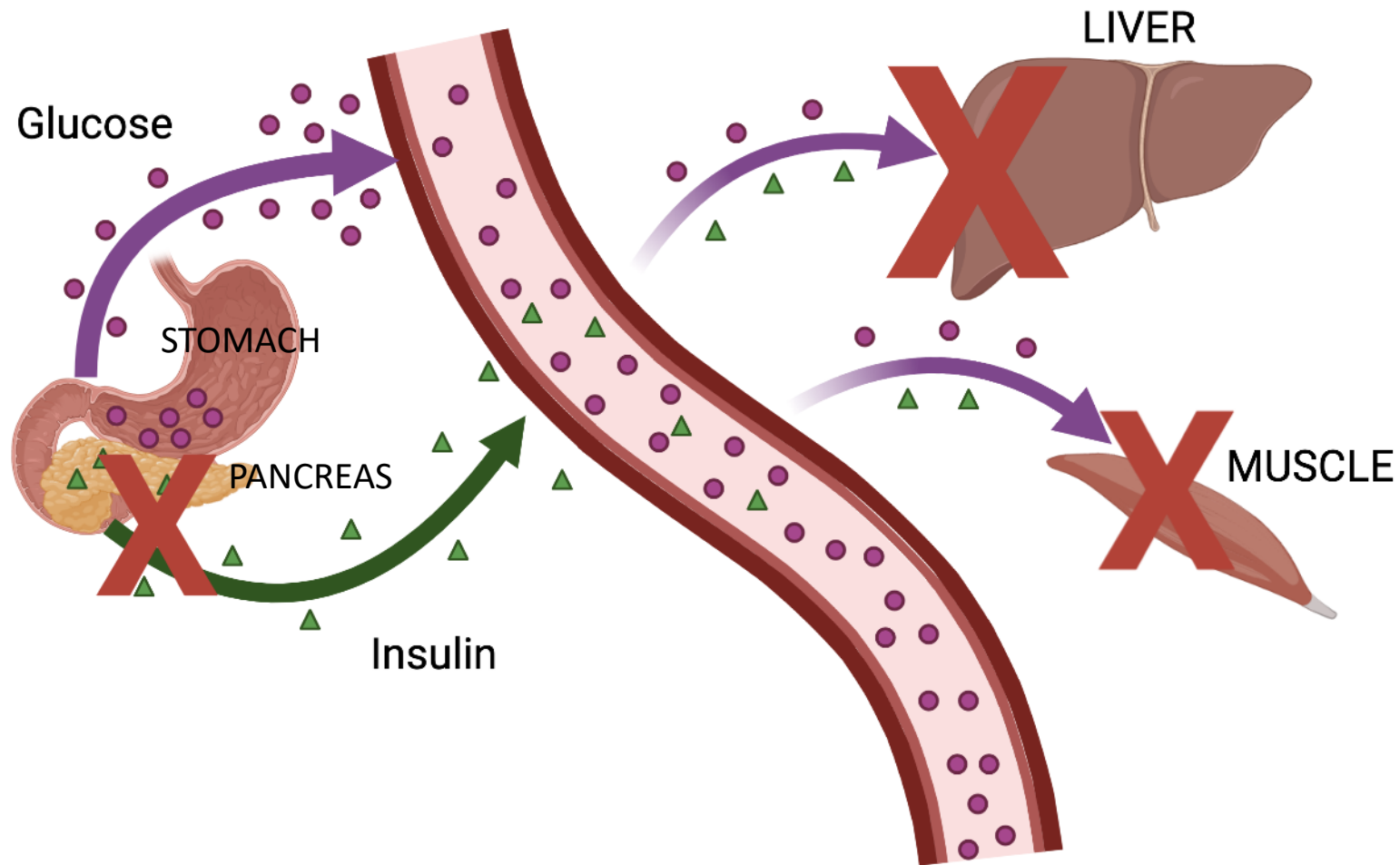
Increased level of glucose in the blood

What is Diabetes Mellitus

Group of metabolic disorders characterized by high levels of sugar in the blood

Glucose

Insulin

Glucose

- **TYPE 1 DIABETES (T1D)**
Beta cells that produce insulin are destroyed, leading to insulin deficiency

- **TYPE 2 DIABETES (T2D)**
Body produces insulin, but can't use it well

- **GESTATIONAL DIABETES (GDM)**
Transient condition during pregnancy

High blood glucose = Hyperglycemia

Diabetes Mellitus Epidemiology

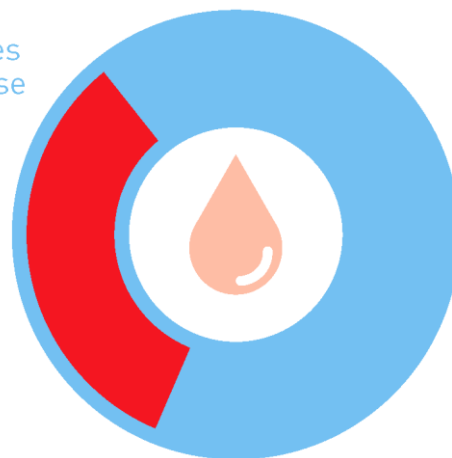DIABETES IS ON THE RISE

422 MILLION

adults have diabetes

THAT'S 1 PERSON IN 11

3.7 MILLION
deaths due to diabetes and high blood glucose

1.5 MILLION
deaths caused by diabetes
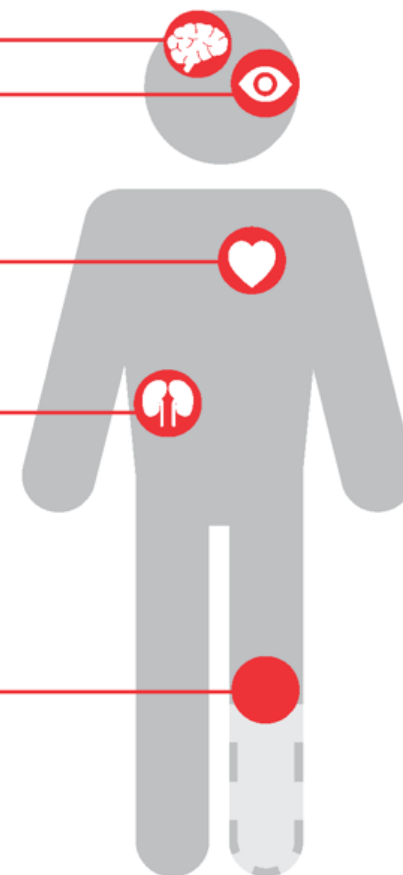
Stroke

Blindness

Heart attack

Kidney failure

Amputation

Diabetes in the US

2.3x greater health care costs for Americans with diabetes

$327B annual cost of diagnosed diabetes in America

34M More than 34 million Americans have diabetes

By county
- less than average: 0-6%
- national average: 7-10%
- above average: 11% or higher

88M More than 88 million Americans have prediabetes

American Diabetes Association.

Type 1 vs Type 2 Diabetes

Type 1

- ~~"Juvenile" diabetes~~
- Insulin-dependent diabetes mellitus (IDDM)
- Autoimmune destruction of insulin secreting beta cells
  - Cannot be prevented
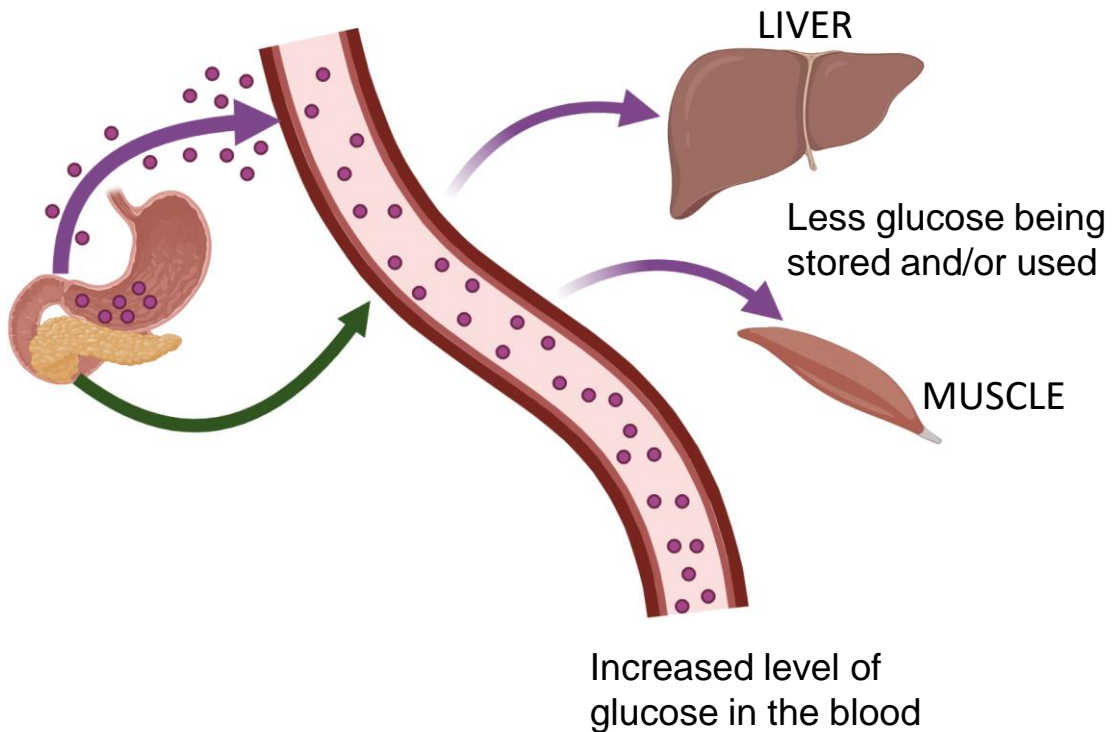- Requires insulin therapy
- 5 – 10 % of all cases

Type 2

- Tends to develop at an older age, but increasingly common in adolescence
- Occurs due to insulin resistance and progressive loss of insulin secretion
- Can be prevented with lifestyle changes
- Managed with diet/exercise and/or oral medications or insulin
- 90% cases

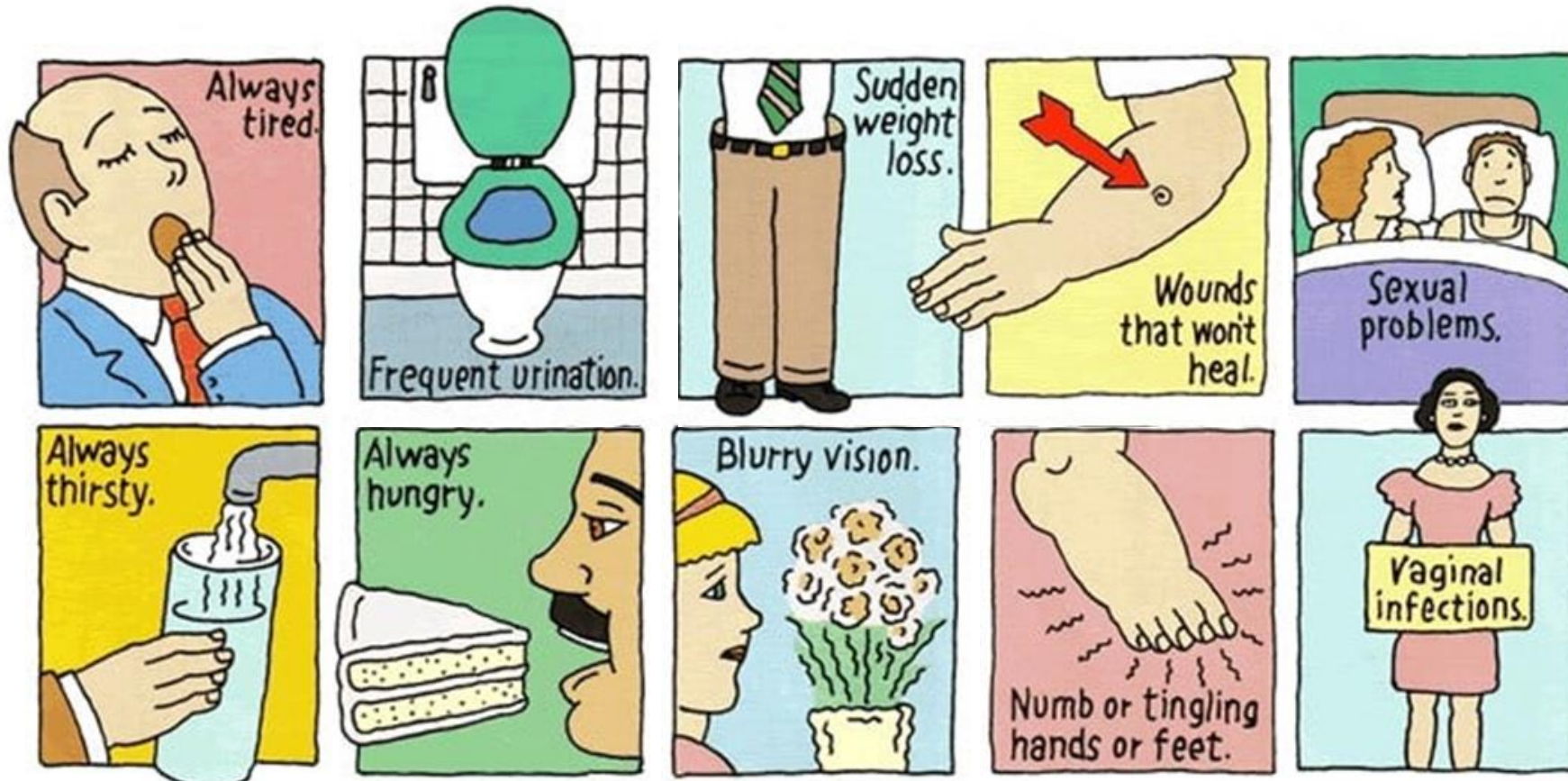# Blood Glucose in Diabetes

Type 1 Diabetes

Insulin deficient

LIVER

Less glucose being stored and/or used

MUSCLE

Increased level of glucose in the blood

Symptoms of Diabetes

http://www.betterfamilyhealth.org/symptoms-of-diabetes.html

Complications of Uncontrolled Diabetes

Acute Complications

- Diabetic ketoacidosis (DKA)
  - Type 1 Diabetes
- Hyperosmolar Hyperglycemic State (HHS)
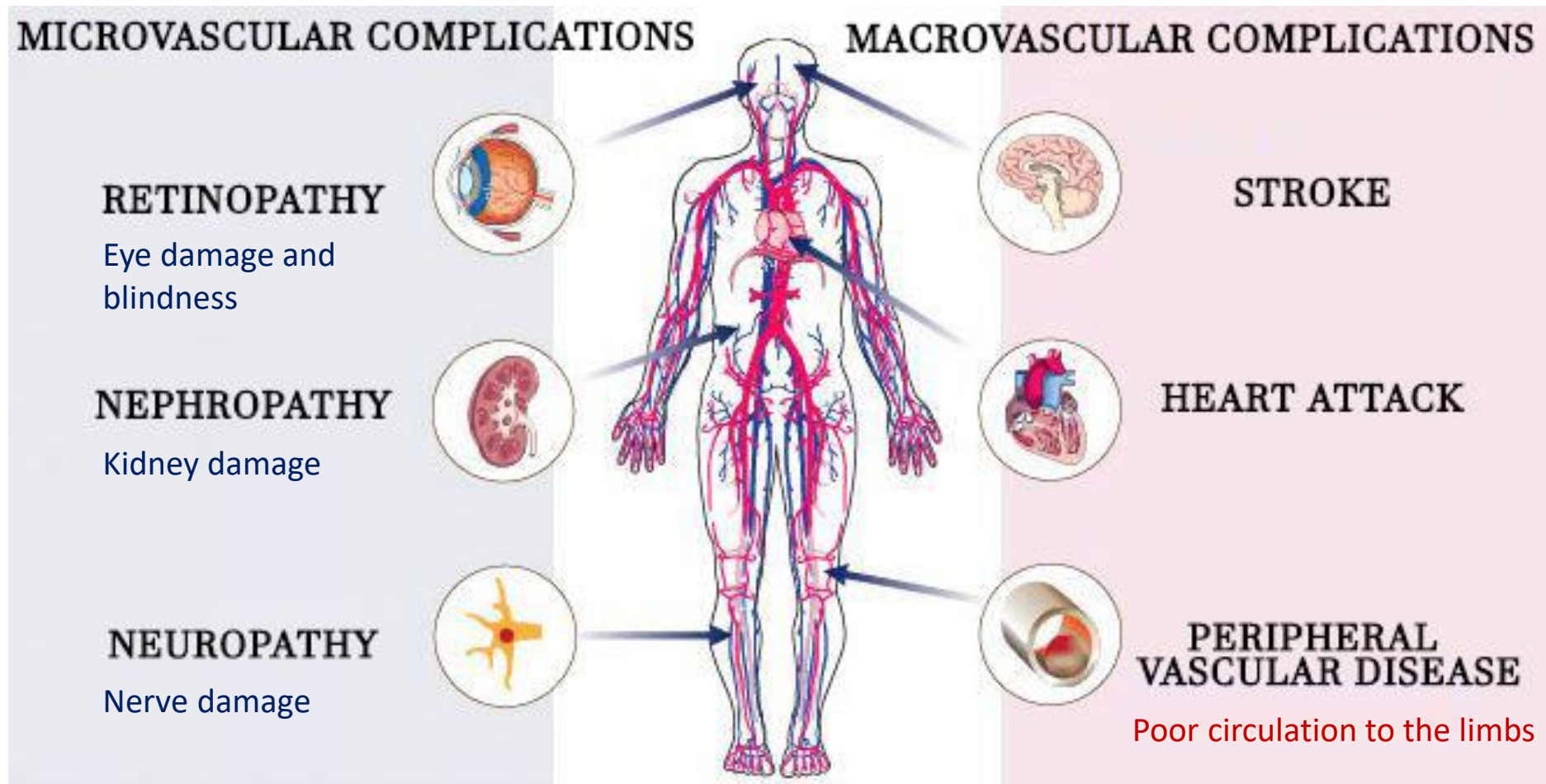 - Type 2 Diabetes
- Hypoglycemia

Chronic Complications

- Microvascular
- Macrovascular

Possible coma and death

Complications of Uncontrolled Diabetes

MICROVASCULAR COMPLICATIONS

RETINOPATHY
Eye damage and blindness

NEPHROPATHY
Kidney damage

NEUROPATHY
Nerve damage

MACROVASCULAR COMPLICATIONS

STROKE

HEART ATTACK

PERIPHERAL VASCULAR DISEASE
Poor circulation to the limbs

http://diabetscontrol.info/microvascular-complications-of-diabetes/

Case Study: Cookies Symptoms

http://www.betterfamilyhealth.org/symptoms-of-diabetes.html

Laboratory Methods for Diagnosis

1 Hb A$_{1c}$

2 Glucose

3 Oral Glucose Tolerance Test (OGTT)

https://www.diabetes.org/diabetescare
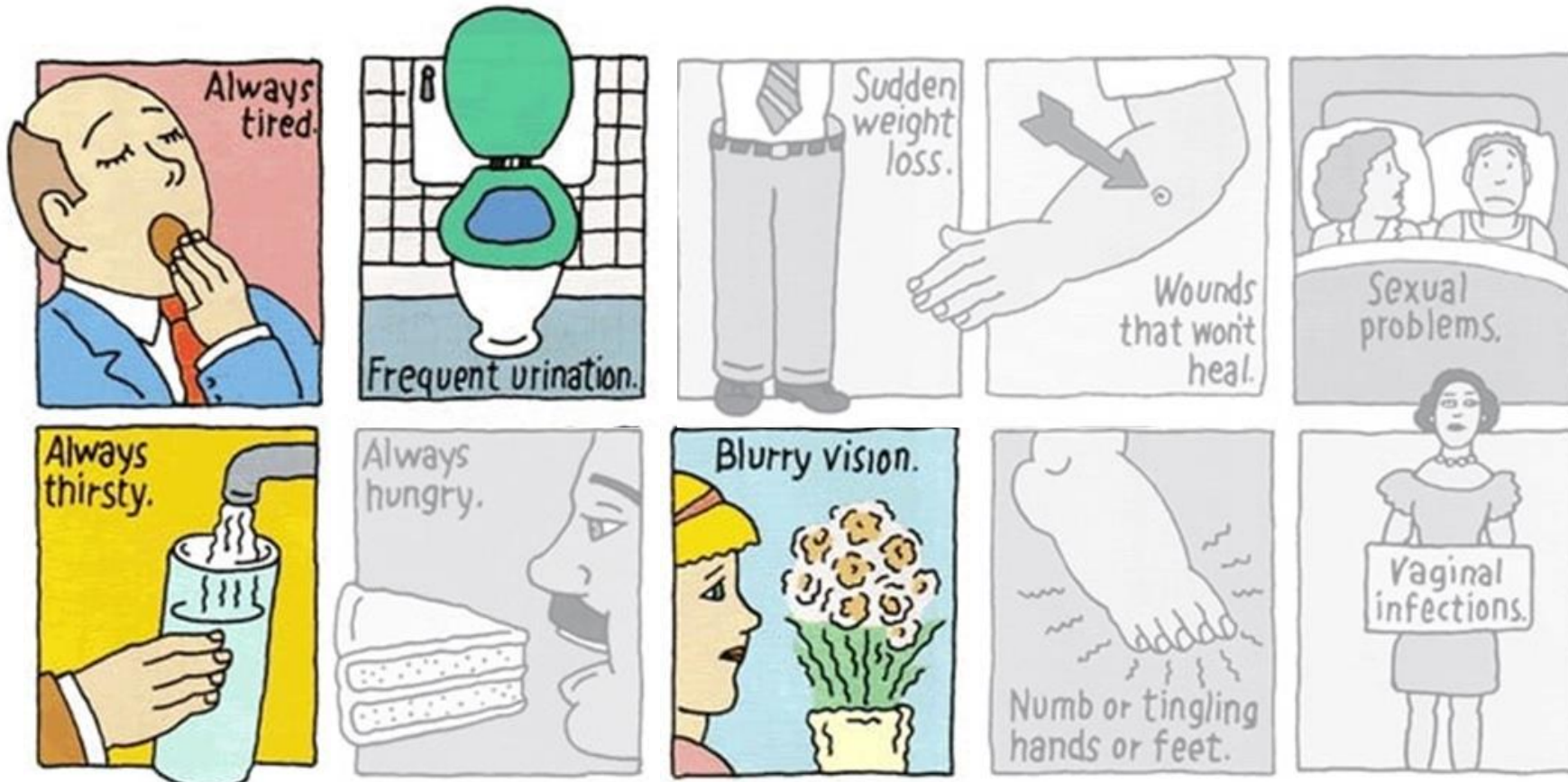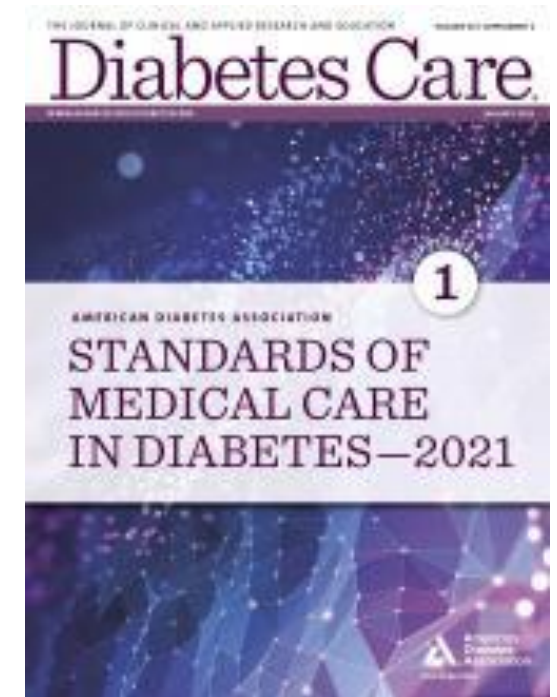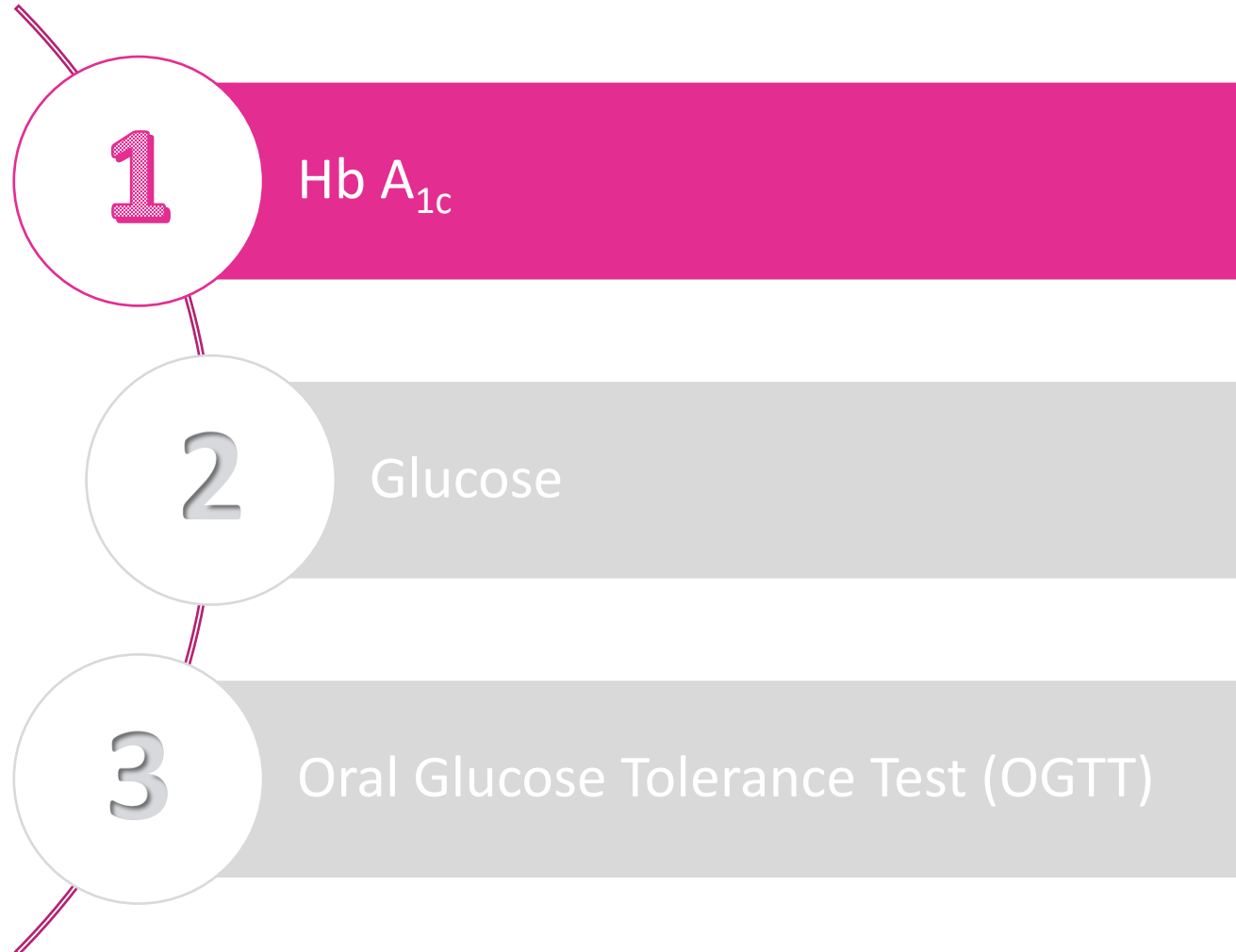
Hemoglobin (Hb) A$_{1c}$

- "Glycated hemoglobin"

Adult Hb

- Hb A
- Hb A$_2$
- Hb F

© 2016 Healthwise

Hemoglobin A1c

Red blood cell

Glucose attaches to hemoglobin
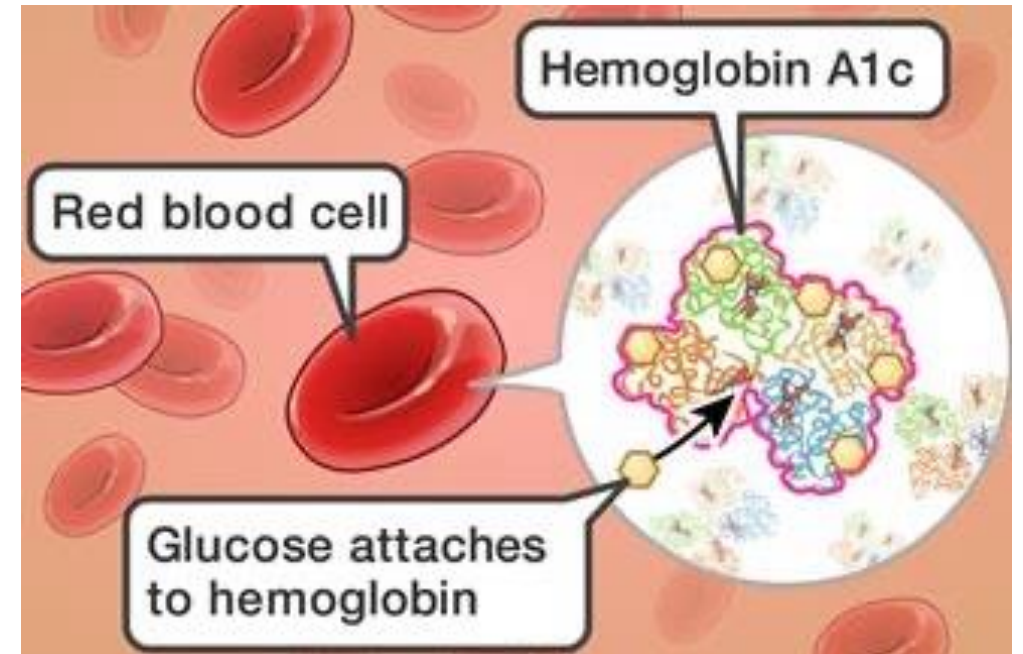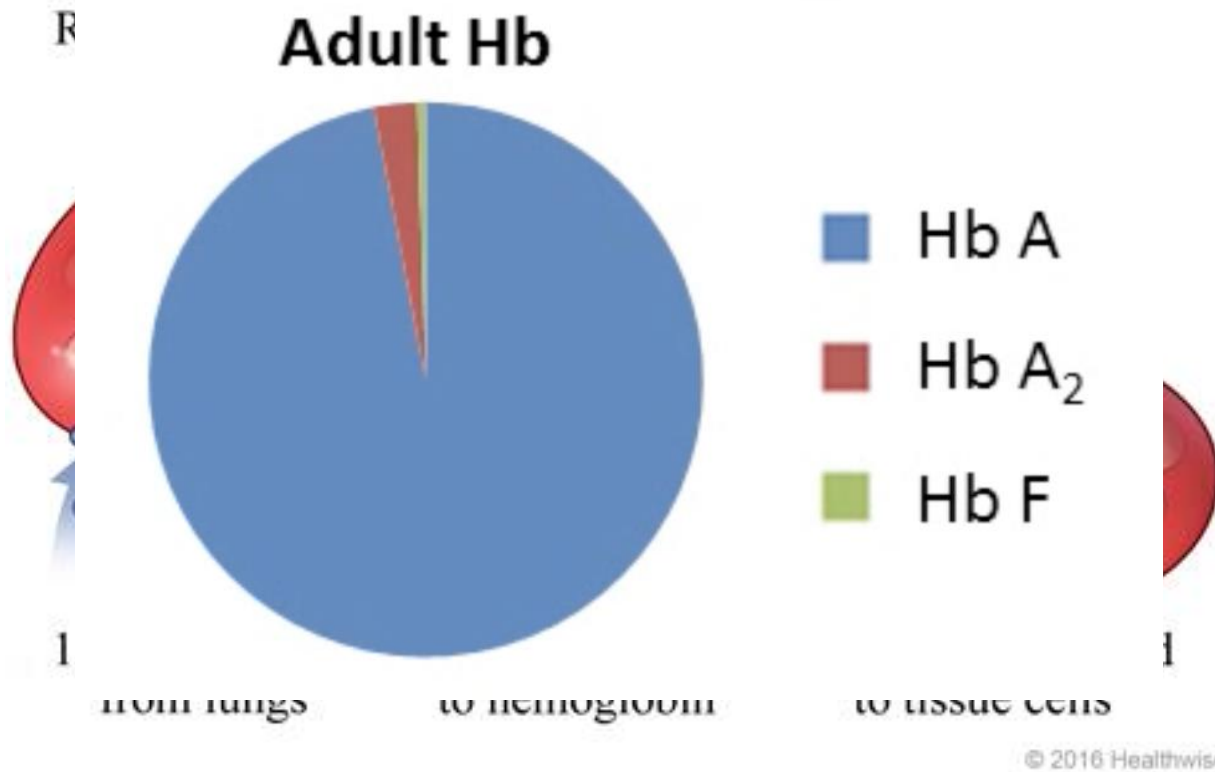
Hb A$_{1c}$

- Test used in diagnosis and monitoring of diabetics
  - Average blood glucose level over previous 3 months

Red Blood Cell

Hemoglobin

Glucose

Healthy Hb A$_{1c}$

High Hb A$_{1c}$
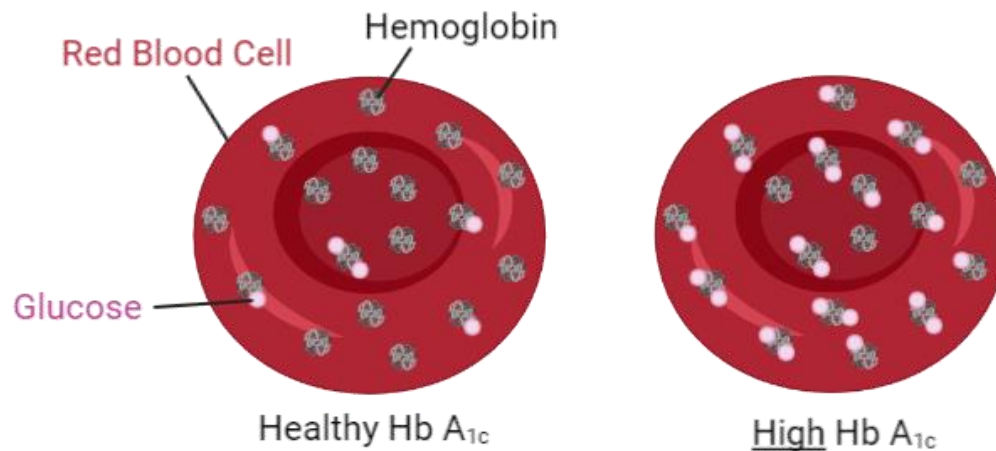
A$_{1c}$ (%)	eAG (mg/dL)
5	97
6	126
7	154
8	183
9	212
10	240
11	269
12	298

Nathan et. al. *Diabetes Care* 2008;31:1473-1478

Calculated Estimated Average Glucose (mg/dL) = 28.7 x HbA$_{1c}$ – 46.7

Hb A$_{1c}$

Advantages

- Assess average glucose over a 3 month window

- Not dependent on fasting

- Greater preanalytical stability

- Less daily variation

- Useful for monitoring patients

Limitations

- Cost

- Lower sensitivity

- Indirect measure
  - Interpretation depends on RBCs having a normal life span
  - Impacted by age, race/ethnicity, HIV treatment, anemia, and hemoglobinopathies

Laboratory Methods to Measure Hb A$_{1c}$

Charge Differences

- Ion-Exchange High Performance Liquid Chromatography (HPLC)*
- Capillary Electrophoresis

*Most common methods

Structural Differences
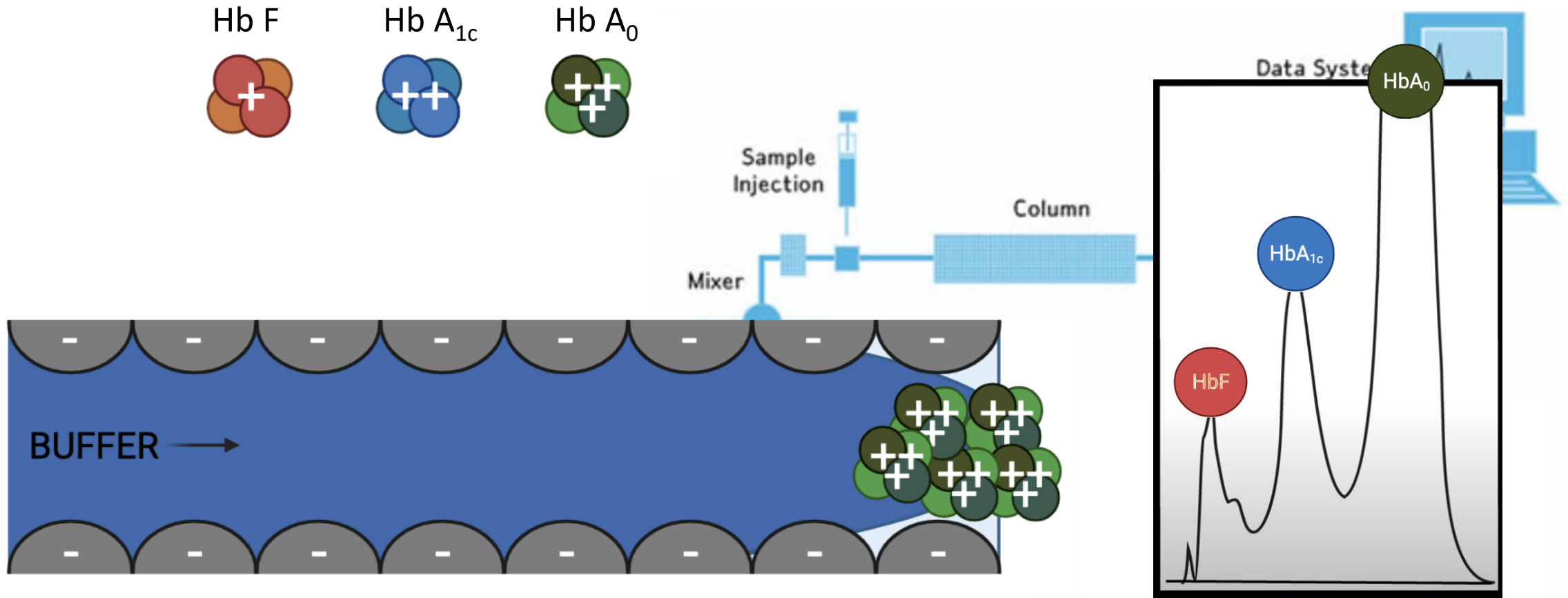
- Immunoassay*
- Affinity Chromatography

Point of Care devices

Image: https://www.medicaldevicedepot.com/Siemens-DCA-Vantage-HbA1c-Analyzer-CLIA-Waived-p/
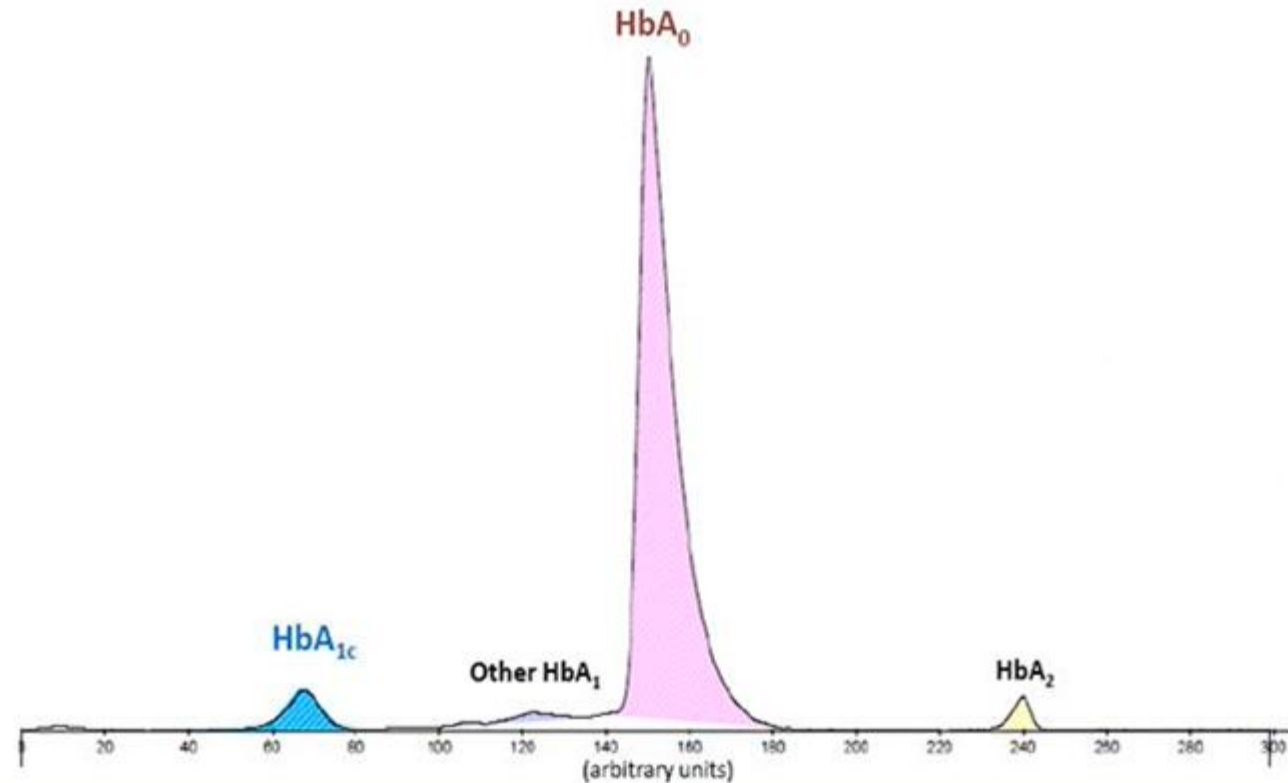
Hb A$_{1c}$ by HPLC

- Separates Hb A1c and other Hb based on charge differences
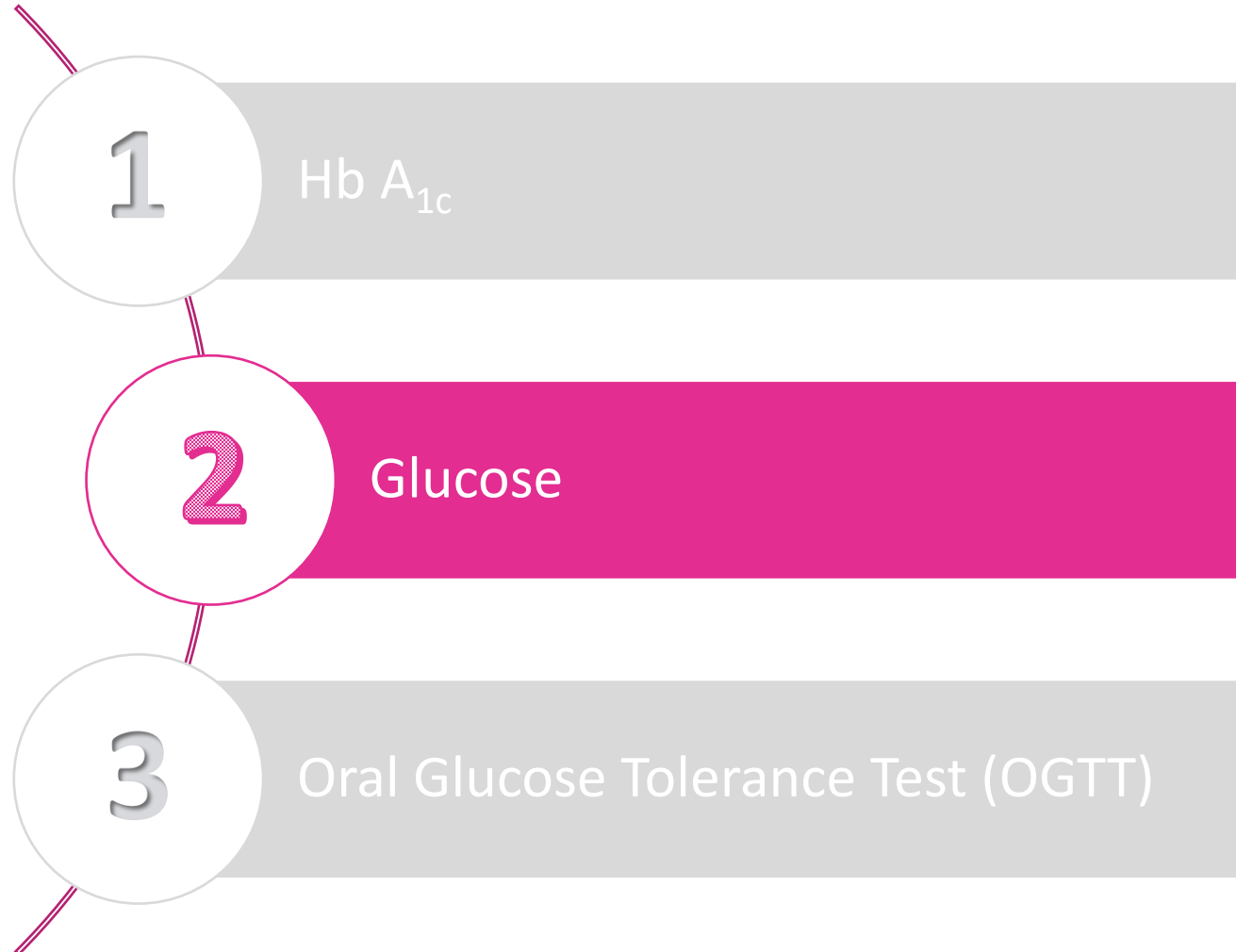
Hb A$_{1c}$ by Capillary Electrophoresis

- Silica capillary

- High voltage applied to separate molecules by electrophoretic mobility (size and charge)

- Detection at 415 nm – specific to hemoglobin

HbA1c Assay Interferences:
http://www.ngsp.org/interf.asp

Image: sebia.com

Methods for Diagnosis

1   Hb A$_{1c}$

2   Glucose

3   Oral Glucose Tolerance Test (OGTT)

Measurement of Glucose

- Specimen
    - Plasma: Grey top tube (sodium fluoride) – inhibits glycolysis
    - Whole blood (glucometers)
    - Interstitial fluid (continuous glucose monitors)
    - Urine – dipstick; screening only
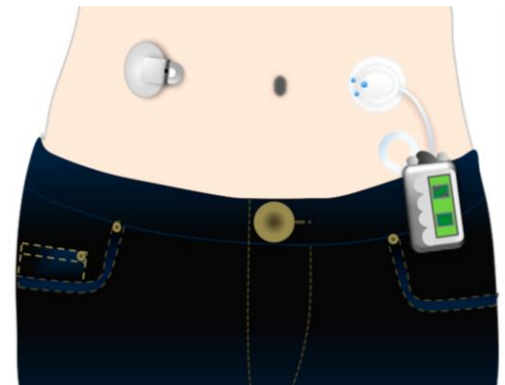
Sample Type Matters

- Capillary/whole blood vs. plasma
- Reference intervals differ based on sample type

~93% H₂O

~80% H₂O

PLASMA

RBCs

Glucose in blood fractions

PLASMA 100 mg/dL RBCs

PLASMA 88 mg/dL RBCs

PLASMA 70 RBCs

Methods for Measurement of Glucose

- Enzymatic methods with photometry or amperometry detection
  - Hexokinase – reference method
  - Glucose oxidase
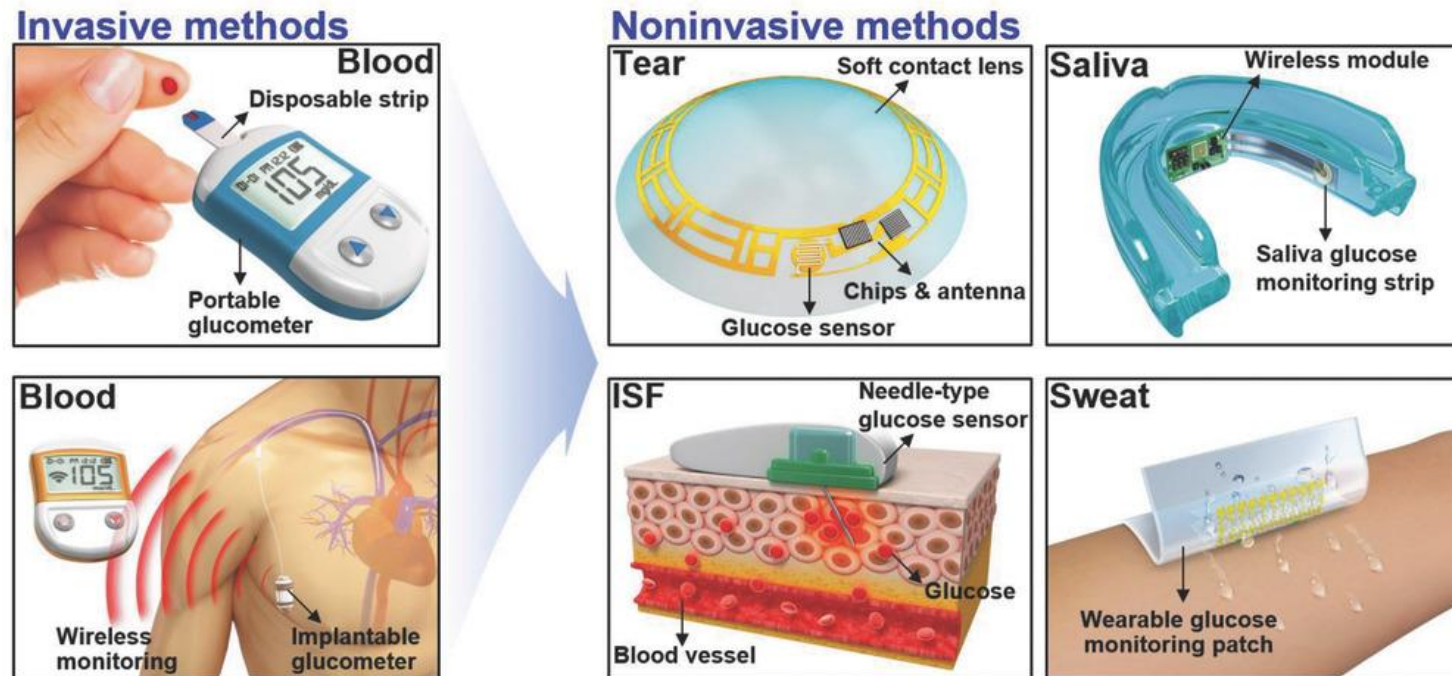
Hexokinase Method

- Most automated analyzers

$$\text{Glucose} + \text{ATP} \xrightleftharpoons[]{\text{HEXOKINASE}} \text{Glucose-6-phopshate} + \text{ADP}$$

$$\text{Glucose-6-phopshate} \xrightleftharpoons[]{\text{GLUC-6-PD}} \text{6-Phosphogluconate}$$

NAD   NADH
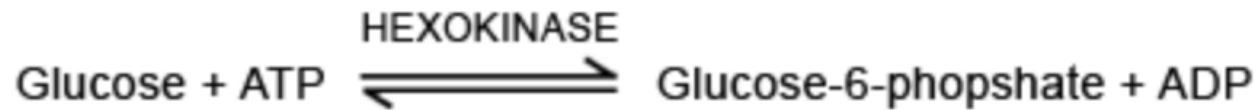
NADH production measured photometrically at 340 nm
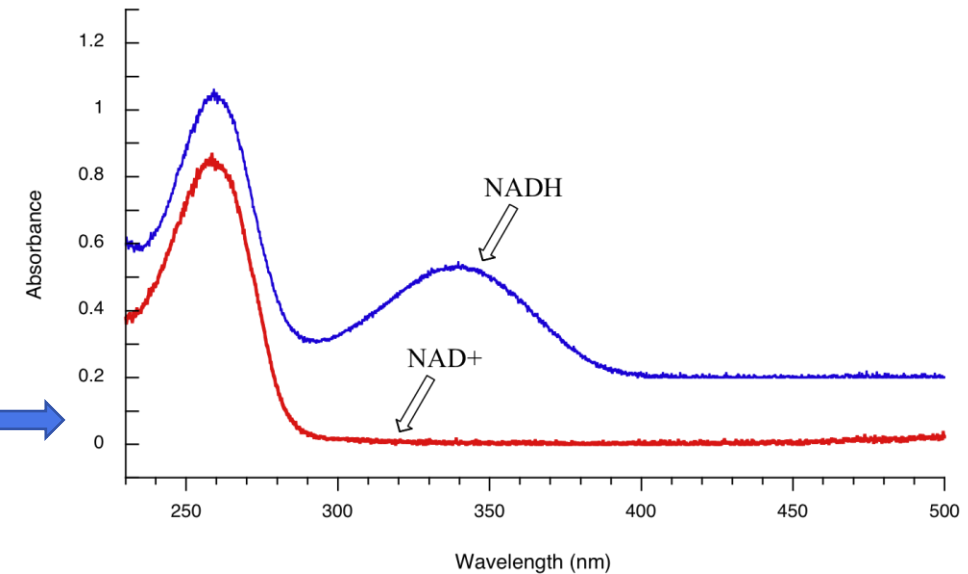
Glucose concentration is <u>directly proportional</u> to change in absorbance

Glucose Oxidase Method

- Lab-based and point-of-care systems
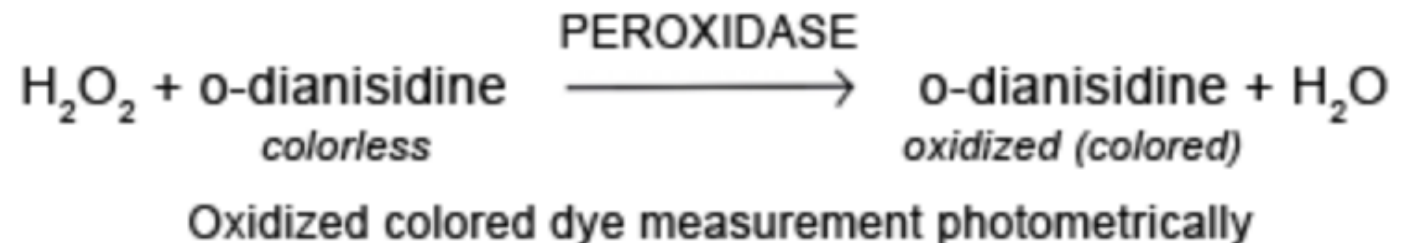- Photometric or Amperometric detection

GLUCOSE OXIDASE

$$Glucose + O_2 + 2H_2O \rightleftharpoons Gluconic\ Acid + 2H_2O_2$$

Hydrogen peroxide production measured amperometrically
Oxygen consumption measured amperometrically

PEROXIDASE

$$H_2O_2 + o\text{-dianisidine} \longrightarrow o\text{-dianisidine} + H_2O$$

colorless   *oxidized (colored)*

Oxidized colored dye measurement photometrically
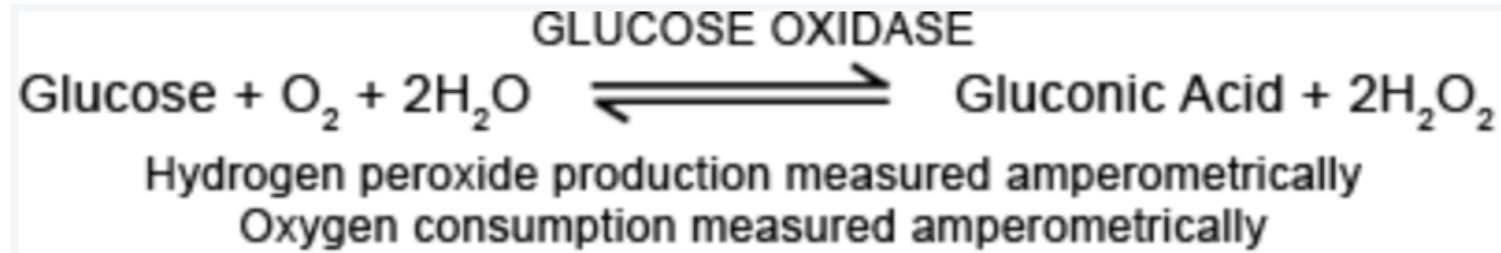
Glucose concentration is directly proportional to intensity of color

Laboratory Methods for Diagnosis

1 Hb A$_{1c}$

2 Glucose

3 Oral Glucose Tolerance Test (OGTT)
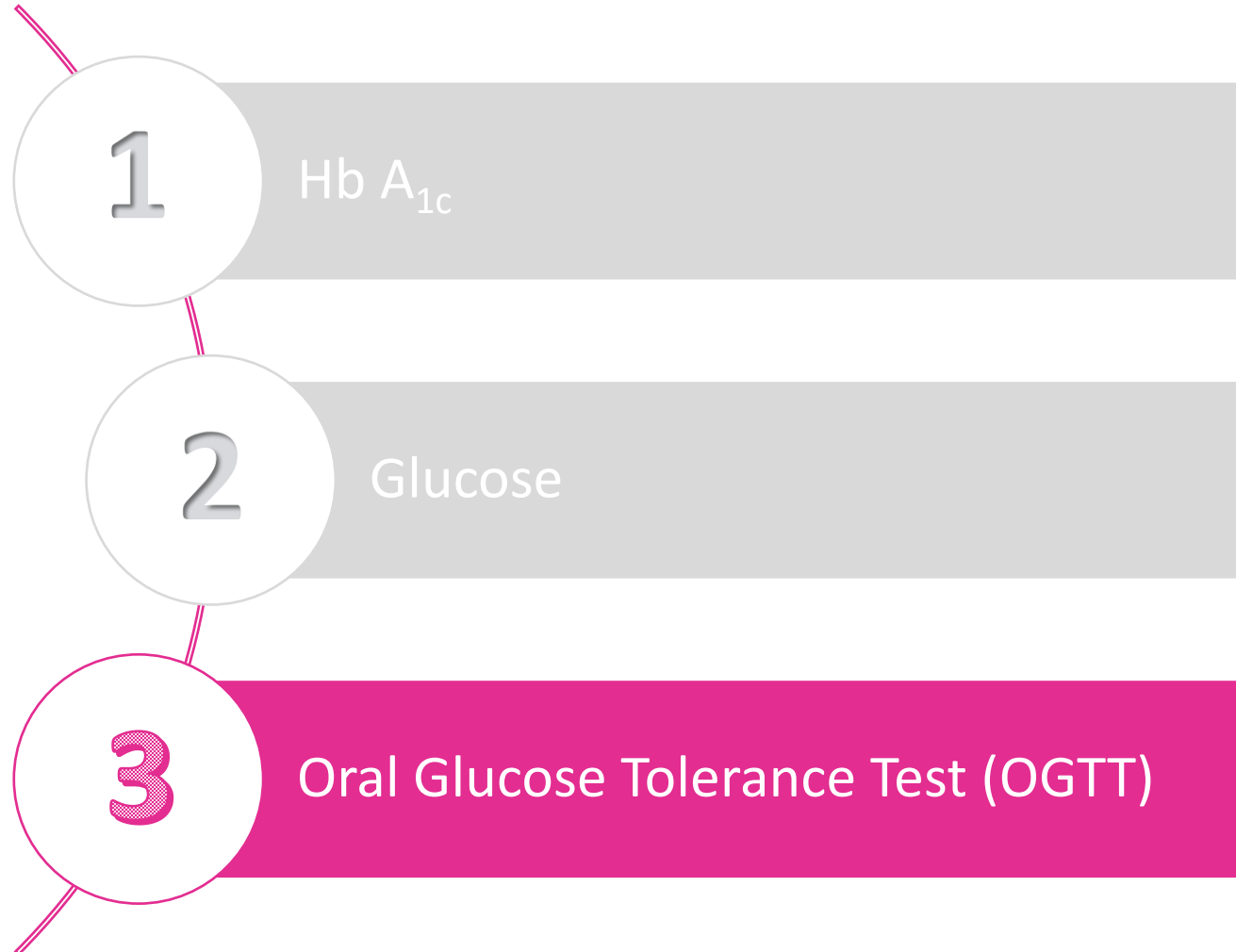
Oral Glucose Tolerance Test (OGTT)
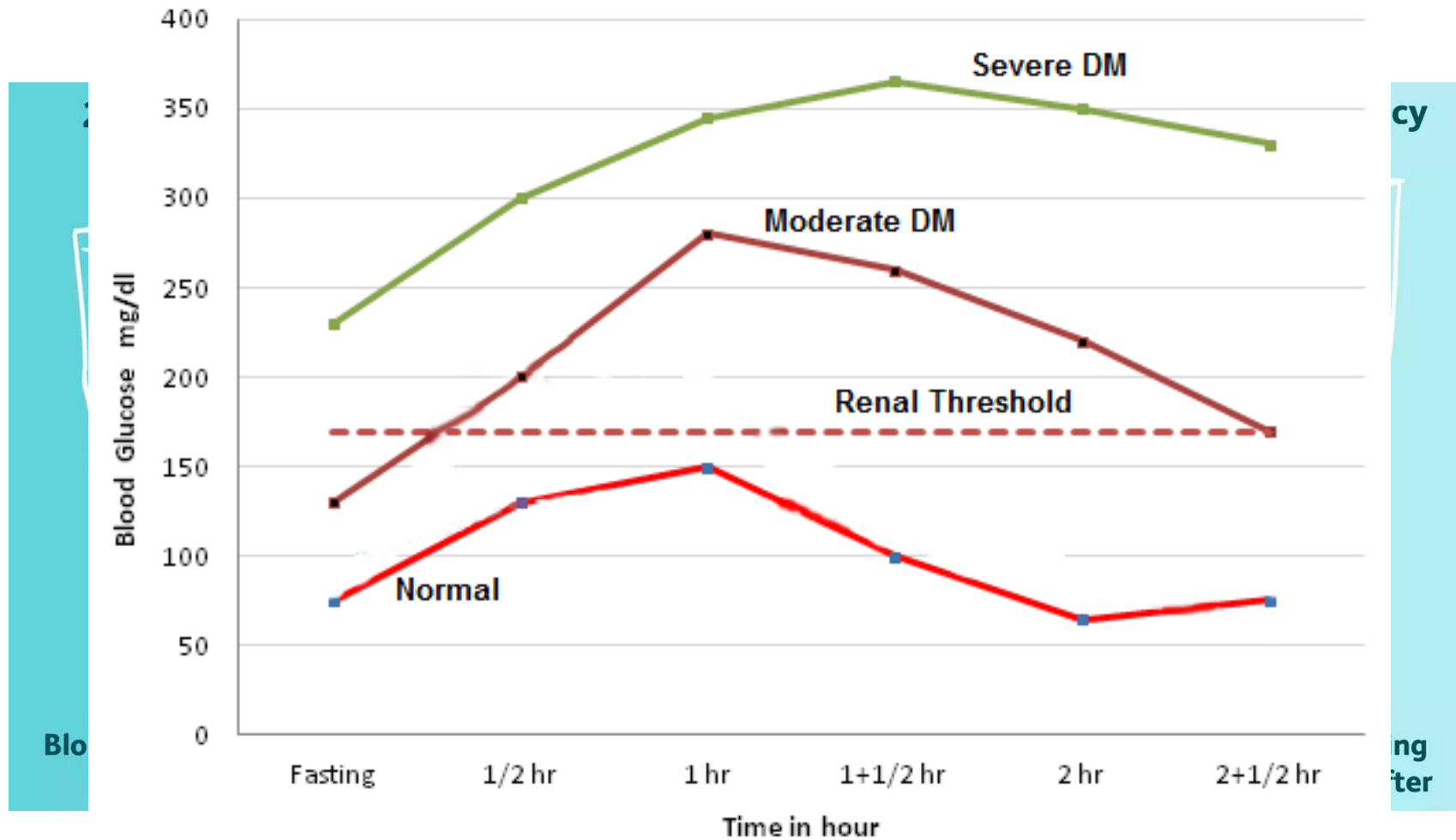
OGTT

Advantages

- High sensitivity (81-93%)
- Detects early impairment

Limitations

- Time consuming
- Extensive pre-test fasting
- Influenced by stress, illness, and medications
- Improper handling or storage of sample can skew results

Diagnosis of Diabetes

Diagnosis should include **2** abnormal results

Random glucose ≥ 200 mg/dL

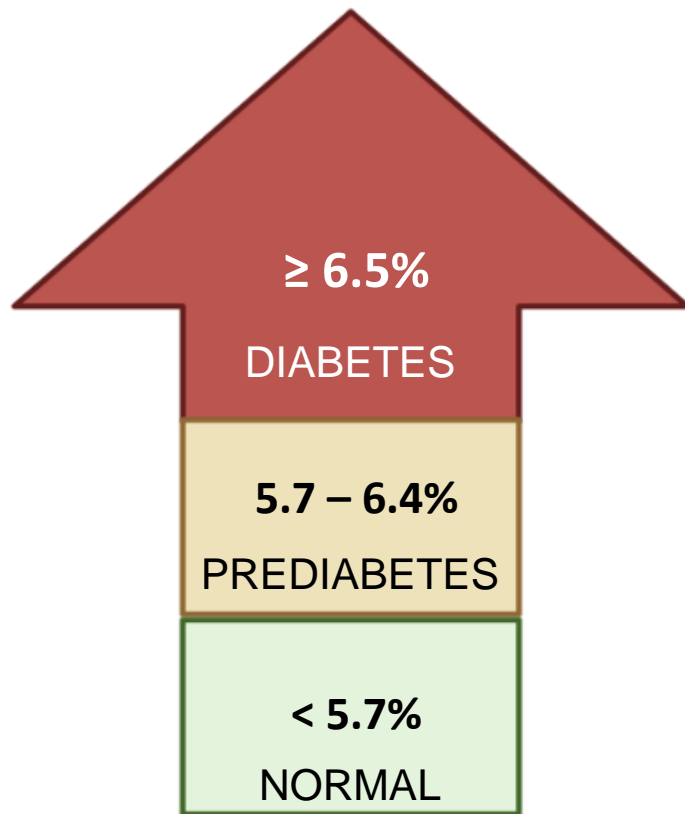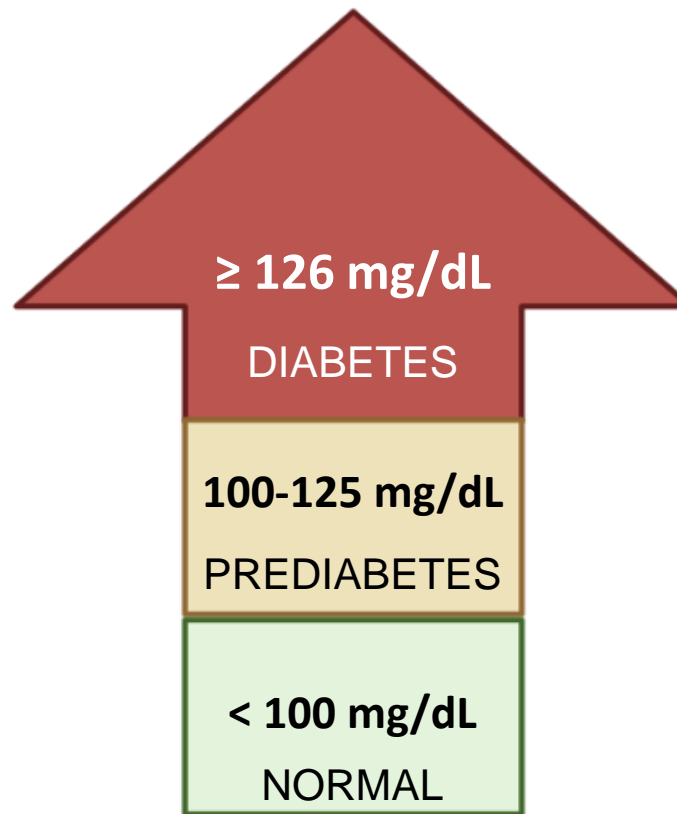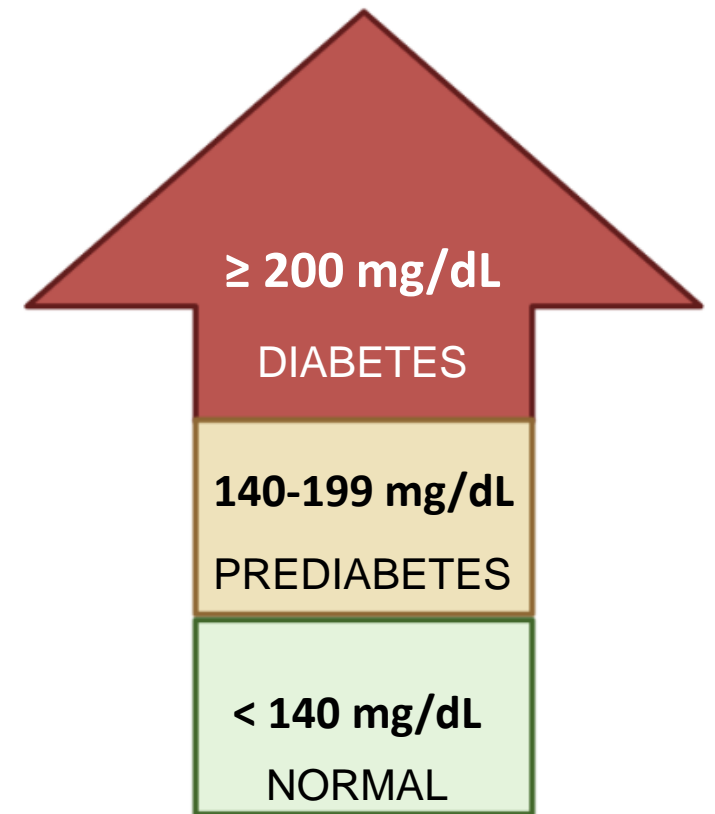| ≥ 6.5% DIABETES	≥ 126 mg/dL DIABETES	≥ 200 mg/dL DIABETES
5.7 – 6.4% PREDIABETES	100-125 mg/dL PREDIABETES	140-199 mg/dL PREDIABETES
< 5.7% NORMAL	< 100 mg/dL NORMAL	< 140 mg/dL NORMAL
A1C	**Fasting Plasma Glucose**	**Oral Glucose Tolerance Test** **2-hour measurement**

https://www.diabetes.org/diabetescare

Case Study: Patient Testing

Chart/Lab Table format results	Patient Result	RI
Hb A$_{1C}$	**8.0%** **H**	< 5.7%
Fasting Plasma Glucose	**154 mg /dL** **H**	< 100 mg/dL
Triglycerides	152 mg/dL	
LDL cholesterol	97 mg/dL	
HDL cholesterol	35 mg/dL	

- Diagnosis = Type 2 Diabetes

≥ 6.5%
DIABETES

5.7 – 6.4%
PREDIABETES

< 5.7%
NORMAL

A1C

≥ 126 mg/dL
DIABETES

100-125 mg/dL
PREDIABETES

< 100 mg/dL
NORMAL
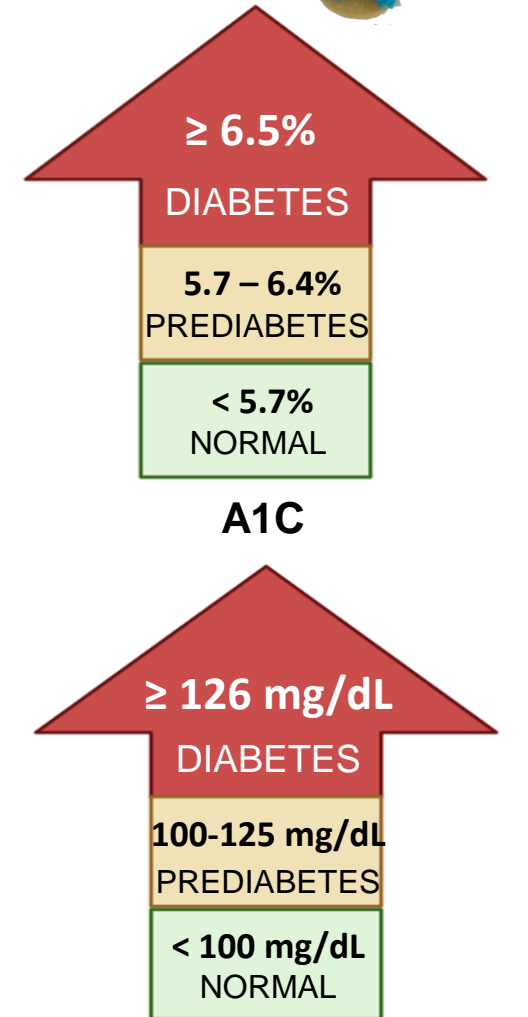
Fasting Plasma Glucose

Treatments

Treatments

INSULIN
All people with T1D need to take insulin every day. Only some people with T2D require this medication

MEDICATIONS
Individuals with T2D may take a daily cocktail of one or more medications (and sometimes insulin) to help keep blood sugar in a healthy range.

DIET AND EXERCISE
Although T1D cannot be managed with lifestyle changes, eating a healthy diet and regularly exercising can provide big benefits to those with T2D.

SELF-MONITORING
Treatment starts at home where blood glucose should be tested everyday (multiple times per day). Based on the glucose levels patients can adjust what and when to eat. For T1D this also helps determines how much insulin to inject
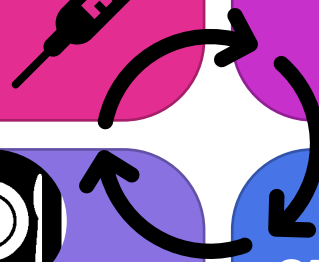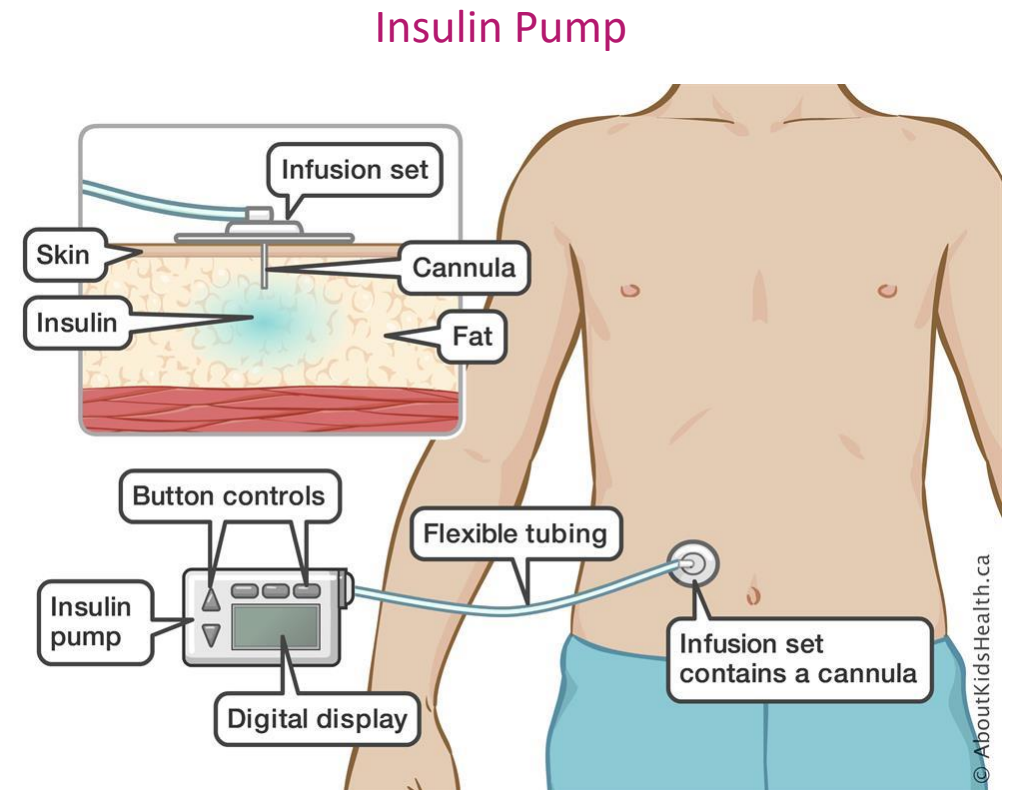
Insulin

- Insulin administered daily to keep blood glucose levels close to target range, without causing <u>hypogl</u>ycemia
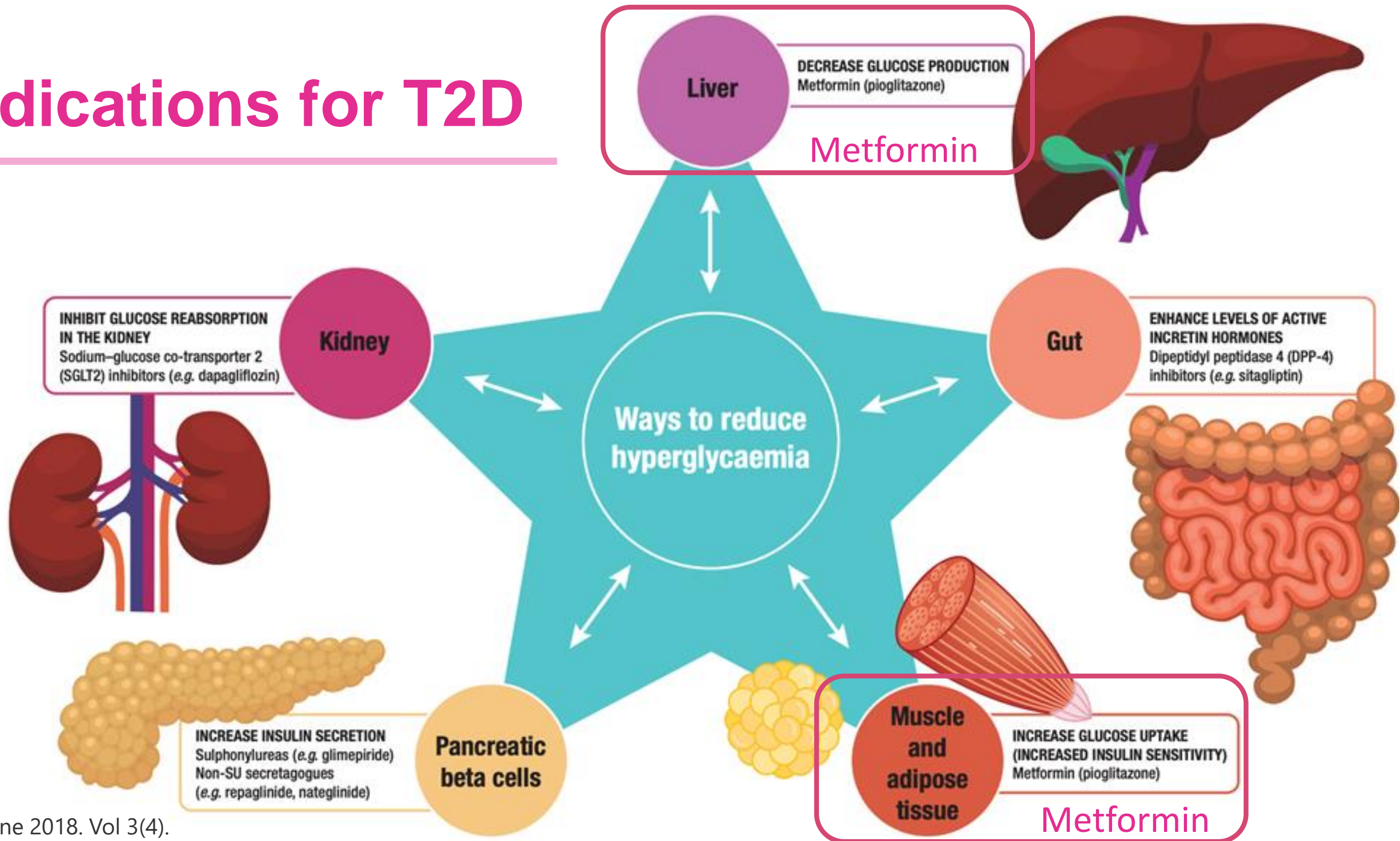

Syringe/pens

Inhaler

Insulin Pump

© AboutKidsHealth.ca

Medications for T2D

Liver — DECREASE GLUCOSE PRODUCTION — Metformin (pioglitazone)
Metformin

Kidney — INHIBIT GLUCOSE REABSORPTION IN THE KIDNEY — Sodium–glucose co-transporter 2 (SGLT2) inhibitors (*e.g.* dapagliflozin)

Gut — ENHANCE LEVELS OF ACTIVE INCRETIN HORMONES — Dipeptidyl peptidase 4 (DPP-4) inhibitors (*e.g.* sitagliptin)

Ways to reduce hyperglycaemia

Pancreatic beta cells — INCREASE INSULIN SECRETION — Sulphonylureas (*e.g.* glimepiride) Non-SU secretagogues (*e.g.* repaglinide, nateglinide)

Muscle and adipose tissue — INCREASE GLUCOSE UPTAKE (INCREASED INSULIN SENSITIVITY) — Metformin (pioglitazone)
Metformin

Glucose Monitoring

Glucometer

Continuous Glucose Monitor

Insertion of CGM Sensor

Transmitter

Sensor

Skin

Cell

Glucose

Interstitial fluid

Blood vessel
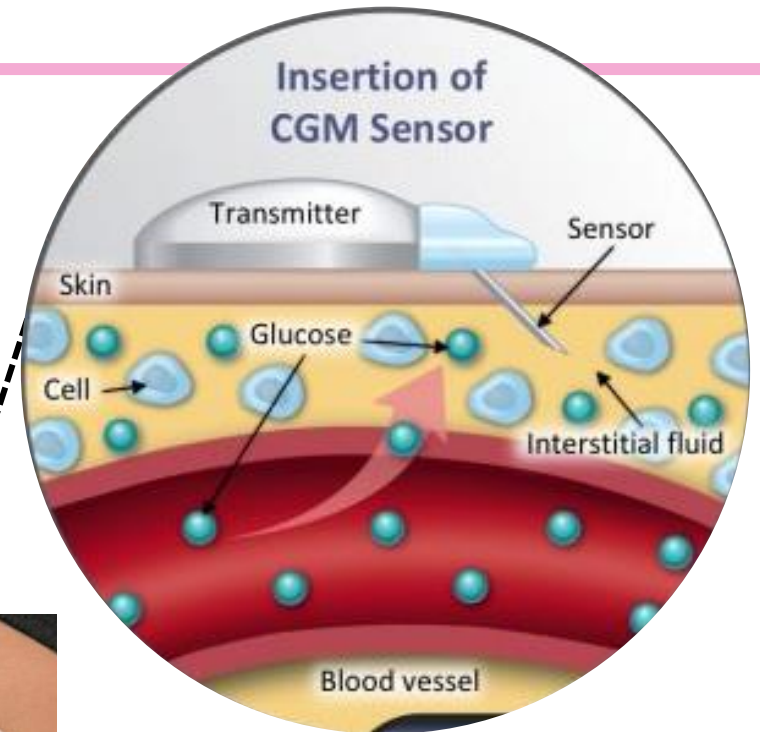
Diet and Exercise

Healthy Diet
- Reduce sugars, starches, and fatty foods

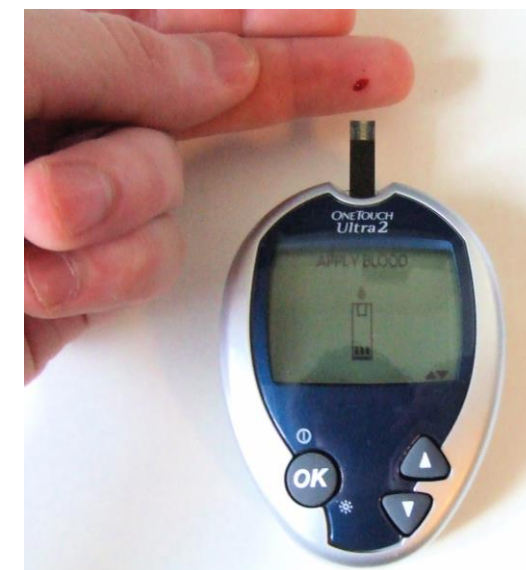## Exercise Regularly
- Reduce insulin resistance

Weight Loss
- Can aid in reduction of blood glucose

BLOOD SUGAR LEVEL

LOW   HIGH

Images: https://stock.adobe.com/tr/search

Case Study: Treatment Plan

- Referred to Diabetes clinic for patient education

- Worked with nutritionist to improve diet

- Discussed importance of exercise
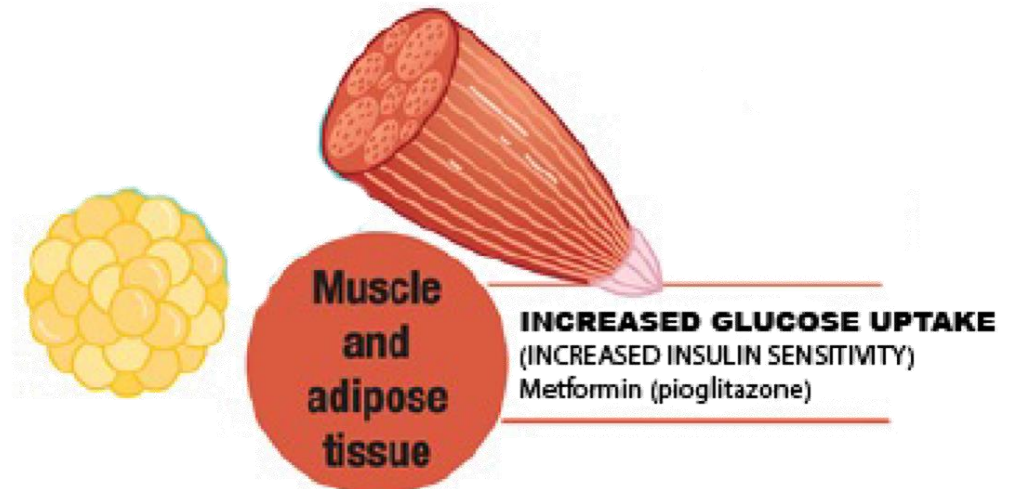
- Learned how to use glucose monitor

Case Study: 3-month Follow-up

Measurement	Result at diagnosis	Current result
Weight	220 lbs	222 lbs
Hb A$_{1C}$	8.0% H	8.2% H

- Self-management not enough

- Prescribed 500 mg metformin 2x per day with meals

Liver DECREASE GLUCOSE PRODUCTION

Muscle and adipose tissue

INCREASED GLUCOSE UPTAKE
(INCREASED INSULIN SENSITIVITY)
Metformin (pioglitazone)

Conclusions

- Diabetes is a group of metabolic disorders characterized by high levels of sugar in the blood

- Diagnosis requires measurement of fasting plasma glucose, Hb A$_{1c}$, and/or OGTT

- Treatment requires regular glucose monitoring and may include insulin or therapeutics designed to increase insulin secretion or decrease hepatic glucose production
  - Diet and lifestyle choices are also very important factors in successful treatment

THANK YOU...

Case Study

- Patient: Cookie

18: suggest larger diagram of HPLC system
       - do you want to include cations? show competition?
27: Dress up slide now that you split it
40: picture credits
31: boxes are difficult to see - such a great slide and important information - would not want to lose the audience
- what are the most common treatments, why, and are multiple given simultaneously?

35: diagnosis of type 2 diabetes based on age? anything more to confirm that it is type 2 and not type 1?
good job of using reminders

Other ideas:
- reduction in risk by weight loss and diet e.g., X% reduction in body mass leads to a reduced risk of T2D of X%
- individual cost and national cost of DM