Not Your Grandmother's Sugar

The Pathologies, and Treatment of Type 2 Diabetes

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Disclosures:

- Speaker for Takeda Pharmaceuticals.

How Bad Is it?

- USA Today September 15, 2014

- _____% of Americans over 20 have diabetes, either diagnosed or undiagnosed.
- Another_____% have "pre-diabetes."
- Up _____% from a decade ago.
- "Pre-diabetes" increases the risk of cancer by _____%
- Up to _____% of people with "pre-diabetes will develop Type 2 diabetes within 5 years.

How Bad Is It?

- The CDC reports that _____% of the _____ million affected adults know they have "pre-diabetes."

Let's Talk Definitions:

How do you diagnose Type 2 Diabetes?

What is "Pre-Diabetes?

What is Impaired Fasting Glucose?

What is Impaired Glucose Tolerance?

Hemoglobin A1c?

Hemoglobin A1c

- Accuracy? 0.5% higher or lower.
- African, Mediterranean, Southeast Asians, patients with Sickle Cell Anemia, thalassemia, variant hemoglobin, anemia (false low), low iron (false high), kidney disease, liver disease.

History of Type 2 Diabetes.

- 1552 BC—First Known Description of Diabetes Symptoms, found on Egyptian Papyrus
- 1920—Diabetes associated with deficiency of insulin
- 1921—Insulin is isolated
- 1922—First insulin injection (from a dog)
- 1923—Nobel Prize in Medicine for the Discovery of Insulin.
- 1935—Distinction between Type 1 and Type 2 Diabetes

History of Type 2 Diabetes

- 1942—Sulfonylureas discovered (looking for treatment for Typhoid)
- 1957—Orinase by UpJohn 1st generation
- 1973—I graduated from nursing school
- 1984—FDA approves Pfizer's Glucotrol 2nd generation
- 1986—I graduated from medical school
- 1995—FDA approves Amaryl (glimepiride) 3rd generation
- 1995—FDA approves Squibb's Glucophage (biguanide) (1958-UK; 1972-Canada)

History of Type 2 Diabetes

- 1996—FDA approves Pharmacia & UpJohn's Glyset (oral alpha-glucosidase inhibitor)
- May 1999—FDA approves SB's Avandia (TZD)
- July 1999—FDA approves Takeda's Actos (TZD)
- 2002—FDA approves Metformin (biguanide)
- 2005—FDA approves Avandamet
- 2005—FDA approves Amylin's Symlin
- 2005—FDA approves Amylin's Byetta
- 2005—FDA approves Takeda's ActoplusMet

History of Type 2 Diabetes

- 2006—FDA approves Merck's Januvia (DPP-4)
- 2009—FDA approves BMS's Onglyza (DPP-4)
- 2010—FDA approves Novo Nordisk's Victoza
- 2010—Tel Aviv University Study Finds Diabetes Doubles Cancer Risk in Women
- 2013—FDA approves Takeda's Oseni (TZD and DPP-4)
- 2013—FDA approves Janssen's Invokana (SGLT-2)
- 2014—FDA approves BMS's Farxiga (SGLT-2)
- 2014—FDA approves GSK's Tanzeum (GLP-1)

What is Type 2 Diabetes?

Initially: too little insulin; too much glucose.

1990's – 2000's: Insulin resistance in muscle and liver cells; β-cell failure.

2000's: ?

Current Pathologies of Diabetes

- Muscle cells: Insulin resistance.
- Liver cells: Insulin resistance.
- β-cell failure / loss of β-cells.
- Fat cells: Accelerated lipolysis
- Fat cells: Adiponectin
- α-cell: hyperglucagonemia.
- Kidney: Increased glucose reabsorption.
- Brain: Insulin resistance.
- GI tract: incretin deficiency/resistance.

How to Treat?

- One medication or more than one?
- Treat to failure?
- Based on known pathology?
- Treat to reduce A1c?
- Aggressive treatment early?/late?
- Age?
- Based on severity of disease?
- Based on insulin levels?
- Based on Adiponectin levels?

Options:

- Sulfonylureas
- Biguanides:
- Meglitinides
- Bile Acid Sequestrants
- Dopamine receptor agonists
- Synthetic analogues of amylin
- Oral alpha-glucosidase inhibitors
- TZD's (Thiazolidinediones)
- DP4 Inhibitors
- GLP-1
- SGLT-2's
- Insulins

Sulfonylureas

- Glimepiride (Amaryl)
- Glyburide (Diabeta, Micronase)
- Glipizide (Glucotrol, Glucotrol XL)
- Micronized glyburide (Glynase)

- *Stimulates the pancreas to release more insulin, both right after a meal and then over several hours.*
- *Risks of hypoglycemia.*
- *Accelerates β-cell failure.*
- *UKPDS: no significant protection against atherosclerotic CV complications.*

Biguanides

- Metformin (Glucophage) Metformin liquid (Riomet)
- Metformin extended release (Glucophage XR, Fortamet, Glumetza)

- *Primarily suppresses hepatic glucose production.*
- *Increased insulin sensitivity.*
- *Enhances peripheral glucose uptake.*
- *Decreases insulin-induced suppression of fatty acid oxidation.*
- *Decreases absorption of gluocose from the GI tract.*
- *Increases peripheral use of glucose.*

Meglitinides

- Repaglinide (Prandin)
- Nateglinide (Starlix)
- Mitiglinide (Glufast)

- *Stimulate the pancreas to release more insulin right after a meal.*

Bile Acid Sequestrants

- Colesevelam (Welchol)

- *Mechanism of action is not completely understood. However since it is not absorbed, it must work in the GI tract.*

Dopamine Receptor Agonists

- Cycloset (bromocriptine mesylate)

- *It's not clear how Cycloset improves glycemic control in humans.*
- *Studies in diabetic animals show that boosting dopamine activity at a particular time of day can "reset" the biological clock to improve metabolism problems related to diabetes.*

Synthetic analogues of Amylin

- **Pramlintide** (Symlin)

- Synthetic analogue of the peptide hormone **amylin**, which is produced by the **pancreatic beta cells** (so it is also deficient in type 1 diabetes mellitus).
- Amylin inhibits glucagon secretion and also slows stomach emptying.
- Pramlintide is recommended as an adjunct to insulin therapy for type 1 and type 2 diabetics who are having difficulty with glycemic control.
- Injectable.

Oral alpha-glucosidase inhibitors

- Acarbose (Precose)
- Miglitol (Glyset)

- *Slows the absorption of carbohydrate into the bloodstream after eating.*

TZD's (Thiazolidinediones)

- Pioglitazone (Actos)
- Rosiglitazone Maleate (Avandia)

- *Potent insulin sensitizer.*
- *Inhibits the increased rate of gluconeogenesis.*
- *Potent insulin sensitizer in muscle.*
- *Preserves β-cell function*
- *Significantly increases levels of adiponectin.*

Adiponectin

- Discovered 1995.
- Expressed primarily by adipocytes.
- Plasma levels are inversely correlated with visceral adiposity.
- Low concentration of adiponectin, so-called hypoadiponectinemia, is closely associated with obesity- related diseases including hypertension, type 2 diabetes, and cardiovascular disease.

Adiponectin

Numerous experimental studies have shown that adiponectin displays a variety of protective actions on obesity-induced pathological conditions, including

- Hypertension
- Insulin resistance,
- Hepatic steatosis,
- Atherosclerosis,
- Ischemic heart disease.

Adiponectin

- *Provides a metabolic regulatory function (via increasing insulin sensitivity, increasing glucose utilization, and increasing fatty acid oxidation).*
- *Has vascular protective function (by enhancing NO production, and stimulating angiogenesis).*
- *Has an anti- inflammatory role (through decreasing both neutrophil adhesion and macrophage activation).*
- *Has a cardioprotective/anti-ischemic function.*

What Will Increase Adiponectin?

- TZD's (pioglitazone and rosiglitazone)
- Omega 3 Fatty Acids (DHA and EPA)
- ACEI's and ARB's
- Dietary Fiber
- Exercise
- Weight loss (>8 – 9%)
- Low carbohydrate diet
- Vitamin D (obese children) (cord blood)
- Tomatoes (post menopausal women)
- Smoking cessation

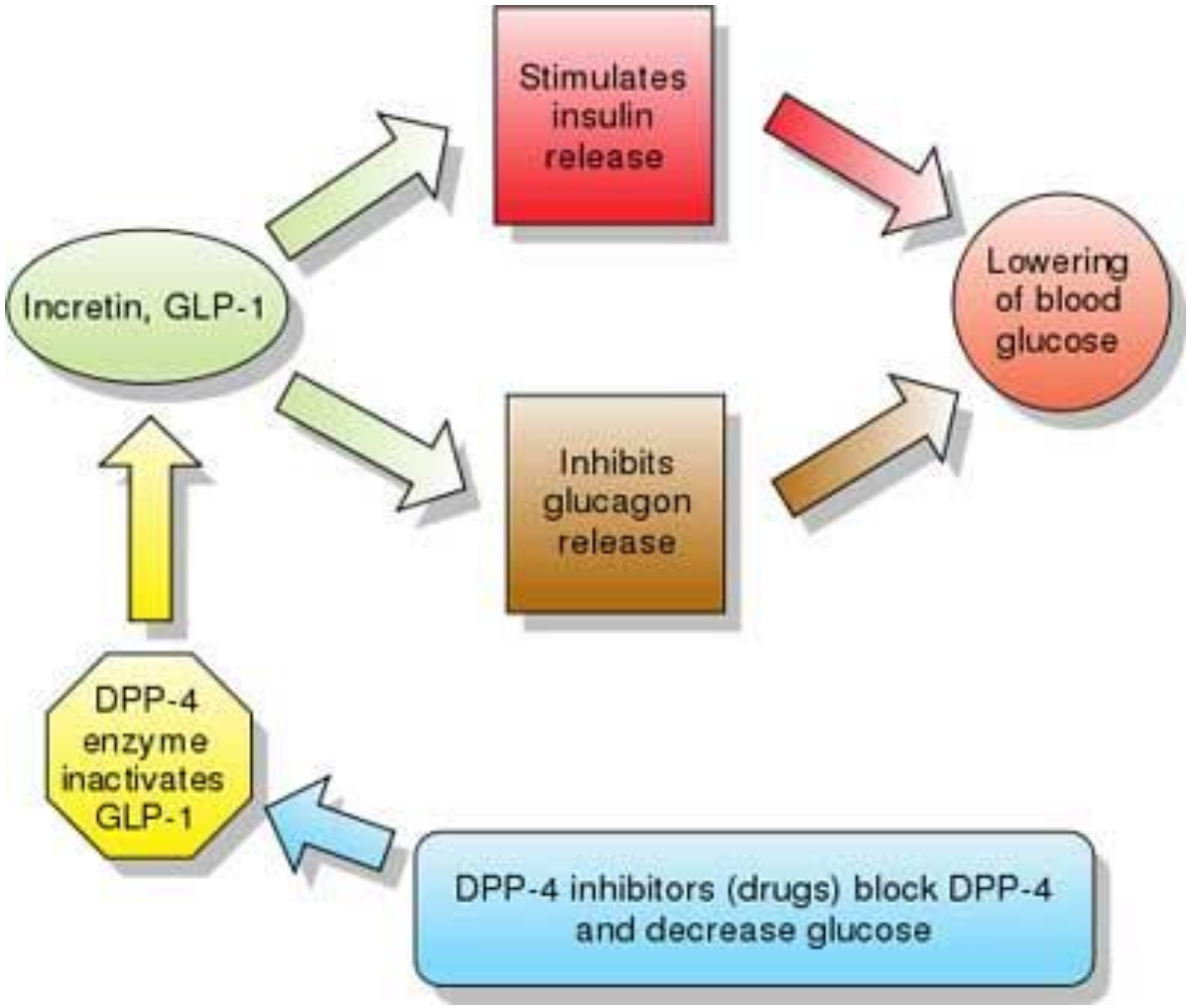
Adiponectin and Alzheimer's

- Adiponectin Resistance
- In the Alzheimer's disease brain, level of insulin and insulin like growth factor-1 (IGF-1) decreases definitely compared to normal brain.
- Adiponectin modulates brain metabolism and sensitivity of insulin, regulating memory and cognitive dysfunction, and it also regulates severe inflammaion observed in mild cognitive impairment and Alzheimer's disease.
- Adiponectin is a potential target to treat Alzheimer's disease.

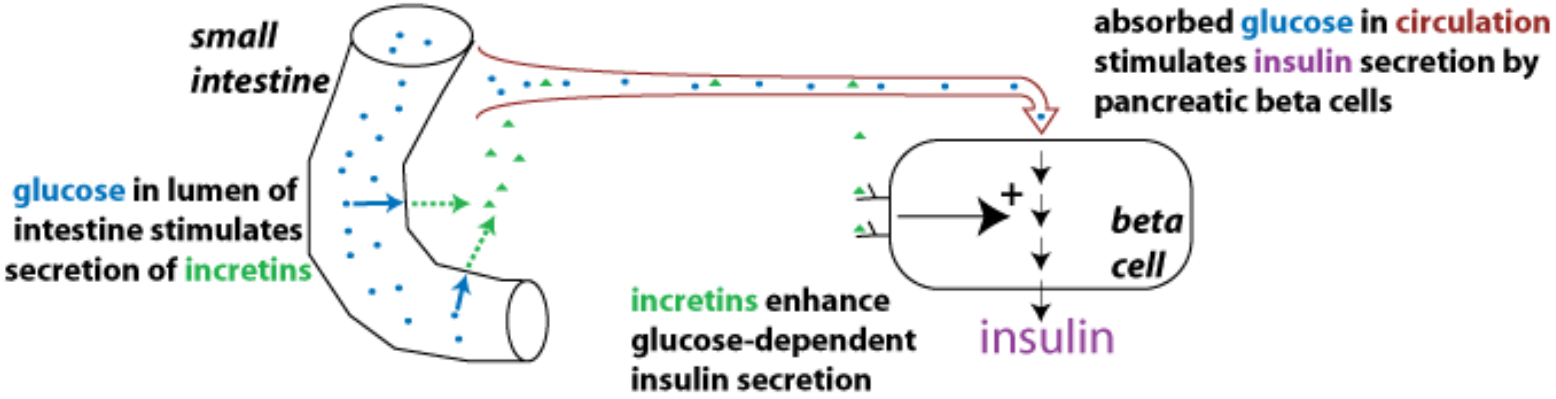
Incretin Effect:

- The incretins are hormones that work to increase insulin secretion and inhibit glucagon release.
- Substantially more insulin secreted in response to oral glucose versus intravenous glucose.
- There are two main incretin hormones in humans, GIP (glucose-dependent insulinotropic peptide; also known as gastric inhibitory peptide) and GLP-1 (glucagon-like peptide-1).
- Both hormones are secreted by endocrine cells that are located in the epithelium of the small intestine.

DPP-4 and GLP-1 Actions



Incretin Effect: GLP-1 and GIP



Dipeptidyl Peptidase 4 (DPP-4) **Inhibitors**

- Sitagliptin - Januvia
- Saxagliptin - Onglyza
- Linagliptin - Tradjenta
- Alogliptin –Nesina

- *DPP-4 inhibitors ("gliptins") prolong the action of native incretins.*

Gucagon-Like Peptide-1 (GLP-1) AGONIST – Incretin Mimetic

- Exenatide (Byetta, Buydurion)
- Liraglutide [rDNA origin] (Victoza)
- Albiglutide (Tanzeum)

- *GLP-1 agonists are peptide drugs with a longer half-life than the native hormone because they are resistant to digestion by the protease DPP-4. DPP-4 inhibitors*
- *GLP-1 delays stomach emptying into the small intestine.*

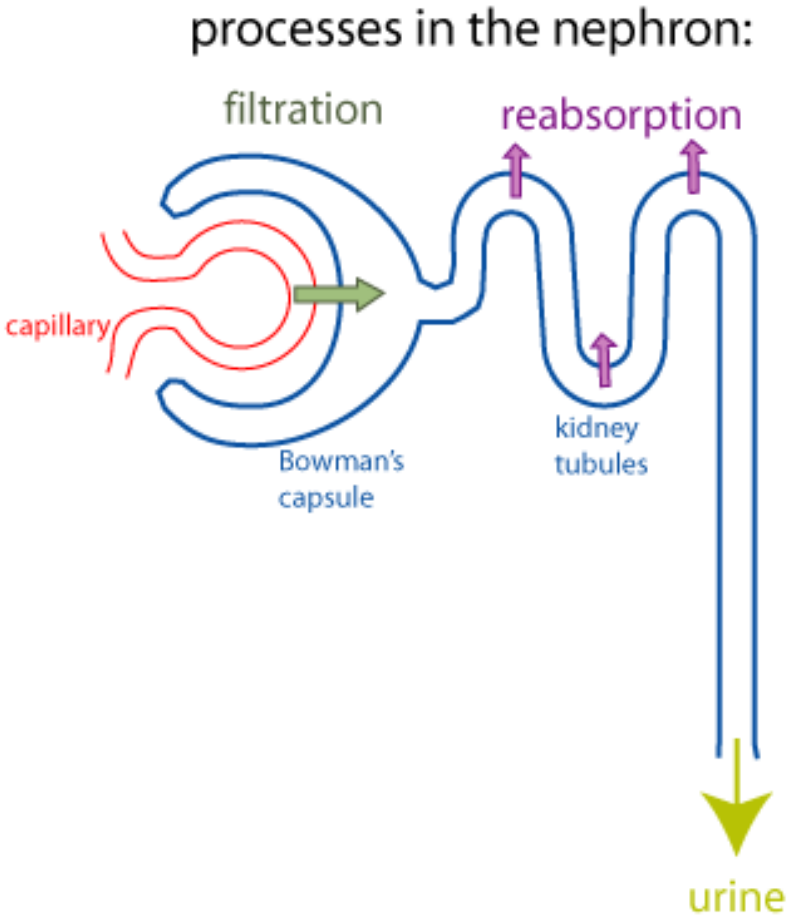
Sodium-Glucose co-Transporter 2 (SGLT2) inhibitors

- **INVOKANA (canagliflozin)**
- **FARXIGA dapagliflozin**
- **JARDIANCE (empagliflozin)**

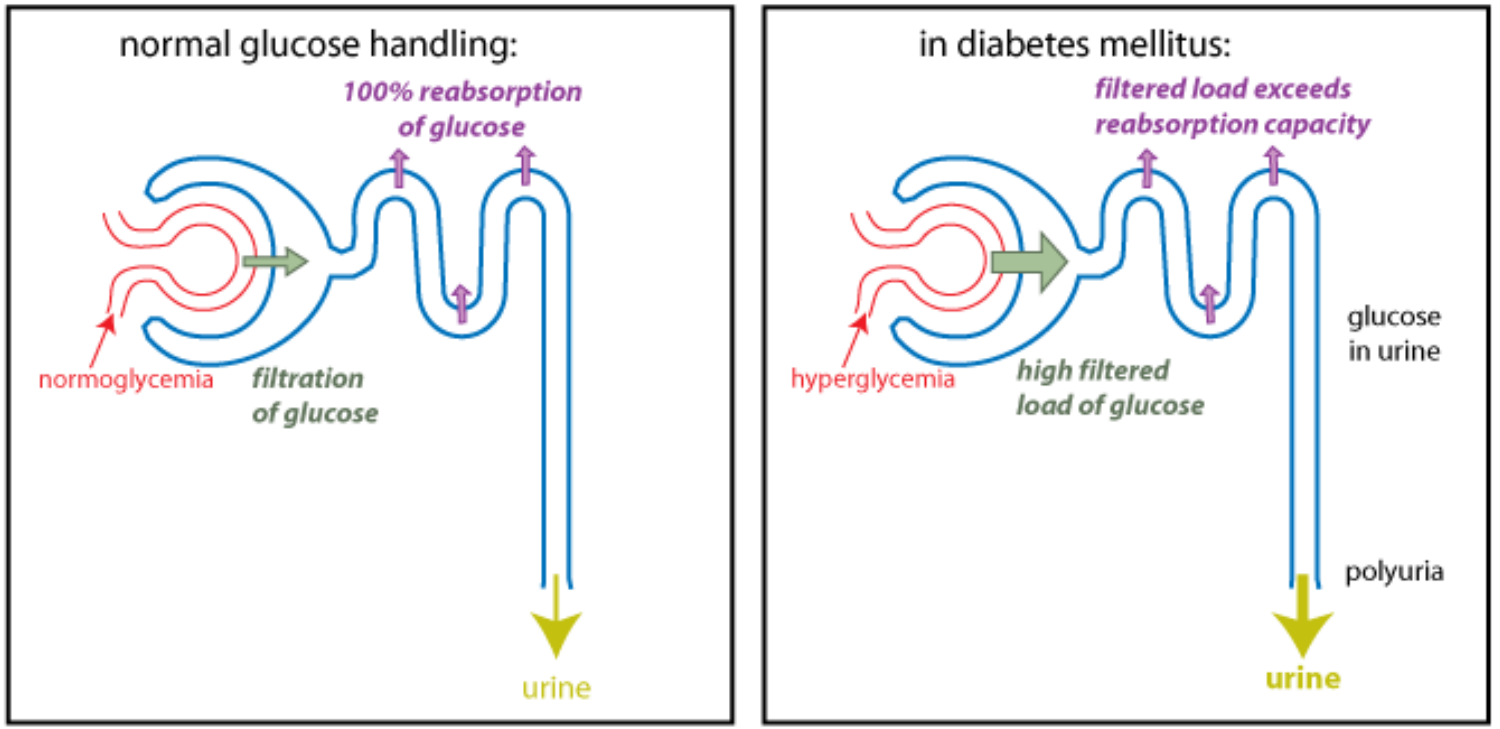
Mechanism of Action of SGLT2 Inhibitors

- Inhibition of renal tubular Na+-glucose cotransporter ➔ reversal of "glucotoxicity."
- SGLT2 is a low-affinity, high capacity glucose transporter located in the proximal tubule in the kidneys. It is responsible for 90% of glucose reabsorption.
- Inhibition of SGLT2 leads to the decrease in blood glucose due to the increase in renal glucose excretion.
- The mechanism of action of this new class of drugs also offers further glucose control by allowing increased insulin sensitivity and uptake of glucose in the muscle cells, decreased gluconeogenesis and improved first phase insulin release from the beta cells.
- Decreased Cori Cycle.

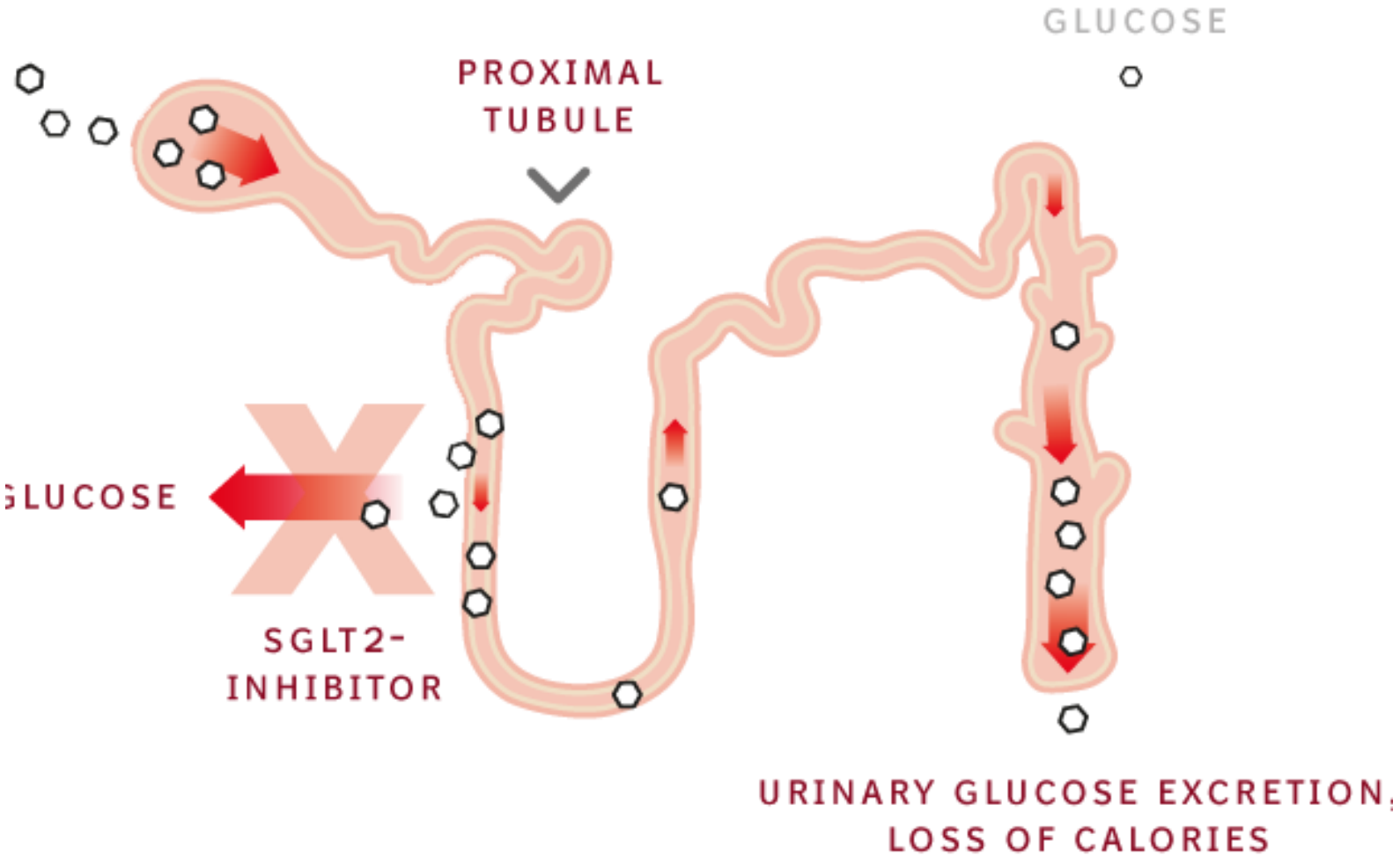
Process in the Nephron



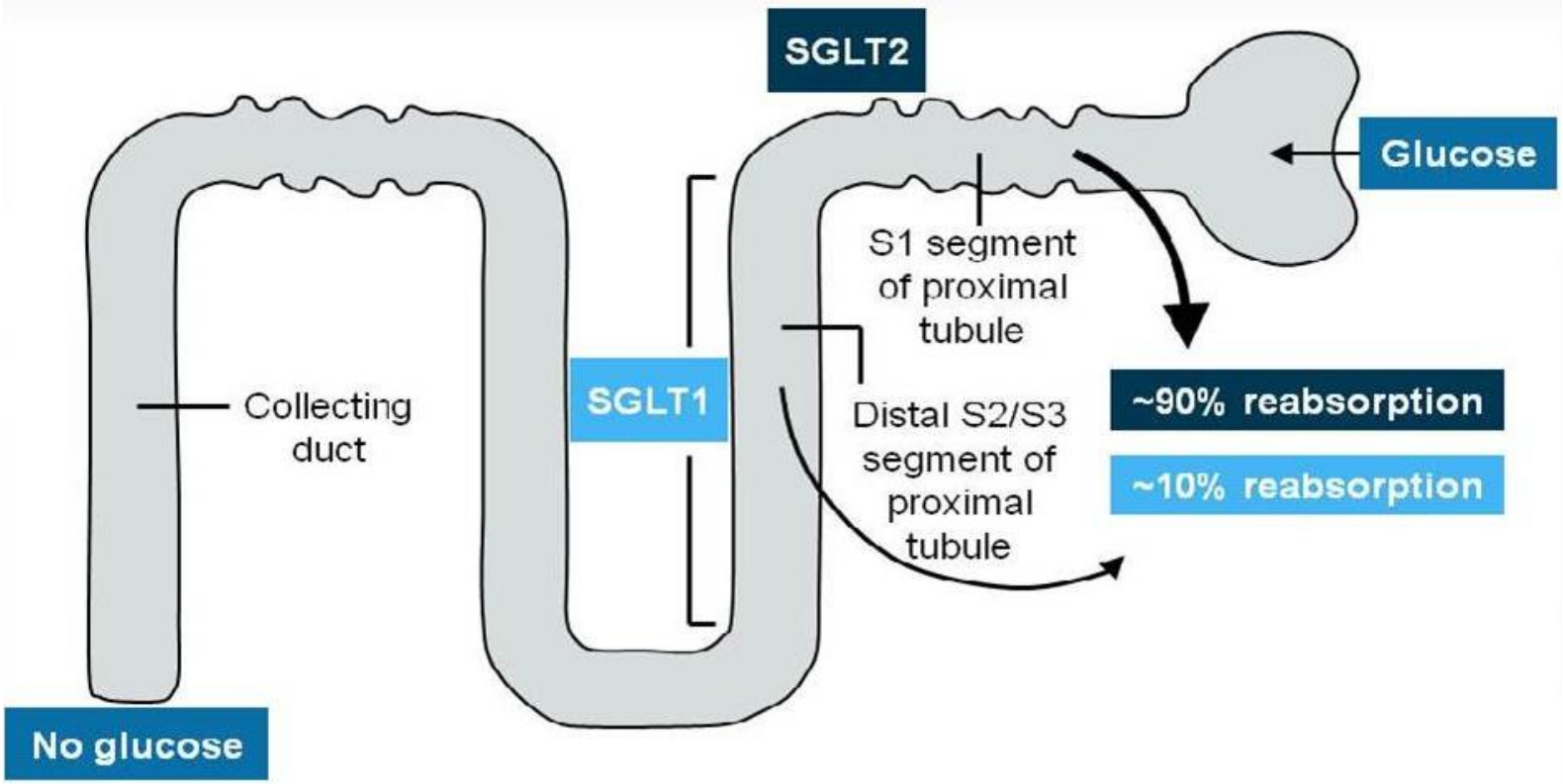
Process in the Nephron



SGLT-2 Mechanism of Action



SGLT2


SGLT2
Glucose
S1 segment of proximal tubule
Collecting duct
SGLT1
Distal S2/S3 segment of proximal tubule
~90% reabsorption
~10% reabsorption
No glucose

Rational Treatment:

- Where to start?
- What to add?
- Lifestyle?
- Education?

"It's what you learn after you know it all that counts."

John Wooden