Newer Classes of Diabetes Medications

Presented by

Bert Mathieson, ND, MA, RD, CDCES

Some History on the Development of Diabetes Medications

- Insulin was fist discovered by Sir Frederick G Banting, Charles H Best, and JJR Macleod at the University of Toronto in 1921.
- Insulin was then extracted from the pancreas of cattle by JJR Macleod and James B Collip.
  https://www.diabetes.org/blog/history-wonderful-thing-we-call-insulin
- Prior to the discovery of insulin most type 1 diabetics did not live more than a year or two.
- We should let that statement sink in for a bit

Flash Forward

- By the late 1950's sulfonylureas came into use
- The first alpha glucosidase inhibitor was approved in the USA in 1995
- Metfomin was also FDA approved in 1995
- I remember working at a diabetes clinic in southern California as a dietitian in 1995 and hearing an endocrinologist say "We finally have another diabetes medication to work with! It's called metformin and they've been using it for years in Europe."

Glinides (Meglitinides) 1997

- Glinides were the next category of diabetes drugs to be approved after metformin
- They were first approved in 1997
- There mechanism of action is similar to sulfonylureas in that they stimulate insulin secretion from the pancreas
- Of note- one medication in that class is derived from benzoic acid which occours naturally in plants (especially berries)
- Another in this glinide is derived from D-phenylalanine

Glitazones 1999

- Then came the first glitazone in 1999. One particular glitazone was very controversial. Some studies showed a connection with heart attacks and heart failure.
- This resulted in multiple law suits for the manufacturer and removal from the market. This drug is currently available again in the USA after additional research disputed the heart failure connection.

“I Want to Get off All these Medications!”

Some general philosophical notes before we take a deep reductionistic dive into the newer diabetes medications:

- If your practice is at all like mine people usually come to me because they want to get OFF medications NOT add more.
- I’ve noted many patients have had time to listen to extensive on-line seminars about natural medicine during the COVID pandemic (“The Truth about This or That”)
- They come in saying “I heard all these things can be treated without medications.”
- In my experience there seems to be a general awakening happening about natural medicine. Many people are curious.
- This sometimes puts NDs in a difficult situation if the patient has unrealistic expectations that they can immediately jump off of all their medications
- Diabetes is a perfect example of this delema
- I try to take these situations as an opportunity to get back to basics and promote the foundations of health (with the carrot that maybe they CAN eventually decrease medication use.)

Realistic Expectations and the Basics

- The basics aren't as flashy as the latest new supplement or medication but they must be in place for diabetes to improve
- It is easy for practitioners to get bored of preaching the basics but we should resist that temptation
- Diabetes treatment (in theory) isn't complicated
- I tell people their are 4 legs on the treatment stool:

1. Diet
2. Exercise/weight management,
3. Medications/supplements,
4. Stress management

- Sometimes we can really help the patient by brainstorming about perceived obstacles to implementing these 4 tools

Realistic Expectations and the Basics

- It is important for type 2 diabetics to know that there is a point of no return at which their beta cells poop out
- if they don't get their blood sugar under control with the basics medications will eventually be needed
- In my experience getting therapeutic inertia going **at the right time** is a real problem with diabetics
- People don't usually "feel" diabetes in the early stages and it is easy to ignore-especially if you are "pre-diabetic."
- The early stages of diabetes is exactly when you can still turn it around and you need get the inertia to do what it takes
- Unfortunately many wait until they have multiple diabetic complications before they start to take it seriously

The New Diabetes Mediations allow more Individualization of Treatment

- “The selection of the best medication or combination of medications for the management of hyperglycemia in patients with T2DM, while based on science, remains to a large degree in the realm of art. Although in some situations the choice of medication is relatively simple, in the majority of situations the decision-making process is complex and does not necessarily lead to a clear-cut choice.”

2019 Guide to Medications for the Treatment of Diabetes Mellitus. American Diabetes Association.

- This sounds a little naturopathic!

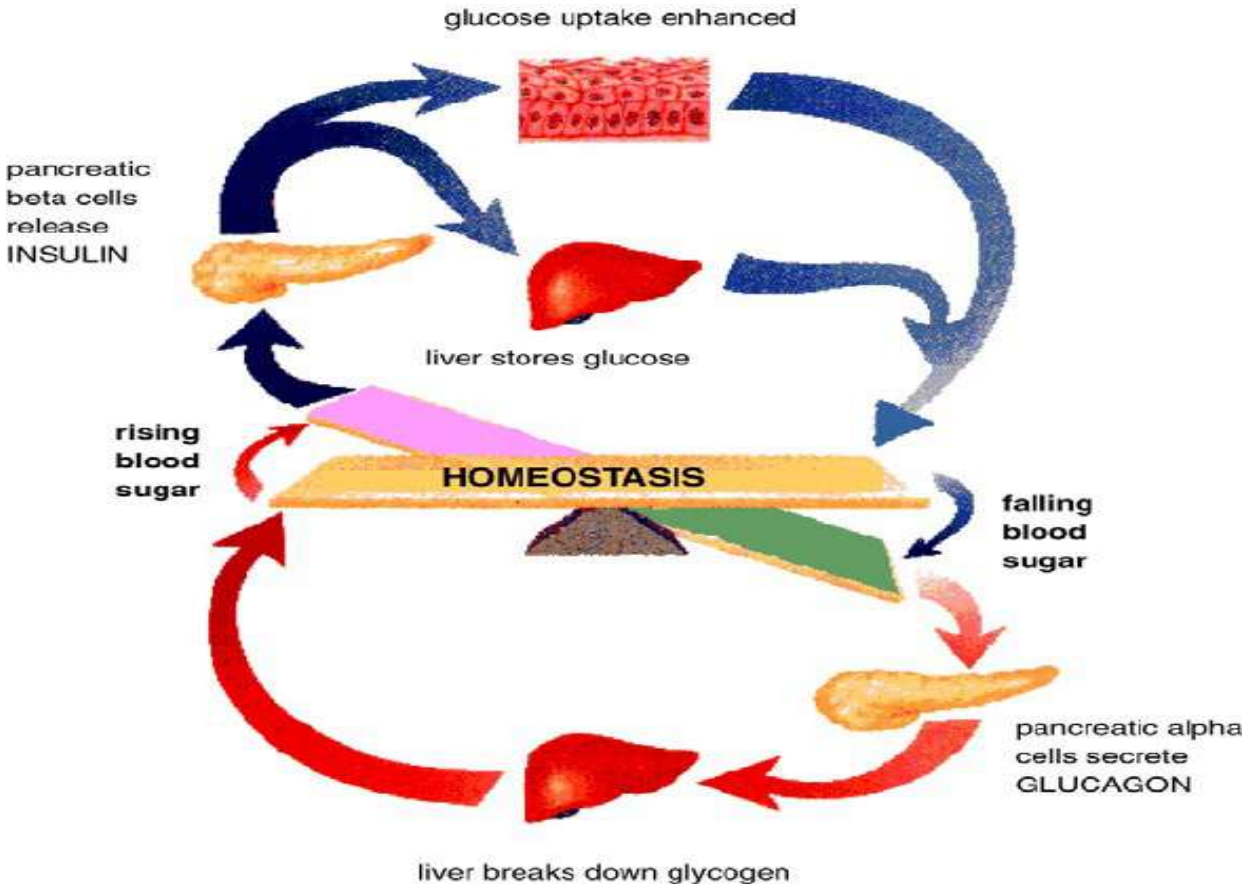
GLP-1 Receptor Agonists

- In 2005 things started to get interesting and the first glucagon-like peptide-1 receptor agonist (GLP-1 RA) was approved
- These are basically “incretin mimetic” drugs
- Incretin hormones are a class of glucoregulatory hormones https://pubmed.ncbi.nlm.nih.gov/24843404/
- GLP-1 (glucagon-like peptide-1) and GIP (gastric inhibitory polypeptide – AKA glucose dependent insulinotropic polypeptide) create the majority of incretin action in our bodies

GLP-1 RA: What's in the Name?

- A quick review of glucagon is in order
- Type I diabetics are encouraged to keep glucagon injections on hand in case their blood sugar goes too low in response to their insulin
- Glucagon is available as an RX in pre-filled syringes
- Glucagon is a hormone produced in the pancreas that causes the breakdown of hepatic glycogen into glucose
- Glucagon production is maladapted in diabetics and they over-secrete glucagon after meals
- This is counterproductive to blood sugar control and results in high postprandial blood sugar

A Review of Glucagon Physiology



Where are GLP-I and GIP Produced?

- GLP-1 and GIP are secreted from The L cells of the Illium and colon in response to the ingestion of food
- They may also be secreted from L cells which are present in smaller number in the upper gut
- This is thought to be true because GIP-I is found in the blood within a few minutes after food ingestion

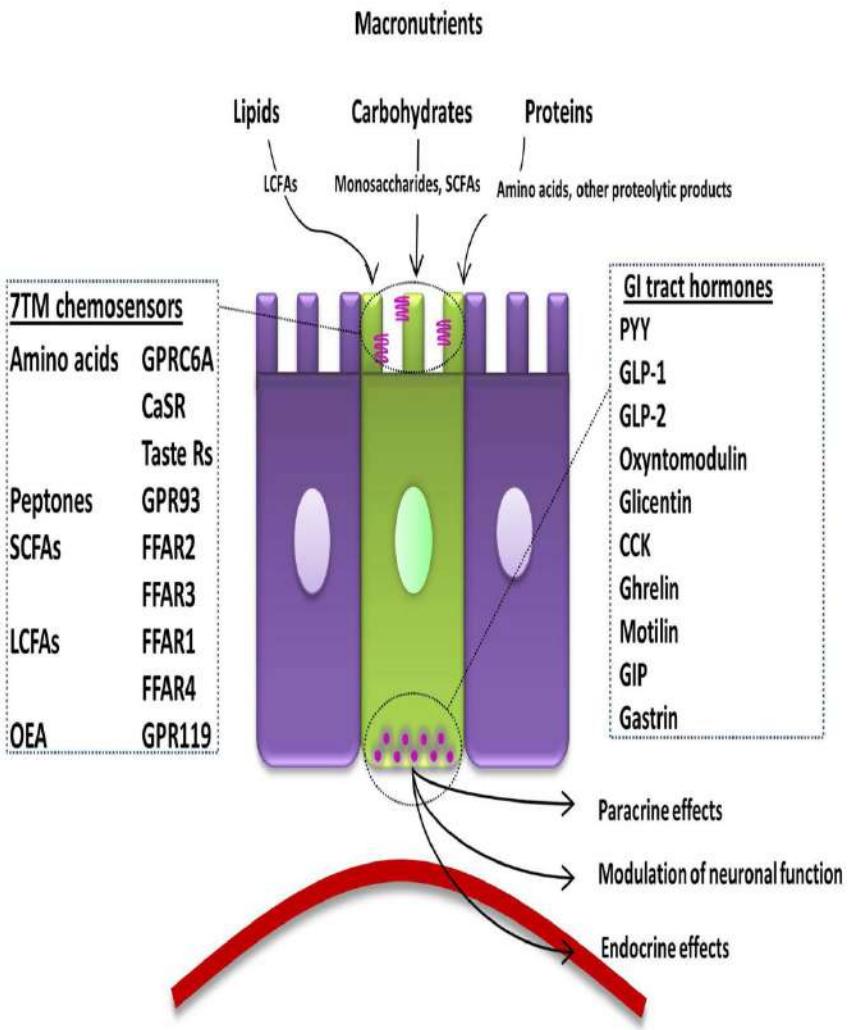
Functions of GLP-1 and GIP

- GLP-1: increases pancreatic Beta cell insulin secretion, slows gastric emptying, and increases satiation
- GIP: slows GI motility and promotes reduced food intake
- "At least part of the gut–brain response seems to be due to direct sensing of macronutrients by L-cells, by mechanisms including specific nutrient-sensing receptors. Such receptors may represent possible pathways to target to decrease appetite and increase energy expenditure. Designing drugs or functional foods to exploit the machinery of these nutrient-sensing mechanisms may offer a potential approach for agents to treat obesity and metabolic disease." https://pubmed.ncbi.nlm.nih.gov/26258126/

What are L Cells?

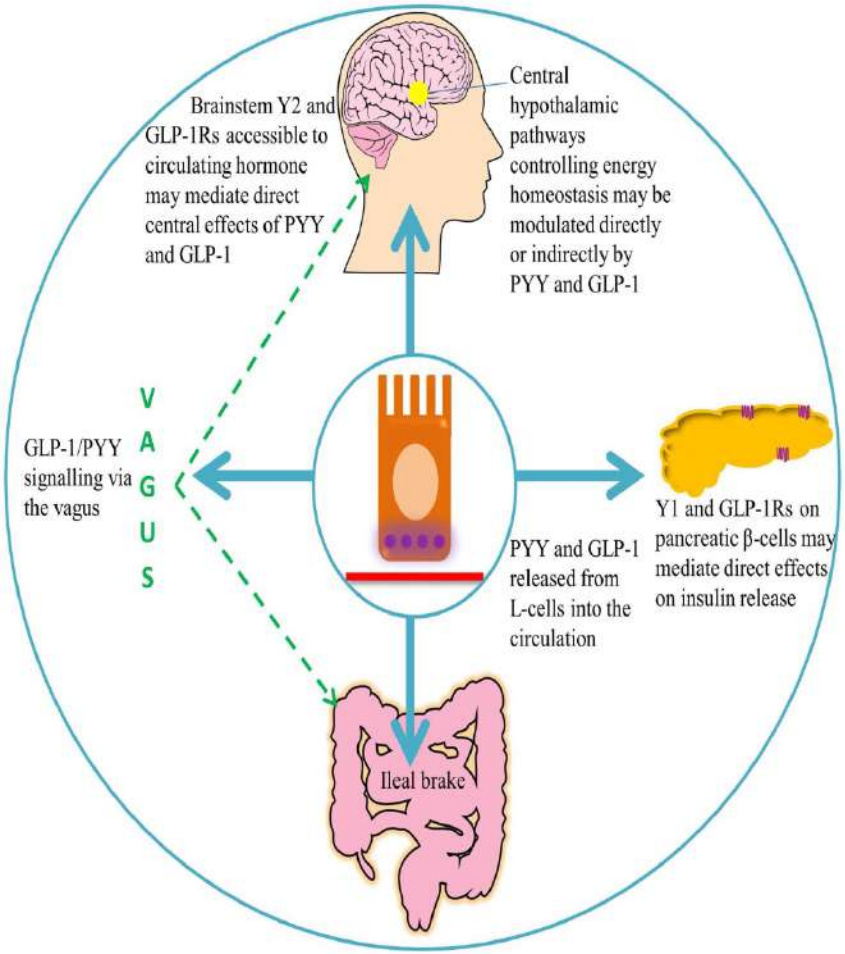
- L cells are a type of “enteroendocrine cell” that form part of the gut-brain axis
- L cells help create satiation after food is ingested
- Trivia: did you know that the GI tract is the largest endocrine organ in the body?
- At first we thought that enteroendocrine cells (EEC) could be neatly categorized. We now know EEC are a broad range of cell types that secrete many different combinations of peptides. Nature outsmarts us again.

The Anatomy of an EEC



- EECs are cone-shaped cells that sense the luninal contents of the GI tract
- Their microvilli are in contact with macronutrients in the lumin through G-protein coupled receptors
- This results in modulation of hormone release

Systemic Effects of GLP-1



- GLP-1 Binds to pancreatic Beta cells
- May communicate though the Vegas nerve with hypthalamic nuclei that affect energy homeostasis
- Circulating hormones can reach the brain directly though parts that have a leaky blood/brain barrier (area postrema)
- Is part of the “illeal break” mechanism that slows digestion of nutrients

Zoom Back Out: An Overview Of GLP-1 RA Medications in Diabetes

- They are not currently recommended as first line agents
- The American Academy of Clinical Endocrinologists (AACE) recommend GLP-1 RAs as the second line agent after metformin
- Some GLP-1 Ras have evidence of cardiovascular prevention are considered the best choices in those with atherosclerotic cardiovascular diseased (ASCVD)
- Thean be combined with other medications such as TZDs, metformin, insulin, and SGLT2 inhibitors

GLP-1 RA Overview Continued

- Not recommended to combine with DPP-4 inhibitors
- Good combination with basal insulin if blood sugar is not controlled with basal insulin
- Good alternative to adding meal-time bolus insulin
- There are combination GLP-1 RA/basal insulin medications for convenience
- Can be used as monotherapy in patients who do not tolerate the first line diabetes medications
- Not yet approved for type I diabetics
- Not recommended in those with gastroparesis
- Given as a sub Q injection twice daily to once weekly

Benefits of GLP-RA Medications

They target several diabetes-specific pathologies:

1) Reduce glucose levels
2) Can help reduce weight (0.3-6.5 kg). Liraglutide was approved by the FDA in 2014 for the treatment of obesity
3) Some meds may have a cardiovascular benefit
4) May preserve pancreatic beta cells
5) Minimal risk of hypoglycemia compared to other medications
6) Have a strong effect on A1C levels (0.4-2.2%.) This is better than DPP-4 inhibitors and similar or better than basal insulin, sulfonylureas, and TZDs.

Disadvantages and Potential Side Effects of GLP-1 RA Medications

- Gastrointestinal side effects (nausea, vomiting and diarrhea) occur in a fairly high percentage of patients and are usually mild
- The shorter acting GLP-1 RAs affect gastric emptying more than the long-acting ones and have more GI side effects.
- GI side effects occur early in the treatment course and then decrease
- There is a subset of patients who can not tolerate the GI side effects
- Cost: out of pocket $500 - $700 monthly
- The need for sub Q injections may inhibit some patients from using them

Disadvantages Continued

- Most GLP-1 RAs have a black box warning regarding a potential increased risk of Thyroid C-cell carcinoma. This was seen in rodent studies and was duration and dose dependent. No reports of thyroid C cell carcinoma have been seen in humans on GLP-1 RAs as of 2019.
- There was some concern with increased risk of pancreatitis. Recent reviews and meta-analysies have NOT seen this correlation. Prescribing info still recommends caution in those with a history of pancreatitis.

More Potential Disadvantages

- The SUSTAIN-6 trial showed an increase in retinopathy with semiglutinide (3% vs. 1.8%: P= 0.02.)
- Among the patients that saw an increase in retinopathy 85% of them had preexisting retinopathy
- Monitor retinopathy carefully if using semiglutinide in a patient with preexisting retinopathy
- Rapid glucose lowering can result in deterioration of retinopathy so it is not clear if the retinopathy effect seen in studies was due the drug or the rapid lowering in blood glucose
- Some post-marketing case reports have shown kidney injury and worsening of chronic renal failure. These are case studies and a cause-effect relationship is not yet established. Perhaps use caution in patient with renal problems.

A Little Naturopathic Relief: Metformin and *Scutellaria*

Combined effects of *Scutellaria baicalensis* with metformin on glucose tolerance of patients with type 2 diabetes via gut microbiota modulation

Abstract

- Metformin is a widely prescribed antidiabetic agent, whereas *Scutellaria baicalensis* (SB) is a commonly used medicinal herb for treatment of type 2 diabetes (T2D). Gut microbiota is involved in pathophysiology of metabolic diseases including T2D, and intestinal microbiota may be one of the important therapeutic targets for the ailment. This study was conducted to investigate the effects of SB combined with metformin on treatment of T2D while evaluating changes in the gut microbiota composition. Patients with T2D were randomized into control and treatment groups. Subjects who had already been prescribed metformin were allotted to additional SB (3.52 g/day) group or placebo group. The initial treatment session was 8 wk, and after washout period for 4 wk they were crossed over to the opposite treatment for another 8 wk. The influence of SB and placebo on the intestinal microbiota was analyzed by MiSeq system based on 16S rRNA gene. Glucose tolerance was lower in the SB group than the placebo group. Similarly, the relative RNA expression of TNF-α was significantly reduced after SB treatment. SB treatment influenced the gut microbiota, especially *Lactobacillus* and *Akkermansia*, which showed remarkable increases after SB treatment. Some subjects showed high liver enzyme levels after SB treatment, and their microbiota composition at baseline differed with subjects whose liver enzymes were not affected. We also predicted that selenocompound metabolism was increased and naphthalene degradation was decreased after SB treatment. These results suggest that SB with metformin treatment may improve the glucose tolerance and inflammation and influence the gut microbiota community in T2D.

https://pubmed.ncbi.nlm.nih.gov/31770016/

Key Findings in the Metformin and *Scutellaria* Study

Key Findings

- "There was a statistically significant improvement in oral glucose tolerance noted in the combined SB/metformin group vs. the placebo group."
- "The gene expression of TNFα (measured as mRNA by real-time polymerase chain reaction [PCR] in blood) showed a statistically significant decrease in the SB/metformin group. There was also a decreased gene expression of IL-6 in the SB/metformin group, but the decrease was not statistically significant."
- "The stool samples from the SB/metformin group showed significantly less *Bifidobacterium* and significantly more *Lactobacillus* and *Akkermansia* than the stool samples from the placebo group."

https://www.naturalmedicinejournal.com/journal/2020-10/shifting-gut-microbiome-people-type-2-diabetes

Clinical Relevance of *Scutellaria* Study

- It is fascinating how much the concept of the human gut as an “ecosystem” has come into vogue with the investigation of the gut microbiota’s effects on just about everything in recent years. It is rather satisfying to see this trend since “treat the gut” has been a common refrain in naturopathic medicine for decades.
- Perhaps we can now effectively harness the power of the gut microbiome to improve outcomes in our patients with type 2 diabetes. Or perhaps we have been doing that for years without knowing? Like a kid in the back of a car, I find myself asking, “Are we there yet?” Can we give a patient with type 2 diabetes a probiotic supplement or an herb to shift their gut microbiota to exert a positive effect on glycemic control?
- Two earlier reviews that addressed this topic essentially concluded that we were not there yet.[1,2] Animal studies appeared promising, but human data were lacking, and the studies were conflicting. However, the current human study does support the idea that shifting the human gut microbiota is a viable way to improve glycemic control.
- Perhaps we can now effectively harness the power of the gut microbiome to improve outcomes in our patients with type 2 diabetes.
- The common tools diabetics have to work with consist of diet, exercise, medication, supplements, stress control, etc. Perhaps we are now in the era when we are realizing that we had another valuable tool all along: the manipulation of the gut microbiota through botanical medicine.

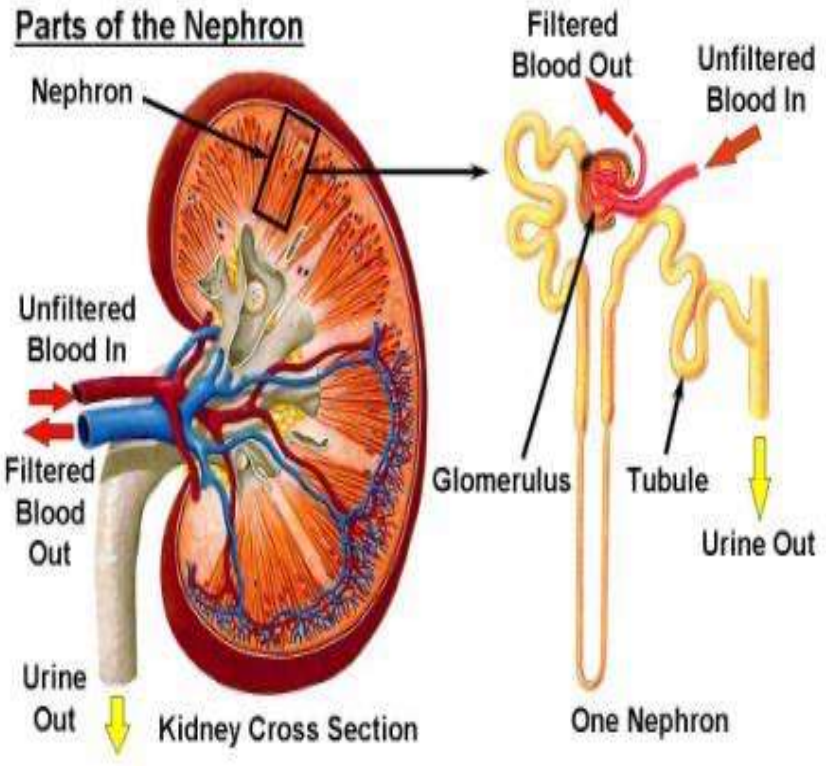
Scutellaria Study Clinical Relevance Continued

- Bodogai et al performed an interesting animal study on "healthy aged" mice and macaques.[3] Their data showed that insulin resistance was provoked by the accumulation of 4BL cells in the gut. The 4BL cells were found to be related to changes in gut commensal bacteria and decreases in the bacterial metabolite known as butyrate. Butyrate is a familiar substance in naturopathic medicine and is sometimes utilized in "gut healing" plans for our patients.
- The proliferation of 4BL cells was caused by interaction with C-C chemokine receptor 2 (CCR2)+ monocytes triggered by gut hyper-permeability and the resulting infiltration of endotoxins into the bloodstream. The gut hyper-permeability was triggered by the depletion of *Akkermansia muciniphila* and reduced butyrate concentration in the gut.
- The interesting thing about the Bodogai et al study was that the resulting insulin resistance was reversible by supplementing the animals with *Akkermansia muciniphila* or using the antibiotic enrofloxacin (which increased the *Akkermansia*). Treatment with butyrate or antibodies to CCR2+ monocytes and 4BL cells also had the same effect.
- In contrast to the Bodogai et al study, the current study under review found that, rather than directly giving a probiotic, you can use *Scutellaria baicalensis* in conjunction with metformin to shift the gut microbiota (specifically *Lactobacillus* and *Akkermansia*) in a direction that positively affects glycemic control and markers of inflammation. I would call this a "positive" medication/herb interaction. The fact that this medication/herbal combination also lowered gene expression of TNFα is another bonus given the inflammatory nature of diabetes.

SGLT2 Inhibitors

- In 2013 the first sodium-glucose transport protein 2 inhibitor (SGLT2 inhibitor) was approved by the FDA
- These drugs act on the kidneys to excrete more glucose thus lowering blood glucose levels
- In the last few decades there has been a growing appreciation of the physiology of the kidneys as it relates to glucose homeostasis

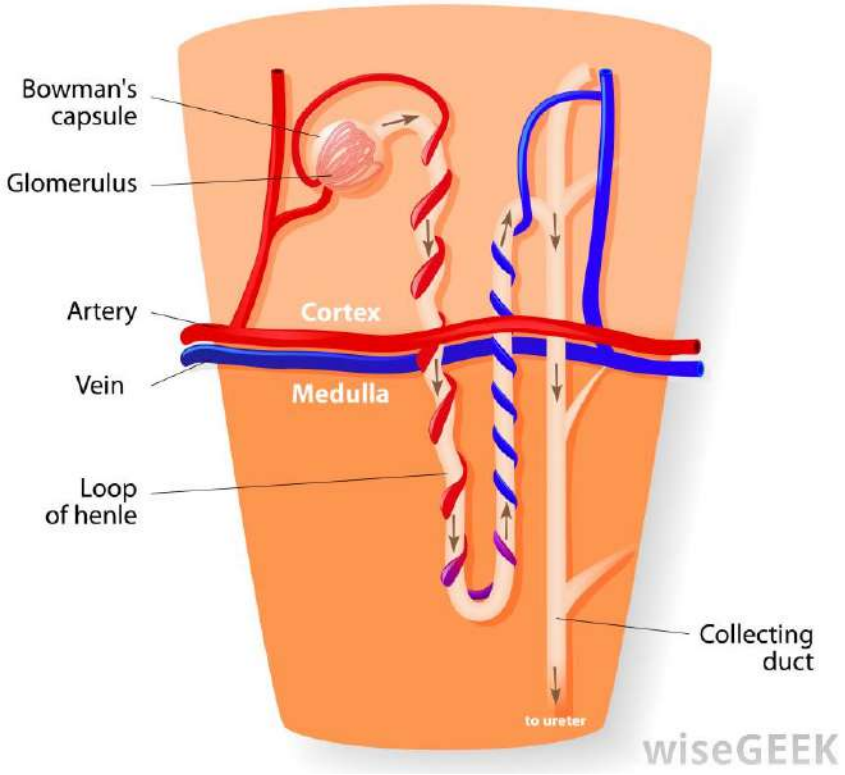
A Review of the Amazing Kidney



A Review of the Amazing Nephron Continued

- The kidneys have 3 sections: the cortex, the medulla, and the renal pelvis
- The renal medulla is arranged into pyramid structures and the bulk of the anatomy of the nephron is in the medulla
- Nephrons are the basic functional unit of the kidney
- Each kidney has somewhere between 800,000 to one million nephrons
- Each nephron is made up of a renal corpuscle and a renal tubule
- The renal corpuscle does the filtering and the renal tubule does the reabsorption
- The corpuscle consists of 1) a glomerulus and 2) Bowmen's Capsule which houses the glomerulus
- The glomerulus is a cluster of capillaries

The Amazing Nephron Continued



- After filtration in the Corpuscle the filtrate flows to the proximal convoluted tubule, the loop of Henle, the distal convoluted tubule, and into the collecting tubule
- 75% of the reabsorption of solids happens in the proximal convoluted tubule (glucose, vitamins, sodium, chloride ions, uric acid, urea, amino acids, lactate, phosphate, etc.)
  https://www.britannica.com/science/human-renal-system/Tubule-function
- The distal tubule is mostly focused on the regulation electrolytes, water, and acid/base balance

The Renal Threshold for Glucose

- The tubules have only so much capacity for reabsorption
- The capacity for reabsorption varies depending on the substance in question
- When blood glucose levels are in a normal range all of the glucose is reabsorbed
- It has been known for many years that if glucose shows up on a urine test the blood glucose has reached a certain threshold and the person has hyperglycemia
- The “renal threshold for glucose” is generally thought to be at about 180 mg/dl of blood glucose
- In effect the SGLT2 inhibitors bypass this physiological control

General Functions of the Kidney in Glucose Homeostasis

The kidneys contribute to blood glucose control by several mechanisms:

1. Glucose reabsorption through the proximal convoluted tubules
2. Gluconeogenesis
3. Glucose utilization
4. Glomerular filtration

- The primary effect of the kidneys on blood glucose control results from glomerular filtration, followed by reabsorption of glucose, followed by excretion of glucose in the urine

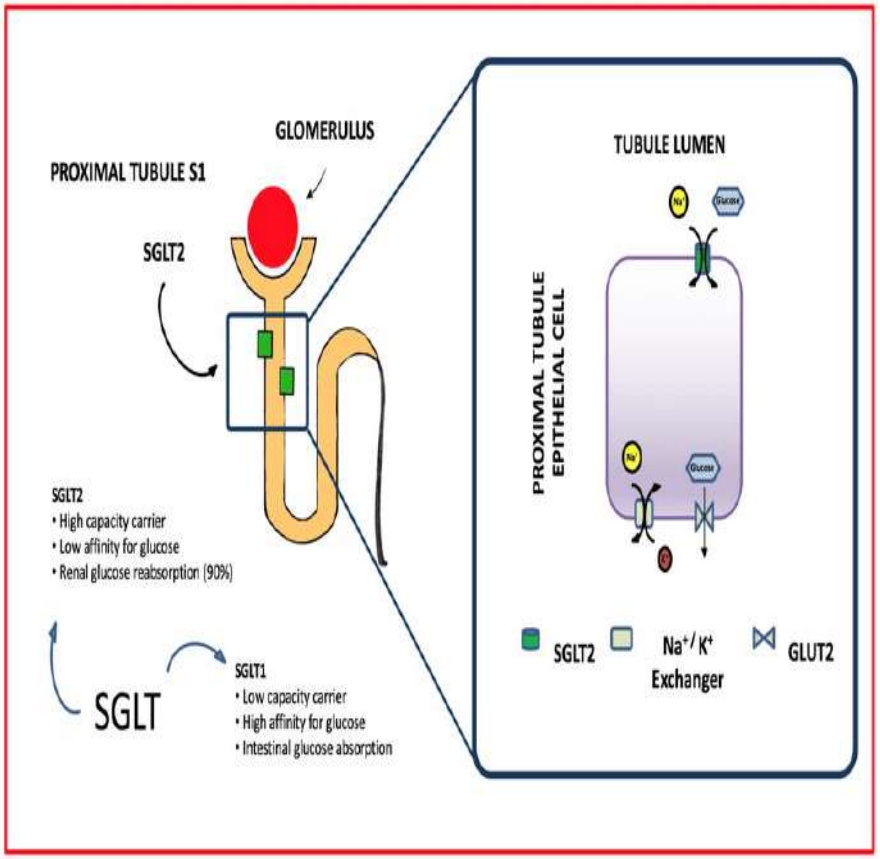
General Functions of the Kidney in Glucose Homeostasis Continued

- Fun fact you may not have learned in school: the kidneys are responsible for 20% of glucose production (gluconeogenesis) that happens in the body
- Glucose production actually INCREASES 300% in Type II diabetics (T2DM) via hepatic and renal production
- This is counterproductive to glucose control
- Unlike in the liver- renal **gluconeogenesi**s INCREASES when we ingest sources of glucose. This is somewhat conunterintuitive.
- In T2DM renal **reabsorption** of glucose also aberrantly INCREASES

The Function of SGLT2 and SGLT1 Membrane Proteins

- An SGLT2 is a sodium- dependent glucose co-transporter
- SGLT2 proteins are found in the S1 segment of the proximal convoluted tubules
- Considered “low affinity and high capacity” transporters that reabsorb 90% of the glucose filtered by the kidneys
- SGLT1 proteins are found mostly in the GI tract and also in the S3 segment of the proximal convoluted tubules
- SGLT1 are high- affinity low-capacity transporters that reabsorb 10% of filtered glucose

How Glucose Gets Back to the Blood after Reabsorption



- After glucose is reabsorbed by SGLT2 and SGLT2 into the proximal tubular epithelial cells it is transported into the interstitium by way of “facilitative glucose transporters” called GLUT1 and GLUT2. From the interstituim it goes back to the blood.

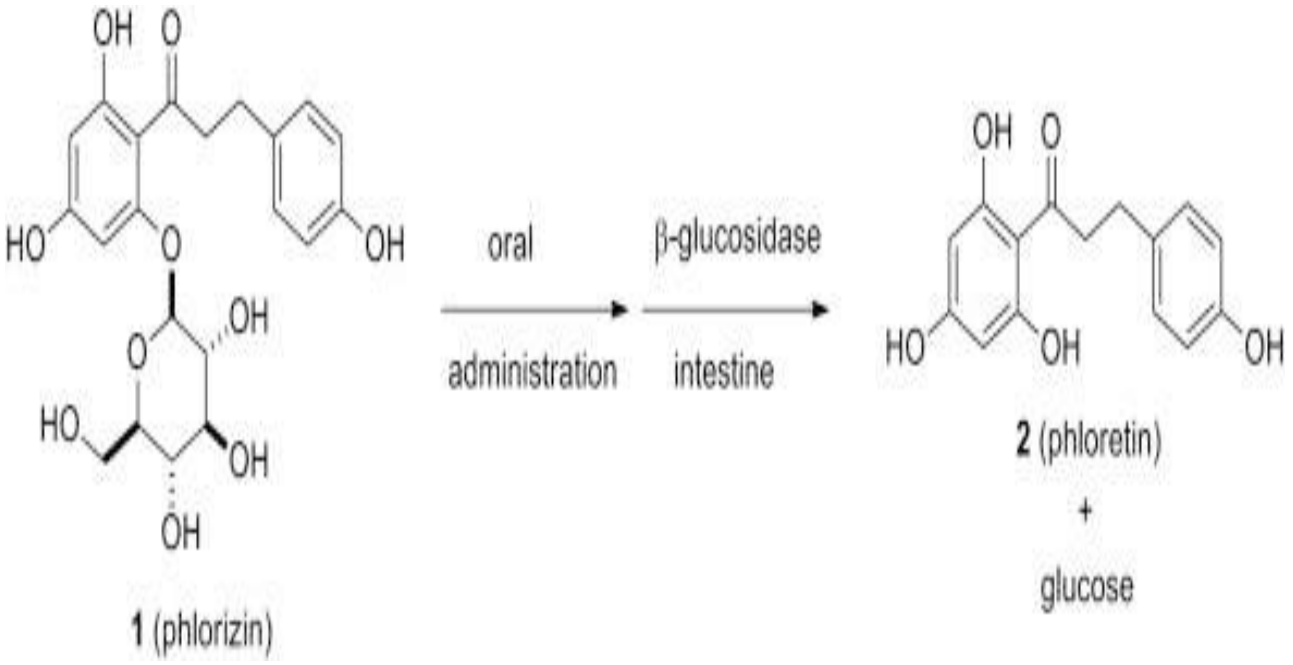
Mechanism of Action of SGLT2 Inhibitors

- SGLT2 inhibitors decrease the action of the SGLT2 membrane proteins and allow the kidneys to excrete (rather than reabsorb) more glucose than is usually possible
- They increase urine glucose excretion (UGE) by 30-50% by essentially lowering the renal threshold for glucose excretion
- As of 2019 there was a “mixed SGLT2/ SGLT1 inhibitor being developed that would act both in the kidneys and the GI tract

SGLT2 Inhibitors are Analogs of Phlorizin

- Phlorizin is a naturally occurring compound found in the bark of fruit trees including pear, apple, and cherry https://www.sciencedirect.com/topics/neuroscience/phlorizin
- The bioavailability of oral Phlorizin is limited because it is converted in the gut into phloretin (which is less active) and thus it would require large oral doses
- Enter the synthetic "flozins" or SGLT2 Inhibitor drugs

Phlorizin Chemical Structure Just in Case You Were Interested



Functional Foods from Apple Pomace?

- “Apple pomace is one of the most abundant wastes; in fact, 10 million tons are produced every year worldwide. It consists of pulp, peels, seeds, and stalks generated from apple juice production [8]. The use of apple pomace for fortification purposes has been investigated in bakery products, such as cakes, muffins, cookies, bread, biscuits, crackers, and extruded snacks; in the enrichment of dairy products, such as yoghurt and ice cream; in apple juice, and in meat products such as chicken patties and beef jerky [9,10].” https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8307736/

Apple Pomace Continued

- “Moreover, the important role against diabetes of the phenolic compounds of the apple, for their anti-hyperglycemic effects, has also been reported [3]. These authors claimed the ability of young apple’s polyphenols to retard the postprandial blood glucose and insulin levels in mice for both acute and 1-week intervention trials. In fact, phloridzin is a well-known competitive inhibitor of glucose transporters (SGLT1 and SGLT2) through the binding of the glucose moiety to the Na+/glucose co-transporter [4].” https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8307736/

Advantages of SGLT2 Inhibitors

- This class of drugs has been fairly well received and are in wide usage
- Usually give about a 0.8% reduction in A1C as compared with a placebo if used alone
- When used in combination with other hypoglycemic meds they give about a 0.6% reduction in AIC
- Most studies show they produce weight loss
- Weight loss has been up to 4.7 kg but it is variable depending the characteristics of the groups studied
- They may have positive effects on the renal and cardiovascular systems
- The EMPA-REG study showed a 14% risk reduction in death from cardiovascular death, nonfatal MI, and stroke for on of he SGLT2 Inhibitors

SGLT2 Inhibitor Advantages Continued

- This study led the American Diabetes Association to recommend that an SGLT2 Inhibitor be the next step for T2DM after lifestyle/diet changes and metformin
- In one study the risk progression of chronic renal disease and death from a cardiovascular event significantly decreased for patients on a particular SGLT2 Inhibitor. www.nejm.org/doi/full/10.1056/NEJMoa2024816
- This effect held true in those with and without type T2DM
- SGLT2 Inhibitors have a low risk of hypoglycemia as a side effect

Disadvantages and Potential Side Effects of SGLT2 Inhibitors

- They are expensive (about $517 dollars per month.) This is less than the GLP-1 RAs but more than most other hypoglycemic meds
- There is a black box warning for Canagliflozin regarding an increased rate of lower limb amputations
- The CANVAS-R study showed 7.5 lower limb amputations per 1000 patients in the treatment group vs. 4.2 in the placebo group https://www.nejm.org/doi/full/10.1056/NEJMoa1611925
- There have been cases of kidney injury reported
- This effect is probably due to the diuresis they cause resulting in blood volume contraction and a decrease in glomerular filtration rate
- The people at greatest risk for acute kidney injury are those with decreased GFR, low systolic blood pressure, on loop diuretics and those on renin-angiotension-aldosterone system medications

Potential Side Effects of SGLT2 Inhibitors Continued

- It is recommended that blood volume status should be investigated and corrected if needed before starting an SGLT2 Inhibitor
- Increased risk of diabetic ketoacidosis (DKA) which is greater in those patients on insulin
- One study showed a 9.4% increase of DKA in type I diabetics
- A recent review of literature concluded that the benefits of using SGLT2 Inhibitors in Type I diabetics outweigh the risks
  https://www.cureus.com/articles/38219-use-of-sodium-glucose-co-transporter-2-inhibitors-in-type-1-diabetics-are-the-benefits-worth-the-risks
- The benefits were perceived to be: Improved arterial function, glucose control, A1C, blood pressure, GFR, and the promotion of weight loss

A Review of DKA

- DKA is a hyperglycemic emergency that we should be cognizant of when dealing with our patients who have diabetes
- A diagnosis of DKA includes 3 factors: high blood sugar, high ionic gap representing metabolic acidosis, and high urine or blood ketones
- Treatment includes: restoring blood volume, insulin, electrolyte replacement, and addressing the cause https://www.nature.com/articles/s41572-020-0165-1#author-information
- It can be fatal and needs to be addressed quickly

Potential Side Effects of SGLT2 Inhibitors Continued

- Glucosuria is a known risk factor for urogenital infections
- Because SGLT2 Inhibitors induce glucosuria the risk of urinary tract and genital infections is increased
- A recent retrospective cohort study in 21,444 SGLT2 Inhibitor users 66 years of age or older showed a 2.27 fold increased risk of genital yeast infections after 30 days of use https://pubmed.ncbi.nlm.nih.gov/31264755/
- This risk is greater in women
- Perhaps providing prophylactic antifungal herbals may be a good idea in our patients on these medications?

An SGLT2 Inhibitor Case Study

- A 59 year old man with a 20 year history of T2DM presented to my office with an infection in his shin that had developed cellulitis
- He had been on Meformin for 5 years but his A1C had recently gone up from the 8.0 to 11.0
- He felt that Meformin was not helping and he wanted to get off of it and "go the natural route."
- He heard some lectures online from an ND regarding nutrients/herbals that can improve glycemic control.
- He wondered if he was taking enough chromium.
- He then had a phone consult with the online ND who recommended that the patient see an ND in person to look at his shin

SGLT2 Inhibitor Case Study Continued

- His history quickly revealed a love for rice and beans, a lack of exercise due to time constraints from his job, and the responsibility of taking care of grandchildren
- He needed education to determine exactly which types of foods contained carbohydrates and at what levels
- He made it quite clear that he did not want to use any medications for cholesterol or blood pressure
- Physical exam revealed: hypertension, 50# over optimal weight, and a 5” X 2” area of cellulitis on his left shin
- Labs revealed: hyperlipidemia, elevated HS-CRP, A1C of 10.8, and mildly reduced renal function

SGLT Case Study Continued

- We discussed dietary changes that he thought he could realistically follow
- I trained him on “carbohydrate counting” and set a daily maximum carbohydrate goal
- He was resistant to adding any exercise to his already overloaded schedule with many non-negotiable responsibilities
- I prescribed an oral antibiotic for the cellulitis and asked him to follow up with me by phone twice in the next week to let me know if it was healing
- He was not maxed out on his dosage of metformin so we increased his dosage
- The cellulitis healed well over the next couple weeks
- Two months later his A1C was still 9.0 and we discussed the possibility of using an SGLT2 inhibitor

SGLT2 Case Study Continued

- We discussed the potential weight loss, cardiovascular and renal protective effects that have been seen with SGLT2 inhibitors and it seemed like a good fit for him so I gave him and RX
- We decided NOT to use canagliflosin since that particular med had been associated with increased rate of lower limb amputations (which seemed like a poor choice for someone prone to lower limb cellulitis) and I prescribed another SGLT2 Inhibitor instead
- I gave him a nutrient/herbal plan to help with his hyperlipidemia and hypertension and discussed dietary manipulations for both of those conditions
- We discussed ways to fit time-efficient exercise into his schedule
- We will see if he filled the RX at his next follow up

Dipeptitdyl Peptidase-4 Inhibitors

- The first DPP-4 Inhibitor was approved by the FDA in 2006
- This class of meds functions by inhibiting the proteolytic breakdown of a class of glucregulatory hormones know as incretin hormones.
- As discussed earlier GLP-1 and GIP are also incretin hormones and
- Review: GLP-1 and GIP account for 90% of incretin (a class of glucoregulatory hormones) hormones and stimulate 60% of the post-prandial insulin response from the pancreas. 2019 Guide to Medicaitons for the Treatment of Diabetes Mellitis. American Diabetes Association.
- GLP-1 and GIP are produced in the L cells of the distal illium and colon. L cells are a type of “enteroendocrine cell” that form part of the gut-brain axis

What is DPP-4?

- DPP-4 is an enzyme that breaks down the incretin hormones GLP-1 and GIP
- Inhibiting DPP-4 results in more GLP-1 and GIP being in the system
- Review: the net results of increased levels of these glucoregulatory hormones is: increased secretion of insulin after eating, decreased secretion of glucagon, and slowing of gastric emptying
- All this results in better glycemic control
- The bottom line is that DPP-4 Inhibitors act on same glucoregulatory system as GLP-1 agonists but in a different way

GLP-1 RAs and DPP-4 Inhibitors are All about the Gut-Brain Axis

- The “gut brain axis” has gotten a lot of attention of late
- GLP-1 is an example of a peptide with gut-brain axis effects
- “Peptide therapy” is getting increased attention in some natural medicine circles
- Body Protection Compound 157 (BPC-157) is an example of another peptide that affects the gut-brain axis https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5333585/
- BPC-157 is present in human gastric juice and is proposed to have many medical applications. This is available as a supplement and is starting to be more widely used predominantly as an immune-modulator.

The General Role of DPP-4 Inhibitors

- DPP-4 Inhibitors are used in T2DM usually combined with other meds such as TZDs, metformin, SGLT-2 inhibitors, insulin, or sulfonylureas
- DPP-4 Inhibitors can be taken orally as opposed to GLP-1 RAs which must be injected because they are degraded in the GI track
- DPP-4 inhibitors are not approved for Type 1 diabetes
- They have a modest effect on A1C compared to other diabetes medications

Advantages of DPP-4 Inhibitors

- This class of meds is well tolerated by most patients
- There are some DPP-4 Inhibitor combination products available making dosing more convenient (-ie- alogiptin/metformin, linagliptin/empagliflozin, etc.)
- DPP-4 inhibitors have a glucose-dependent mechanism of action as opposed to injected insulin which works whether or not you have ingested glucose
- Given this mechanism of action they have a relatively low risk of hypoglycemia
- DPP-4 inhibitors do not promote weight gain

Advantages of DPP-4 Inhibitors Continued

- DPP-4 inhibitors are given once daily so they are more convenient than many other diabetes meds
- A review study concluded that they DPP-4 inhibitors are a cost effective add-on medication for patients who have not reached glycemic goals with monotherapy as compared to adding in sulfonylureas or insulin https://pubmed.ncbi.nlm.nih.gov/25736235/
- This conclusion was reached because of the significant costs involved in treating the side effects of weight gain and hypoglycemia associated with sulfonylureas and insulin

Most Common Side Effects of DDP-4 Inhibitors and Suggested Monitoring

- A study with 8,500 patients showed that 4.2% developed an upper respiratory tract infection, 4.2% headaches, and 4.4% naso-pharyngitis https://onlinelibrary.wiley.com/doi/10.1111/1440-1681.12455
- Periodic monitoring of A1C
- Self monitoring of glucose levels is recommended although the risk of hypoglycemia is low
- Periodic renal and hepatic function testing should be done while using DPP-4 Inhibitors

Disadvantages and Potential Side Effects of DPP-4 Inhibitors

- The DPP-4 inhibitors have NOT shown any benefit in preventing the adverse cardiovascular events associated with diabetes
- This is in contrast to the GLP-1 RAs which have shown some evidence of cardiovascular prevention and are considered the best choice for diabetics with ASCVD
- One meta-analysis showed DPP-4 inhibitors may increase the risk of heart failure https://pubmed.ncbi.nlm.nih.gov/24750644/
- These meds have warnings/precautions on their labels about heart failure-related symptoms but it is not at the level of a “black box warning”

Disadvantages and Potential Side Effects of DPP- Inhibitors Continued

- There have been case reports of pancreatitis with DPP-4 inhibitors and
- they have a warning about pancreatitis risk in their prescribing information
- Several studies have looked at this issue and have seen an increase in cases of pancreatitis with DPP-4 inhibitors but the increase was NOT statistically significant so there does not appear to be a large risk
- Renal and hepatic complications can ocour with some of the DPP-4 inhibitors
- https://www.nejm.org/doi/10.1056/NEJMoa1305889?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%20%200www.ncbi.nlm.nih.gov
-

Renal and Hepatic Considerations for Specific DPP-4 Inhibitors

- The dose of sitagliptin may need to be adjusted for reduced renal function because it is mostly eliminated through the kidneys
- Renal function should be a known quantity before a patient starts sitagliptin 2019 Guide to Medications for the Treatment of Diabetes Mellitus. American Diabetes Association.
- There have been some reports of liver failure associated with alogliptin
- Liver function tests should be performed if a patient is considering startng alogliptin

The Issue of Therapeutic Inertia: A Case Study

- In 2012 a 57 year old woman presented to my office with chief concerns of “High blood sugar, poor sleep, and left knee pain”
- She had sub-clinical hyperthyroidism, osteoarthritis, PCOS, and a history of T2DM
- Her A1C was previously at 13 before she had recently started making diet and lifestyle changes
- and she stated she was motivated to get back on track
- She had a job that she found very stressful and it she felt it had become an obstacle to self care
- Her current A1C was 9.5
- Her maximum adult weight was 260 # and she was now at 185#
- She stated that she did “not want to use any drugs”
- We discussed some of the basics such as exercise and carbohydrate counting and did a body composition analysis

Therapeutic Inertia Case Study Continued

- I started her on alpha lipoic acid and an herbal/nutritional blood sugar support formula
- I asked her to record her blood sugar levels, food intake, and exercise in preparation for several diabetes education visits
- We set a goal of lowering her A1C to 8.0 within 3 months with an ultimate goal of 7.0
- We agreed that if her average postprandial blood sugars were not below 170 within one month she would start metformin
- We met several times over a month for ongoing diabetes education and diet diary/blood sugar record review
- I asked her to test her blood sugar 3X per day to note patterns
- She kept good diet and blood sugar records and her postpraindial blood sugars were varying between 140-212 depending on her meals and exercise levels
- Her fasting blood sugars were 139-183
- This was a good experiment for her to see how she reacted to specific meal compositions

Overcoming Therapeutic obstacles: the Next Steps

- Within a month she was making steady progress lowering her postprandial blood sugars but she had not yet met our blood sugar goals so we started metformin 500 mg qd
- It took her quite a while to work up to even 500 mg of metformin due to gastric upset sometimes associated with the medication
- At our next follow up she started an additional blood sugar support tincture
- she started physical therapy, acupuncture, and joint support supplements for her knee pain (osteoarthritis) which was inhibiting her ability to exercise
- She followed up again in a month to discuss increasing metformin and to retest her body composition in the hope that her diet/exercise and lifestyle changes were paying off

Overcoming Therapeutic Obstacles Continued

- At our next follow up her blood sugars had continued to improve, she was able to get to 500 mg bid of metfomin, her body composition had improved slightly, and she had been able to exercise more due to a reduction in knee pain
- She was still having trouble nailing down her dietary changes due to her busy shedule
- She had a temporary setback in blood sugar due to a brief prescription of steroids for knee pain from her PCP
- We agreed to follow up in 3 months and by that time her blood sugar was in good control
- In 2013 we followed up several times to work on her subclinical hyperthyroidism and to monitor her blood sugar
- In 2014 she started to slide back on her exercise and diet, started to gain weight again, and her average blood sugar was 145-155.

The Ebb and Flow of Therapeutic Inertia

- She was lost to follow up until 2017 at which time her job stress had increased and she felt like she “had to get back on track” with her diabetes
- She had been put on basal insulin and meal time quick-acting insulin by an endocrinologist at that point
- She was concerned that she was learning how to “feed her insulin” because it was too easy to take insulin to control her blood sugar if she overate
- She had gained significant weight from “feeding her insulin”
- She felt she needed accountability to get back on track with foundational dietary, exercise, and stress management habits
- Next time I saw her she was also on an SGLT inhibitor, had been able to decrease her insulin, and was seeing some weight loss

T2DM Can Be More Than Meets the Eye: a Case Study

- A 59 year old man presented to my office who had been DX with T2DM in 2014
- He was thin and didn't fit the typical T2DM picture
- His A1C in 2014 had been in the low range for diabetes and his PCP was more concerned about his cholesterol levels and prescribed a statin which the patient did not take
- He changed his diet and started exercising more which made him "lose too much weight"
- He brought up the possibility of Latent Autoimmune Diabetes of Adulthood (LADA) with his endocrinologist and was told "not to worry about it"

More than Meets the Eye Continued

- He was put on metformin which kept his blood sugar in control for a year
- He felt like he “skipped the pre-diabetes range and went right to diabetes”
- He was then put on a GLP-1 RA injection once weekly
- He liked this for the convenience but could not tolerate the GLP-1 RA due to the GI side effects
- Started on a combination mediation which contained metfomin and a DPP-4 inhibitor
- This combination lowered his average blood sugars from the 300’s to the 200’s
- He had done lots of experimentation with diet changes and exercise and found that nothing was controlling his blood sugar (even fasting for 2 days and exercising while fasting.)
- He was very frustrated that his endocrinologist kept telling him to change his diet and start exercising

Time to Look a Little Deeper

- I ran some labs: beta 2 microglobulin (a urine marker that is a sensitive measure of kidney compromise), thyroid labs, C-peptide, insulin, A1C, vitamin D, glutamic acid decarboxylase antibody (GAD), and a Cardio IQ panel
- Noted C-peptide and insulin were on the low end, GAD was high, TPO was slightly elevated, and beta 2 microglobulin was slightly elevated
- We determined that he had LADA and his thyroid peroxidase antibodies spoke of early autoimmunity

LADA it Is

- Given the LADA his blood sugars were starting to react more like a type I diabetic which is why he was having poor success with diet, lifestyle, and T2DM medications
- I started him on 10 units of basal insulin nightly and educated him about the (low) risk of hypoglycemia on basal long-acting insulin
- We started on a plan to decrease potential triggers of autoimmunity with the hope of slowing down the autoimmune process
- He restarted metformin only 500 mg bid since he tolerated metformin better than either the DPP-4 Inhibitor and the GLP-1 RA
- We will follow up after 2 weeks on insulin and see how it goes

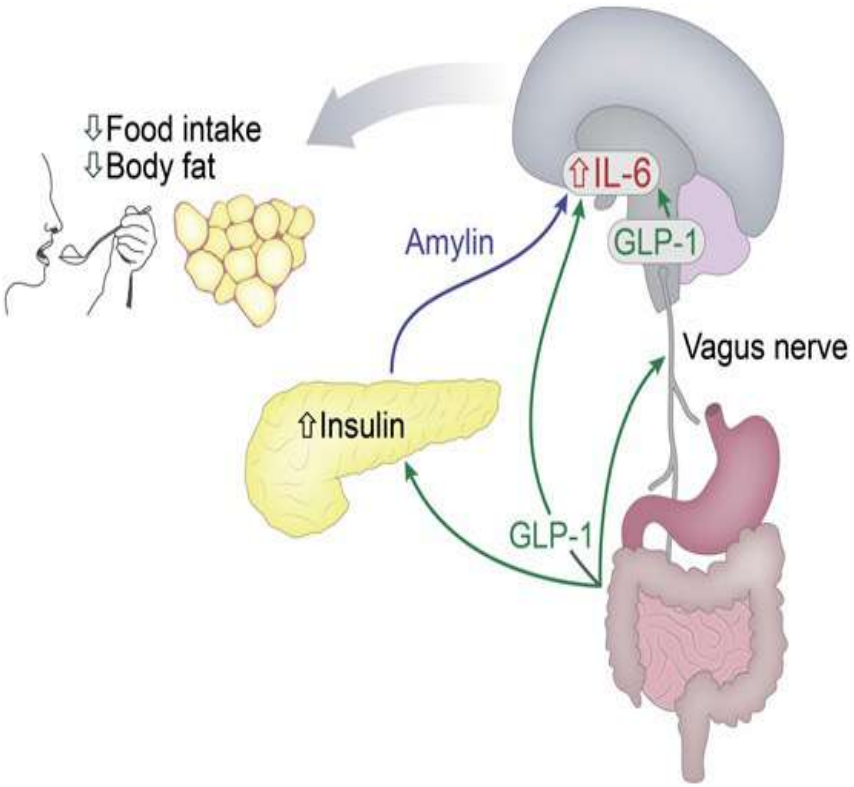
Pramlintide

- Pramlintide was approved by the FDA in 2005
- 2005 was a big year for diabetes medications because the GLP-1 RAs were also approved in that year
- Pramlindide is an amylin analogue and is the only drug currently approved in this class
- Amylin is a peptide that is secreted from the pancreas
- Amylin acts as a “neurohormone”

Amylin has Much in Common with Insulin

- Amylin is produced in the pancreatic beta cells and secreted in response to the same stimuli as insulin (food intake)
- Amylin rise after food intake (like insulin) is absent in Type I diabetes
- Amylin can be increased (like insulin resistance), low, or normal in T2DM
- With the progression of T2DM amylin (like insulin) goes down as pancreatic beta cell function deteriorates
- Insulin, amylin, and glucagon all work together to maintain blood sugar balance
- Amylin decreases glucagon after meals, slows gastric emptying, and promotes satiety via the gut- brain axis

The Connection Between Amylin and GLP-1



" Amylin is co-secreted with insulin from b-cells, while GLP-1 is secreted from the gut, increasing the insulin secretion from the b-cells. Both amylin and GLP-1 are released after meals and improve glucose metabolism. They both decrease food intake and body weight via effects on the brain, and GLP-1 also acts via the vagus nerve. Recent evidence indicates that increased production of IL-6 in the hypothalamus can mediate decreases in food intake and body weight as well as increased leptin sensitivity in response to amylin and GLP-1 (3,8,19). Earlier data indicate that brain IL-6 by itself can decrease body fat mass (13,14)."

https://diabetes.diabetesjournals.org/content/64/5/1498

Pramlintide Mechanism of Action

Pramlintide mimics the mechanism of action of amylin and lowers blood glucose three ways:

1. Lowering glucagon
2. Reducing the speed of gastric emptying
3. Promoting satiety by the gut-brain connection

Advantages of Pramlintide

- Can be used in both T2DM and Type 1 diabetics who are on insulin who have not been able to achieve optimal glucose control on insulin alone
- Gives a modest decrease in A1C and postprandial glucose in those patients
- It can allow decreased insulin usage which makes weight loss easier
- Promotes better glucose stability vs. insulin alone
- Better effects on weight control vs. insulin alone

2019 Guide to Medications for the Treatment of Diabetes Mellitus. American Diabetes Association.

Effects in Type I Diabetics

- Studies have shown improvements in A1C and decreases in body weight in type I diabetics on the combination of insulin and pramlintide https://pubmed.ncbi.nlm.nih.gov/11919132/
- The A1C improvements were NOT accompanied with an increased risk of severe hypoglycemic events
- However the average A1C improvements tended to decrease with time with low point being at week 52 (-0.12%)

Effects in Type I Diabetes Continued

One study showed that, although the AIC decrease in patients on pramlindide was no different from the placebo group, pramlinitide made it possible to titrate down insulin dosages resulting in less variable after-meal glucose levels and reduced weight.

Conclusions: ”Pramlintide dose escalation with reduced mealtime insulin was effective during therapy initiation in patients with type 1 diabetes. While both groups experienced equivalent A1C reductions relative to placebo, pramlintide-treated patients experienced reductions in postprandial glucose excursions and weight, not achievable with insulin therapy alone.”

https://pubmed.ncbi.nlm.nih.gov/17003291/

Disadvantages and Potential Side Effects of Pramlintide

- There is a risk of hypoglycemia when combined with insulin (which is the recommended mode of administration)
- Initiation can be complicated because you have to monitor glucose levels carefully as you titrate down the insulin dosage and titrate up the pramlintide dosage
- Requires up to three injections per day
- The effects on A1C, weight, and post-prandial glucose are small and may not persist over time

2019 Guide to Medications for the Treatment of Diabetes Mellitus. American Diabetes Association.

Disadvantages and Potential Side Effects of Pramlintide Continued

- It is not a recommended agent for T2DM because it costs more and is less effective than other meds
- It carries a black box warning for severe hypoglcyemia when used with insulin. This usually happens 2-3 hours after the injection.
- The most common side effects are abdominal complaints such as nausea and abdominal pain
- These side effects ocour in 14.8-63% of patients on Pramlintide as compared to 10-36% on placebo
- Abdominal effects can be reduced by starting with a low dose and titrating up slowly

2019 Guide to Medications for the Treatment of Diabetes Mellitus. American Diabetes Association

Let's End with something Naturopathic!

Gut microbiome-related effects of berberine and probiotics on type 2 diabetes (the PREMOTE study)

"Human gut microbiome is a promising target for managing type 2 diabetes (T2D). Measures altering gut microbiota like oral intake of probiotics or berberine (BBR), a bacteriostatic agent, merit metabolic homoeostasis. We hence conducted a randomized, double-blind, placebocontrolled trial with newly diagnosed T2D patients from 20 centres in China. Four-hundre and nine eligible participants were enrolled, randomly assigned (1:1:1:1) and completed a 12-week treatment of either BBR-alone, probiotics+BBR, probiotics-alone, or placebo, after a one-week run-in of gentamycin pretreatment. The changes in glycated haemoglobin, as the primary outcome, in the probiotics+BBR (least-squares mean [95% CI], −1.04[−1.19, −0.89]%) and BBR-alone group (−0.99[−1.16, −0.83]%) were significantly greater than that in the placebo and probiotics-alone groups (−0.59[−0.75, −0.44]%, −0.53[−0.68, −0.37]%, $P < 0.001$). BBR treatment induced more gastrointestinal side effects. Further metagenomics and metabolomic studies found that the hypoglycaemic effect of BBR is mediated by the inhibition of DA biotransformation by Ruminococcus bromii. Therefore, our study reports a human microbial related mechanism underlying the antidiabetic effect of BBR on T2D." (Clinicaltrial. gov Identifier: NCT02861261).
https://doi.org/10.1038/s41467-020-18414-8 **OPEN**

Clinical Implications of The PREMOTE Study

- “I remember when berberine first started being used to improve glycemic control. I had a couple questions that immediately came to mind. First, “Is it a good thing to use berberine on a long-term basis? Will that alter gut microbiota too much and cause other issues?” Secondly, “How in the world does berberine lower blood sugar?” I think many of my peers may have wondered the same things.
- Many of us are familiar with the use of berberine to affect dysbiosis. Berberine has generally been thought of as an agent that can spare the “good” gut microbes and decrease “dysbiotic” organisms. It is often recommended based on the results of functional stool testing of microbiota populations, where berberine is a suggested agent to decrease dysbiosis, be it fungal or bacterial. This is the first study of which I am aware that begins to answer some of my initial questions regarding the use of berberine to improve glycemic control.
- Clinically it is interesting to note that this study did, in fact, show that berberine kills some gut microbes and enhances others. This supports the long-existing naturopathic idea that berberine is a gut microbiome *modulator*. For centuries, people have also used berberine-containing plants in traditional Chinese herbal formulas to support gut health without specifically understanding their gut microbiome–modulating properties.[2]

Clinical Implications of the PEMOTE Study Continued

- In naturopathic terms, the use of berberine in this study may be considered an example of gently pushing the body in the direction of microbiome homeostasis. I find it fascinating that the downstream domino effect of giving berberine is an improvement in glycemic control through the modulation of end products of gut-microbe metabolism.
- The depths of data analysis used in this study was hardly imaginable 30 years ago. This research group performed in-depth "metagenomic" and "metabolomic" analysis of their data. Like a Sherlock Holmes novel, they boiled down the data to a final deduction: Berberine inhibited the biotransformation of deoxycholic acid by inhibiting *Ruminococcus bromii*, which then lowered the gut activity of FXR, a regulator of glucose and lipids in the body. This chain of events may have caused the noted antidiabetic effect. Talk about a domino effect."

Clinical Implications of the PREMOTE Study Continued

- The secondary findings of this study are intriguing. The authors make an interesting statement in their results section. They state, “The reconstitution of the gut microbiome after probiotics was similar to that after Plac treatment except for the enrichment of the ingested probiotic species.” They then go on to clarify, “Thus, probiotics treatment showed similar effects not only on glycemic control but also on resilience of the gut microbiota after gentamycin pretreatment with placebo.”
- If taken at face value, these statements would seem to indicate that the probiotics in this study, when used alone, were no better than placebo at recovering overall gut microbiota and improving glycemic control after gentamicin pretreatment.
- Upon further consideration, one may think that “enrichment of the ingested probiotics species” would be a significant benefit to a patient after an antibiotic treatment. This is especially true given the known beneficial effects of the various probiotic species used in this study.[3]
- To me, it is somewhat surprising that, despite probiotic use, the subjects’ gut microbiota populations were not back to baseline 13 weeks after their antibiotic treatment. Not to induce guilt in practitioners when an antibiotic prescription is indicated, but this is good to keep in mind. Perhaps some “prebiotics” may be of use here?

Clinical Indications of the PREMOTE Study Continued

- Now let's look at the other side of the coin. The authors state that probiotics may *delay* the recovery of the microbiome "symbiosis" after antibiotic treatment. I found this statement counterintuitive at first glance. If we look at this from a completely different perspective, this may be a good thing. The authors aptly note that this situation might represent an opportunity to "reset" the diseased microbiome known to be associated with diabetes in the first place.
- The noted lack of effect of probiotics on glycemic control in this study differs from previous studies. A meta-analysis of randomized, placebo-controlled studies on probiotics found improvements in HbA_{1C}, triglycerides, C-reactive protein (CRP), fasting insulin, fasting blood sugar, and blood pressure across multiple studies.[4]
- To conclude, it is tempting to mention another secondary finding of this study. The genomic analyses showed that berberine enhanced microbes involved in xenobiotic degradation. I cannot help but wonder if berberine could help improve detoxification and hormonal balance in diabetics and other populations. This question will, I hope, be answered by future studies that we will be reviewing in years to come.

https://www.naturalmedicinejournal.com/journal/2021-03/berberine-and-glycemic-control