DIABETES MEDICATIONS

There are a variety of medications used to treat diabetes. At the root of all types of diabetes is the pancreatic hormone Insulin. More specifically, the disease is a dysfunction of insulin. In type 1 or advanced type 2, you don't produce any functioning insulin (or it is really not working well) so you need to inject it. Without it, you die quickly. Insulin may still not be working well and you may need a lot of it. The only way to improve its function is to improve your lifestyle, especially improve your diet by eliminating fats which cause insulin resistance, especially from animal products, and doing other healthy things like exercising. If your disease is not advanced enough to require insulin you can get away with oral medications with a variety of things outlined below. But keep in mind this simple fact: taking drugs to lower blood sugar and even improve your A1c, an indicator of long-term blood sugar levels, does NOT improve longevity or lower your risk of diabetic complications like cardiovascular disease and stroke. You MUST improve your lifestyle. Don't be fooled by improved bloodwork.

INSULIN – Discovered in 1921 in Toronto by Dr. Frederick Banting, a surgeon, and his research assistant Charles Best, it was first used in humans the following year and has saved probably many thousands, if not millions of lives of the last 100 years. The first successful insulin preparations came from cows (and later pigs). The pancreatic islets and the insulin protein contained within them were isolated from animals slaughtered for. The bovine (cow) and porcine (pig) insulin were purified, bottled, and sold. They worked very well (and still do!) for the vast majority of patients, but some patients develop an allergy or other types of reactions to the foreign protein (a foreign protein is a protein which is not native to humans). In the 1980's technology advanced to the point where we could make human insulin. The advantage would be that human insulin would have a much lower chance of inducing a reaction because it is not a foreign protein (all humans have the exact same insulin, so we do not "see" this as a foreign protein). The technology which made this approach possible was the development of recombinant DNA techniques. In simple terms, the human gene which codes for the insulin protein was cloned (copied) and then put inside of bacteria. A number of tricks were performed on this gene to make the bacteria want to use it to constantly make insulin. Big vats of bacteria now make tons of human insulin. From this, pharmaceutical companies can isolate pure human insulin.

Insulin is a therapeutic biological product (or 'biologic'), rather than a chemically synthesized molecule. This means it cannot be made as generic in the same way as other drugs. 90% of the insulin worldwide is made by only 3 companies. These are the 2 main reasons why insulin remains an expensive medication. There are some other factors such as politics, lobbying by the pharmaceutical industry as well as simple corporate greed, but it is the patients who pay the ultimate price, some forgoing treatment because of the costs.

The pancreas is the organ which makes insulin. It produces insulin in two different ways:

BASAL insulin (sometimes called background insulin) regulates glucose levels between meals and is released 24 hours a day, whether or not a person eats. This is the low level, stable amount of insulin you continuously have around. It is slowly absorbed, takes a long time to peak and a long time to clear. This does nothing for the food you are about to eat.

BOLUS insulin is released by the pancreas in direct response to the ingestion of food in order to manage the rise in blood glucose that immediately follows. If your pancreas does not make insulin (type 1 diabetes) or your insulin control is so poor and your pancreas has burned out (advanced type 2 diabetes), you need to take exogenous insulin. This short acting, rapidly absorbed and rapidly cleared

insulin is also the most dangerous because if you take too much or don't eat as much as you planned, your blood sugar can drop to dangerously low levels.

There are six main types of insulin available, basically based on how quickly and for how long they act.

- Rapid-acting: These include Apidra, Humalog, and Novolog. They have an onset in less than 15 minutes, peak in 30 to 90 minutes, and duration of two to four hours.
- Regular (short-acting): These include Humulin R and Novolin R. They have an onset of a half an hour, a peak of two to three hours, and duration of three to six hours.
- Intermediate-acting: These include Humulin N and Novolin N. They have an onset of two to four hours, a peak at four to 12 hours, and duration of 12 to 18 hours.
- Long-acting: These include Levemir and Lantus. They have an onset of several hours, minimal or no peak, and a duration of 24 hours or more.
- Ultra-long-acting: These include Toujeo. They have an onset of six hours, no peak, and a duration of 36 hours.
- Combinations/pre-mixed: These combine intermediate-acting insulins with regular insulin and are convenient for people who need to use both. These include mixtures of Humulin or Novoline, Novolog Mix, and Humalog Mix.
- Inhaled insulin: This became available in 2015 and is used in combination with long-acting insulin. Afrezza has an onset of 12 to 15 minutes, a peak of 30 minutes, and duration of three hours.

RISKS and SIDE EFFECTS:

- Hypoglycemia. This is the most dangerous as it can cause coma and death if unattended.
- Weight gain. Insulin not only transports sugar, it also transports fatty acids in your bloodstream into fat cells, increasing their size.
- Growth Hormone. It stimulates all kinds of cells, including cancer cells to grow.
- Gut metabolism and calorie absorption. Insulin also impacts on how you gut deals with food and it changes the proportion of nutrients, including protein, fat and carbohydrates, get absorbed. This is partly how artificial sweeteners contribute to weight gain. They still raise insulin levels. As a result, you absorb more calories from your GI tract.

BIGUANIDES. These are the most commonly prescribed oral diabetes medication worldwide. They have 3 modes of action. They work primarily by preventing the production of glucose in the liver by preventing it from converting fat cells into glucose. Secondly, they improve the body's sensitivity to insulin by activating the enzyme 5' AMP-activated protein kinase (AMPK) which helps cells to respond more effectively to insulin. Thirdly, they reduce the amount of sugar absorbed by the intestines.

The most common side effect is diarrhea which subsides as your body gets used to the drug. In rare cases, lactic acidosis, a serious and potentially buildup of lactic acid in the blood, can occur but this is rare and usually only seen in patients with kidney disease and with significant alcohol consumption. There is a naturally occurring form of this drug, Berberine, a compound found in a number of trees and berries.

The two pharmaceutical forms of biguanides are:

- Metformin
- Glucophage

SULFONYLUREAS. These were the first diabetes drugs. They are cheap and effective. They are secretgogues, basically forcing your pancreas to make and secrete more insulin. They bind to an ATP-dependent K^+ (K_{ATP}) channel on the cell membrane of pancreatic beta cells leading to increases in the concentration of intracellular potassium, which causes the electric potential over the membrane to become more positive. This depolarization opens voltage-gated Ca^{2+} channels. The rise in intracellular calcium leads to increased fusion of insulin granula in the cell membrane, and therefore increased secretion of (pro) insulin. They basically act like insulin and can lead to hypoglycemia. One of their side effects is weight gain, a result of increases in circulating insulin. It's cleared by the kidneys, so you have to be careful in patients with kidney disease, common in diabetics.

Some examples are:

- Glynase (glyburide)
- Diabeta (glyburide)
- Micronase (glyburide)
- Glycron (glyburide)
- Glucotrol (glipizide)
- Amaryl (glimepiride)
- Tolinase (tolazamide)
- Tol-Tab (tolbutamide)

MEGLITINIDES. This newer class of drugs basically do the same thing as sulfonylureas, ie make the pancreas work harder to produce more insulin. They bind to an ATP-dependent K^+ (K_{ATP}) channel on the cell membrane of pancreatic beta cells in a similar manner to sulfonylureas but have a weaker binding affinity and faster dissociation from their binding site.

Some examples are:

- Prandin (repaglinide)
- Starlix (nateglinide)
- Glufast (mitiglinide)

GLP-1 RECEPTOR ANTAGONISTS. Also called incretin mimetics, they are based on the action of hormones called incretins, which help control how the pancreas works. One type of incretin, called glucagon-like-peptide-1 (GLP-1), causes your pancreas to produce more insulin after you eat and helps keep blood glucose levels in the normal range. They copy, or mimic, the action of GLP-1 made by your body. The effects of GLP-1 only last for a few minutes, but GLP-1 receptor agonist medications can last for hours or days. It also slows emptying of the stomach and decreases production of glucagon, a peptide hormone, produced by alpha cells of the pancreas which works to raise the concentration of glucose and fatty acids in the bloodstream.

Examples of GLP 1 receptor agonists include:

- Byetta (exenatide)
- Trulicity (dulaglutide)
- Adlyxin (lixisenatide)
- Soliqua (lixisenatide)
- Victoza (liraglutide)
- Saxenda(liraglutide)

RISKS. They have been linked to pancreatic cancer, thyroid cancer, pancreatitis and severe GI upset. There is a low risk of hypoglycemia and they do help with weight loss.

GLP-1 AGONISTS. GLP-1 is a hormone produced in the small intestine that stimulates insulin secretion and inhibits glucagon secretion, thereby lowering blood sugar. Shorter-acting agonists of the GLP-1 receptor are particularly effective at lowering post-meal glucose spikes, whereas longer-acting GLP-1 agonists have more balanced effects on lowering post-meal and fasting glucose levels. This drug activates the glucagon-like-peptide-1 (GLP-1) receptor, increasing insulin secretion, decreasing glucagon secretion, and slowing emptying of the stomach. Glucagon is a peptide hormone, produced by alpha cells of the pancreas. It works to raise the concentration of glucose and fatty acids in the bloodstream, and is considered to be the main catabolic hormone of the body.

Some of the RISKS include:

- Thyroid C-cell Tumors (cancer)
- Pancreatitis
- Diabetic Retinopathy Complications
- Hypoglycemia
- Acute Kidney Injury [see Warnings and Precautions

Examples include:

- Byetta/Bydureon (exenatide)
- Victoza (liraglutide)
- Lyxumia/Adlyxin (lixisenatide)
- Tanzeum (albiglutide)
- Trulicity (dulaglutide)
- Ozempic (semaglutide)
- Rybelsus (oral semaglutide)

DPP-4 INHIBITORS. These by blocking the action of DPP-4, an enzyme which destroys the hormone incretin. Incretins help the body produce more insulin only when it is needed and reduce the amount of glucose produced by the liver when it is not needed. They are expensive, have a low risk for hypoglycemia and have no impact on weight. They include:

- Januvia (sitagliptin)
- Janumet (sitagliptin + metformin)
- Onglyza (saxagliptin)
- Tradjenta (linagliptin)
- Nesina (alogliptin)

SGLT2 INHIBITORS. Sodium-glucose Cotransporter (SGLT)-2 inhibitors lower blood sugar by causing the kidneys to remove sugar from the body through the urine and block the kidneys ability to reabsorb it. Under normal circumstances, the kidney reabsorbs sugar however its ability to do so is capped when the blood sugar level reaches 180. Above that, the kidney can't keep up and that's when you start to see sugar in the urine. When this happens, as the concentration of sugar in the urine rises with poorer and poorer blood sugar control, you start to lose water and this is what causes the excessive urination that diabetics experience. This also leads to the fatigue and weight loss some may experience if this goes on for too long. This is also how diabetic ketoacidosis (DKA), a life-threatening condition, occurs. One of the side effects of these drugs is in fact dehydration and the possibility of going into DKA. If a

patient also happens to have heart failure, a condition where there is an overload in fluid because the heart is not pumping well, then this drug may help both problems but patients need to be monitored closely. These drugs can also put an excessive amount of pressure on the kidneys and contribute to kidney disease itself. In fact, 50% of patients who start such drugs will experience some degree of kidney disease.

Drugs in this class include:

- Invokana (canagliflozin)
- Invokamet (canagliflozin + metformin)
- Farziga (dapagliflozin)
- Xigduo (dapagliflozin + metformin extended release)
- Jardiance (empagliflozin)
- Steglatro (ertugliflozin)

THIAZOLIDINEDIONES (TZDs). These drugs improve insulin sensitivity by stimulating production of new fat cells, which are more sensitive to insulin. If you're insulin resistant, your cells don't allow insulin to do its job (which is to get glucose into the cells). The new fat cells can eventually lower your blood glucose level by making your body use insulin and glucose better.

Side effects include:

- Cause or worsen heart failure by causing fluid retention.
- Patients may experience fluid retention and weight gain while taking thiazolidinedione drugs. The weight gain is thought to be partly because of the fluid retention but also a result of decreased leptin (the satiety hormone) leading to increased appetite. Levels
- May be linked to the development of bladder cancer but evidence is not conclusive
- Women who take these drugs may be more prone to bone fractures because of changes in the bone marrow leading to increased cells which break down bone.

Examples include:

- Avandia (rosiglitazone)
- Actos (pioglitazone)

ALPHA-GLUCOSIDASE INHIBITORS (AGIs) are saccharides (sugar molecules) that act as competitive inhibitors of enzymes needed to digest carbohydrates. As a result, less sugar gets absorbed through the gut lining into the bloodstream. The main side effect is excessive flatulence because of the leftover sugars in the gut which bacteria break down producing gas. AGIs are naturally occurring in maitake mushrooms. Examples of AGIs include:

- Precose (precose)
- Glucobay (precose)
- Glyset (miglitol)
- Voglib (voglibose)

Dopamine agonist

Mechanism of action: stimulates dopamine receptors, inhibits pituitary prolactin secretion (dopamine agonist); precise mechanism for improved glycemic control unknown: modulates neurotransmitters centrally, decreasing fasting and postprandial (after meal) hyperglycemia without increasing insulin levels. Bromocriptine (Cycloset) is a dopamine agonist (a chemical that binds to a receptor and activates

the receptor to produce a biological response). Dopamine is a neurotransmitter that helps control the brain's reward and pleasure centers agonist. It's not known exactly how this drug works to treat type 2 diabetes. It may affect rhythms in your body and prevent insulin resistance.

NATURAL SUPPLEMENTS AND TREATMENTS

There are a number of vitamins and supplements which can also help control blood sugar as well as some of the side effects of diabetes. Below is a list of some of the more commonly known ones which do have some scientific support:

CINNAMON is a fragrant spice that comes from the bark of a tree. It is a popular ingredient in sweets, baked goods, and other dishes. It has a taste that can add sweetness without any additional sugar. It is popular with people with type 2 diabetes for this reason alone, but it may also offer other benefits. There are 2 forms of cinnamon, Ceylon and Cassia.

Cassia is the most common form and can be derived from a few different species of Cinnamomum trees. It's generally inexpensive and is found in most food products and the spice aisle of your grocery store.

Ceylon cinnamon, on the other hand, is specifically derived from the Cinnamomum verum tree. Cassia cinnamon is not only lower in antioxidants, it's also high in a potentially harmful substance called coumarin, an organic substance found in many plants. Several studies in rats have shown coumarin can be toxic to the liver, leading to concern that it can cause liver damage in humans as well

Both varieties of cinnamon likely lower blood sugar and fight diabetes, but Ceylon seems to provide more benefits than Cassia.

Studies involving humans have shown that cinnamon may improve the following:

- fasting glucose levels
- insulin and insulin sensitivity
- lipids, or fats, in the blood
- antioxidant status
- blood pressure
- lean body mass
- digestion
- less total cholesterol and "bad" low-density lipoprotein (LDL) cholesterol
- higher levels of "good" high-density lipoprotein (HDL) cholesterol
- a reduction in triglycerides, or fat, in the blood

In both studies, the researchers note that the results may depend on:

- the type of cinnamon, as the amount of active ingredient depends on the type
- the amount or dose
- the individual's response to cinnamon
- other medications the person may be taking

BITTER MELON. Momordica charantia, or bitter melon, is a medicinal fruit. Practitioners of traditional Chinese and Indian medicine have used it for centuries. People can cook the fruit and use it in many dishes. Some scientists have been looking into its potential medicinal uses. There is some evidence

that bitter melon may help with the symptoms of diabetes. One review has noted that people have used many parts of the plant to help treat diabetes.

Research has shown that taking bitter melon in the following forms can lead to a reduction in blood sugar levels in some people:

- seeds
- blended vegetable pulp
- juice
- supplements

Eating or drinking the bitter melon can be an acquired taste, but taking supplements may make it more palatable. There is not enough evidence to support using bitter melon instead of insulin or medication for diabetes. However, it may help people rely less on those medications or lower their dosages.

MILK THISTLE. Milk thistle may have anti-inflammatory properties, making it potentially useful for people with diabetes. People have used milk thistle since ancient times for many different ailments, and especially as a tonic for the liver. Silymarin, the extract from milk thistle that has received the most attention from scientists, is a compound with antioxidant and anti-inflammatory properties. These are the properties that may make milk thistle a useful herb for people with diabetes.

FENUGREEK is another seed that may help lower blood sugar levels. The seeds contain fibers and chemicals that help to slow down the digestion of carbohydrates and sugar. There is also some evidence that the seeds may help delay or prevent the onset of type 2 diabetes. Findings of a 3-year investigation published in 2015 noted that people with prediabetes were less likely to receive a diagnosis of type 2 diabetes while taking powdered fenugreek seed.
The researchers concluded that taking the seed led to:

- increased levels of insulin in the body, leading to a reduction in blood sugar
- lower cholesterol levels

The study involved 66 people with diabetes who took 5 grams (g) of the seed preparation twice a day before meals, and 74 controls, who did not take it.

GYMNEMA. Gymnema sylvestre is a herb that comes from India. Its name means "sugar destroyer." A 2013 review noted that people with both type 1 and type 2 diabetes who took gymnema showed signs of improvement. In people with type 1 diabetes who took the leaf extract for 18 months, fasting blood sugar levels fell significantly, compared with a group who received only insulin. Other tests using gymnema found that people with type 2 diabetes responded well to both the leaf and its extract over various periods.
Some people experienced:

- lower blood sugar levels
- higher insulin level

GINGER. There is some evidence that ginger can lower blood sugar levels. Ginger is another herb that people have used for thousands of years in traditional medicine systems. People often use ginger to help treat digestive and inflammatory issues. However, in 2015, a review suggested that it may also help treat diabetes. The results showed that ginger lowered blood sugar levels, but did not lower blood insulin levels. Because of this, they suggest that ginger may reduce insulin resistance in the body for type 2 diabetes.
People can take ginger:

- by adding ginger powder or chopped, fresh ginger root to raw or cooked food

- brewed into tea
- as a supplement in capsule form
- by drinking it in a ginger ale

CHROMIUM has been studied and debated for several years. You need the mineral to make glucose tolerance factor, which helps insulin work better. It also increases the number of insulin receptors on muscle and liver cells.

GINSENG. Several types of plants are referred to as ginseng, but most studies have used American ginseng. They've shown some sugar-lowering effects in fasting and after-meal blood sugar levels, as well as in A1c results (average blood sugar levels over a 3-month period). But we need larger and more long-term studies. Researchers also found that the amount of sugar-lowering compounds in ginseng plants varies widely.

MAGNESIUM. Although the relationship between magnesium and diabetes has been studied for decades, we still don't fully understand it. Low magnesium may worsen blood sugar control in type 2 diabetes. Scientists say that it interrupts insulin secretion in the pancreas and builds insulin resistance in the body's tissues. And evidence suggests that a magnesium deficiency may contribute to some diabetes complications. People who get more magnesium in their diet (by eating whole grains, nuts, and green leafy vegetables) have a lower risk of type 2 diabetes.

VANDIUM is a compound found in tiny amounts in plants and animals. Early studies showed that vanadium normalized blood sugar levels in animals with type 1 and type 2 diabetes. When people with diabetes were given vanadium, they had a modest increase in insulin sensitivity and were able to lower their need for insulin.

COENZYME Q10, often referred to as CoQ10 (other names include ubiquinone and ubiquinol), is a vitamin-like substance that's in meats and seafood. CoQ10 helps cells make energy and acts as an antioxidant. But it hasn't been shown to affect blood sugar control. Statins, used to lower cholesterol levels, can diminish production of this mineral in the body so anyone on a statin should take CoQ10.

BERBERINE. Berberine is a compound in several plants, including goldenseal, barberry, Oregon grape, and tree turmeric.
Research has suggested that berberine can help treat diabetes, obesity, and inflammation, among other conditions. However, side effects can include stomach upset and nausea. It is very similar to Metformin but has fewer side effects. In addition to helping control blood sugar, it also has been shown to be an effective antimicrobial against bacteria, fungi, protozoa, viruses, helminthes, and Chlamydia. It antagonizes the effects of cholera and E coli heat-stable enterotoxin. It inhibits intestinal ion secretion and of smooth muscle contraction, reduces inflammation and stimulates bile secretion and bilirubin discharge assisting in fat absorption and excretion.

The fundamental mechanism of action underlying berberine's impact on human health is its action on the adenosine monophosphate-activated protein kinase or AMP-activated protein kinase (AMPK). This enzyme acts as the central energy regulatory control switch regulating how energy is produced and used in the body. AMPK induces a cascade of events within cells that are all involved in maintaining energy homeostasis. The AMPK system senses and responds to changes in energy metabolism both on the cellular and the whole-body level. It is via AMPK that low energy status switches cellular metabolism from ATP-consuming anabolic pathways to ATP-producing catabolic pathways. AMPK regulates an array of biological activities that normalize lipid, glucose, and energy imbalances. Metabolic syndrome (MetS)

occurs when these AMPK-regulated pathways are turned off, triggering a syndrome that includes hyperglycemia, diabetes, lipid abnormalities, and energy imbalances.

ALPHA LIPOIC ACID (ALA). Not to be confused with Alpha Linoleic Acid (also ALA), the omega 3 fatty acid, Alpha Lipoic Acid has been shown to be helpful with neuropathy. High levels of blood sugar are toxic to nerves causing numbness and in some causes burning, tingling and "pins and needles" in the nerves. Usually, the longest nerves are affected first, like the feet, but any nerve in the body can be affected. If it works, it can take 2-3 months of continued use to see improvement in most people. ALA is a potent antioxidant and also helps with boosting cellular energy and liver issues.

HIGH POTENCY MULTIVITAMIN. Even with a diet high in fruits and vegetables, it is easy to be deficient in some vitamins and minerals. In addition, modern, monocropped and hybridized foods have lost much of their nutrient content. Make sure your vitamin has B vitamins, especially B12.

VITAMIN D. Most people are deficient in this important nutrient, mostly because of our sedentary and indoor lives. It serves many functions, not the least of which is to help absorb calcium for strong bones and helps fight cancer.

OMEGA 3 FATTY ACIDS. Omega 3 fatty acids have a wide array of health benefits and are the only ones we should worry about consuming. ALL other fats are not necessary. They can easily be obtained from healthy sources like walnuts, flax and chia seeds and algae. Fish oils are not great sources because of the chemical and plastic contamination.Some of the benefits include:

- lowered triglycerides.
- Reduced inflammation
- Protect the heart and blood vessels.
- Improved insulin sensitivity.
- Boost thyroid function.
- Improve adrenal function.
- Improved emotional well being.
- They also help protect the body against diabetes related complications like peripheral neuropathy.

VITAMIN C.As a potent antioxidant, vitamin c can help with infections. Some studies have shown improvement in hemoglobin A1C. The mechanisms of this benefit are unclear.

BIOTIN has also been shown to increase insulin sensitivity and has been found to work synergistically with chromium.

TOCOTRIENOLS are a special form of vitamin E which prevents the tendency for cholesterol from oxidizing, making it much more inflammatory. This can help prevent atherosclerotic plaques and heart disease.

ALOE VERA. Known for helping with wounds, consuming aloe vera pulp might also help repair and protect the pancreas. Aloe vera is a common plant with many different uses. Many people are aware of its benefits for skin care, but it may also have other benefits, including slowing the progress of type 2 diabetes. Findings suggested that aloe vera might help protect and repair the beta cells in the pancreas that produce insulin. The researchers believed this might be due to aloe's antioxidant effects.

Ways of taking aloe include:

- adding juiced pulp to a drink or smoothie

- taking capsules that contain aloe as supplements