A Review of Type 2 Diabetes Mellitus: Pathogenesis & Treatment

by

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An Undergraduate Thesis Submitted to
The University Honors Program
Auburn University at Montgomery

In partial fulfillment of the requirements for the degree of
Bachelor of Science in Physical Science

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Introduction.

Fundamentally, type 2 diabetes mellitus can be defined as hyperglycemia as a result of insulin resistance (1). This differs from type 1 diabetes, which involves insulin deficiency due to insufficient secretion of the hormone, resulting in hyperglycemia (2). Type 2 diabetes is a serious and growing problem, both for the individual and for the population as a whole. According to the National Diabetes Statistics Report released by the Centers for Disease Control and Prevention (CDC) in 2014, 29.1 million people in the United States (9.3% of the population) have diabetes, with type 2 diabetes accounting for approximately 90-95% of all diagnosed cases. The total estimated cost of diagnosed diabetes in the U.S. in 2012 was $245 billion, with direct medical costs amounting to $176 billion (2.3 times higher than those for people without diabetes) and reduced productivity costing $69 billion annually. In 2010, it was also the seventh leading cause of death in the U.S., though that may be a low estimation due to underreporting (3). A 2004 study estimated the global prevalence of diabetes to be 2.8% in 2000 and predicted this number would increase to 4.4% in 2030 (4). However, the World Health Organization (WHO) reported an estimated prevalence of 9% worldwide in 2014 (5).

Although once referred to as adult-onset diabetes, type 2 diabetes is also becoming more common in children. 5,089 people younger than 20 years were newly diagnosed with type 2 diabetes each year in 2008 and 2009 (3). A 2015 case study highlighted a three-year-old girl diagnosed with the condition, demonstrating just how early issues can arise (6).

There are a number of conditions and complications associated with type 2 diabetes as well, including high blood pressure, high blood LDL cholesterol, heart

disease and stroke, eye problems and blindness (related to diabetic retinopathy), and kidney disease. There is also a greater chance that a non-traumatic lower-limb amputation will need to be performed (3). The majority (84%) of these amputations that are related to diabetes are a result of diabetic foot ulcers (open sores or wounds), which occur in 15% of diabetes patients. Neuropathy (loss of feeling as a result of nerve damage), peripheral arterial disease (lack of blood flow to legs and feet as a result of narrowed blood vessels), and decreased local angiogenesis (creation of new blood vessels) can accompany diabetes and, without proper care, can cause a minor wound to develop into a severe infection (7,8). Due to the aforementioned prevalence of and complications associated with this condition, focus has been put on better understanding it in order to both prevent and treat it.

Glucose Metabolism.

The body obtains glucose from external sources—carbohydrates in food that contain sugars and starches—and through internal processes—glycogenolysis (the breakdown of glycogen, the storage form of glucose, during short term fasting of 8-12 hours) and gluconeogenesis (the production of glucose from noncarbohydrate sources during long term fasting). A number of glucoregulatory hormones play a part in maintaining glucose homeostasis, including glucagon, insulin, amylin, and glucagon-like peptide-1 (GLP-1).

Glucagon, derived from the alpha cells of the pancreas, stimulates liver glycogenolysis and promotes gluconeogenesis when blood glucose levels drop during the fasting state. Insulin, derived from the beta cells of the pancreas, controls blood glucose

levels by promoting increased uptake of glucose into tissues and the use of glucose for energy. It stimulates glycogenesis (the formation of glycogen) and suppresses glucagon secretion in the fed state (therefore decreasing further glucose output). Amylin, also derived from the beta cells of the pancreas, works with insulin to suppress glucagon secretion in the fed state and slows gastric emptying (which determines how quickly glucose will move into the blood). Glucagon-like peptide-1 (GLP-1), derived from the L-cells of the intestine, also suppresses glucagon secretion in the fed state and slows gastric emptying, and promotes beta cell health and insulin secretion as well.

During the fed state, glucose is obtained from the food that is consumed and insulin secretion increases to move glucose into tissues and store it for later use. The high levels of insulin suppress glucagon secretion, preventing glycogenolysis and gluconeogenesis. During the fasting state, glucagon levels will be higher and insulin levels lower, which directs glycogenolysis and gluconeogenesis to occur, causing blood glucose levels to rise (9).

In the case of type 2 diabetes, one becomes resistant to insulin and glucose cannot enter the tissues. Initially, the beta cells of the pancreas produce extra insulin to compensate, but over time they cannot produce enough insulin to maintain normal blood glucose levels. This causes glucose levels to increase in the blood instead of entering the cells and being used for energy (10).

Risk Factors and Causes.

Although the exact cause of type 2 diabetes is unknown, it can be said that both genetics and environment contribute to its development, and a number of risk factors have been identified. The chance of developing the condition over one's lifetime is higher

in children of those with the condition, ranging from approximately 40% if one parent is diabetic to nearly 70% if both parents are (11). Studies of twins have helped to shape understanding of the genetic component, with many demonstrating high concordance in identical twins (rates higher than 50%). In addition, certain genomic regions have been identified as being involved in susceptibility (12). Another indication of a genetic component is the age-adjusted rate of diabetes among different ethnic groups—based on U.S. statistics from 2010-2012, 7.6% of non-hispanic whites, 9% of Asian Americans, 12.8% of hispanics, 13.2% of non-hispanic blacks, and 15.2% of American Indians/Alaska Natives had diabetes (3).

However, cross-sectional and longitudinal studies have shown that genetic testing for the disease may not be particularly useful, as the genetic variants that have been identified "explain only ~10–15% of the heritability of type 2 diabetes." Furthermore, genetic screening is often no more predictive than the clinical risk factors that have already been established (11). In addition, even if an individual has a genetic predisposition, they will not necessarily develop type 2 diabetes, as environmental factors play a major role in its development.

Some environmental factors that have been linked to type 2 diabetes are a sedentary lifestyle combined with overeating, excess weight (visceral fat in particular), high stress levels, alcohol intake, and smoking. Women who have had gestational diabetes (hyperglycemia developed during pregnancy) are at greater risk as well, with 5-10% being diagnosed with type 2 diabetes after pregnancy. Susceptibility also increases with age—in 2014, prevalence was 4.1% among those between the ages of 20 and 44,

compared to 16.2% among those between the ages of 45 and 64 and 25.9% among those who were 65 or older (2,3).

With the correct combination of factors, insulin resistance, dysfunction/failure of the beta cells of the pancreas, and excessive glucose production in the liver occur, causing the characteristic hyperglycemia of diabetes (1). As deterioration of glucose homeostasis progresses, the mass of beta cells has been shown to decrease as well, with autopsies demonstrating an average beta cell mass that was 38-40% lower than normal depending on BMI (13). It has been proposed that prolonged high blood glucose and fatty acid levels, which can accompany type 2 diabetes, cause organ dysfunction and damage due to glucolipotoxicity (a combination of glucotoxicity and lipotoxicity). Over time, this can lead to beta cell deterioration as well as the aforementioned complications such as neuropathy, peripheral arterial disease, decreased local angiogenesis, blindness, heart disease, and stroke (1,10).

Tests and Diagnosis.

Blood tests are used to diagnosis type 2 diabetes as well as prediabetes (the early detection of which can allow for the prevention of the development of type 2 diabetes), and include the A_{1c}, fasting plasma glucose, and oral glucose tolerance tests (10).

The A_{1c} test, also referred to as the hemoglobin A1c, HbA1c, or glycohemoglobin test, is the primary test given and indicates a person's average blood glucose level over the preceding three months in terms of a percentage. It measures how much glucose is attached to hemoglobin in red blood cells, which have an average lifespan of three months. It does not require fasting and can be given at any time of day. A normal level is below 5.7 percent, with a percentage between 5.7 and 6.4 indicating prediabetes and a

percentage of 6.5 or higher indicating diabetes. Results can vary due to fluctuating blood glucose levels and random error, and can be off by ±0.5 percent. Certain conditions can also cause interferences that lead to false results. This is most common in those of African, Mediterranean, or Southeast Asian descent, or with a family history of sickle cell anemia or a thalassemia. Conditions such as anemia can also give low results (14).

The fasting plasma glucose test is the most common diagnostic test and is best given in the morning after a minimum of eight hours of fasting. It reports the amount of free glucose in the blood in milligrams per deciliter. A normal result is 99 mg/dL or lower, with 100 to 125 mg/dL indicating prediabetes and a level of 126 mg/dL or higher that has been confirmed by a second test on a different day indicating diabetes. The comparatively more sensitive oral glucose tolerance test is given after at least 8 hours of fasting followed by another 2 hours after drinking a solution of 75 grams of glucose in water. In this case, normal glucose levels are 139 mg/dL or lower, prediabetes is indicated by a level between 140 and 199 mg/dL, and a level of 200 mg/dL or higher that has been confirmed by a second test indicates diabetes. More than one of these tests may be given in order to make a diagnosis (10,14).

Treatment Options.

Initial treatment of diabetes is aimed at lowering blood glucose levels, with subsequent treatment focused on preventing the other complications that tend to arise as the condition progresses (15). The first, and perhaps most important, treatment option is also a method of prevention: lifestyle changes. Healthier eating and increased physical activity play a large role in managing blood glucose levels, as well as blood pressure and cholesterol. It can also aid those who are overweight in losing weight, which can improve

insulin production and decrease insulin resistance (16). Weight loss may also decrease the risk of developing cardiovascular complications (17).

After or alongside these lifestyle changes, pharmacotherapy may be recommended. The classes of drugs that are prescribed include a biguanide, sulfonylureas, meglitinides, DPP-4 inhibitors, thiazolidinediones, SGLT2 inhibitors, alpha glucosidase inhibitors, a dopamine agonist, a bile sequestrant, GLP-1 receptor agonists, an amylin analogue, and insulin (18).

Drug Treatment.

Typically, the first drug prescribed following diagnosis is metformin, a biguanide that improves insulin response (19). The use of *Galega officinalis*, a traditional herbal medicine, preceded the development of biguanides. It contained a high concentration of guanidine and worked to lower blood glucose. Metformin was introduced to Europe and other regions during the late 1950s along with two other biguanides—phenfomrin and buformin—which, due to a high incidence of lactic acidosis associated with their use, were recalled in the late 1970s. After little application, metformin was introduced in the United States in 1995 (18).

In being the first choice, metformin is perhaps the best known drug, but an exact mechanism for its effects has not yet been proposed. Its aforementioned ability to improve insulin response has been credited to increased insulin receptor expression and tyrosine kinase activity. Another suggestion is that it primarily decreases glucose production by the liver through the inhibition of gluconeogenesis. Among many explanations, it has been suggested that metformin may do this by changing enzyme activity or reducing uptake of gluconeogenic substrates into the liver. Metformin acts

preferentially on hepatocytes (liver cells) because of a significant expression of organic cation transporter 1, which facilitates the uptake of metformin (20).

A second medicine might be prescribed either in place of or in combination with metformin after a few months if the patient's blood sugar and A_{1c} levels are still high. Commonly, this would be glipizide, a short acting sulfonylurea (19). Other sulfonylureas include glyburide, gliclazide, glimepiride, and tolbutamide. This class of drugs increases the amount of insulin produced by the body, effectively lowering blood sugar levels by about 20 percent (19). The ability of sulfonamides to lower blood sugar levels was discovered after reportedly causing hypoglycemia in typhoid and pneumonia patients to whom they had been prescribed, leading to the introduction of sulfonylureas in the 1950s (18).

Sulfonylureas increase the amount of insulin produced by the pancreatic beta cells by binding to ATP-sensitive potassium channels on the cell membrane and causing them to close; inhibition of potassium channels is performed by glucose under normal biological conditions. This action depolarizes the cell membrane, causing an influx of calcium ions that increases calcium ion concentration within the cell. This in turn stimulates the exocytosis of granules which contain insulin, releasing insulin outside of the cell (21).

Drugs that lower blood sugar in a similar way to sulfonylureas are meglitinides, including repaglinide and nateglinide, which were introduced in the late 1990s. These differ in that they work more quickly, their effects last for a shorter amount of time, and they are taken with meals to reduce the usual postprandial blood sugar spike.

Another alternative to sulfonylureas is a thiazolidinedione drug such as pioglitazone or rosiglitazone. This class was introduced in 1997 along with troglitazone, which was promptly recalled because of its association with idiosyncratic hepatotoxicity (liver damage) (18). Thiazolidinediones help the body to utilize glucose and reduce the amount of fatty acids that may be used as energy for gluconeogenesis in the liver. They are high affinity ligands for the transcription factor peroxisome proliferator-activated receptor-gamma (PPAR-γ), which can control the expression of many genes. After PPAR-γ is activated by a thiazolidinedione, it binds with an activated retinoid X receptor. The heterodimer that is formed is then used to locate peroxisome proliferator response element sequences found in regions of genes that promote insulin action, lipid and glucose metabolism, and adipocyte differentiation. Insulin-sensitive adipocytes are produced and fatty acid concentrations are reduced (18,22).

Though not quite as effectively as metformin or the sulfonylureas, alpha-glucosidase inhibitors lower blood glucose by working postprandially in the intestines to slow carbohydrate digestion and the subsequent entrance of glucose into the blood. They achieve this by preventing intestinal cell surface glucosidases from cleaving disaccharides and oligosaccharides into monosaccharides. This class includes acarbose, miglitol, and voglibose, the former being the first introduced in the 1990s (18,19).

If no first-line medication is an option or lowers blood sugar levels enough, dipeptidylpeptidase-4 (DPP-4) inhibitors are available. Examples include alogliptin, sitagliptin, saxagliptin, linagliptin, and vildagliptin (though the latter is only available in Europe). These increase postprandial insulin release in response to glucose. Available only since 2007, little is known about the long-term effects of this drug.

Glucagon-like peptide-1 (GLP-1) has been recognized as an important antidiabetic hormone. An increased concentration of GLP-1 causes insulin levels to increase and glucagon levels to decrease. It may also help to increase the number of beta cells and prevent their death. The proteolytic enzyme DPP-4 inactivates GLP-1 by cleaving it. DPP-4 inhibitors prevent this inactivation and therefore increase the concentration of GLP-1 (23,24).

Glucagon-like peptide-1 (GLP-1) receptor agonists work in a similar way to DPP-4 inhibitors by increasing the concentration of GLP-1, but have the added benefits of aiding in weight loss and not causing hypoglycemia. This class includes liraglutide, albiglutide, dulaglutide, lixisenatide, and exenatide, the latter of which was the first to be introduced in 2007. These drugs have been modified to avoid an earlier issue of being inactivated by DPP-4 inhibitors when the two are used in combination (18,19).

A drug class that is similar in potency to DPP-4 inhibitors are sodium-glucose co-transporter 2 (SGLT2) inhibitors, including dapagliflozin, canagliflozin, and empagliflozin. This class of drug is relatively new, having been introduced in 2013, and is not routinely used as result; it is also somewhat weak in comparison to other options (18,19).

Sodium-glucose co-transporters (SGLTs) play an important role in glucose filtration and reabsorption by the kidneys. There are two types of SGLTs, and the selective inhibition of SGLT2 is important as inhibition of SGLT1 causes gastrointestinal issues. SGLT2 inhibitors work by inhibiting SGLT2, preventing the kidneys from reabsorbing the glucose that was filtered. This causes an increase in the amount of glucose that is excreted in urine, thereby lowering the amount in the blood. Because this

mechanism is dependent on blood glucose levels and works independently from insulin, there is a low risk of hypoglycemia and beta cell overstimulation or fatigue (25).

Another medication that is not widely used is an analogue of human islet amyloid polypeptide (IAPP) called pramlintide. It was introduced in 2005 and is typically given in combination with insulin to control blood sugar as well as body weight. Insulin may also be used on its own, and is usually given later in the course of treatment if hyperglycemia is still severe following the use of other drug therapies (18,19).

In addition to insulin, pancreatic beta cells also produce IAPP, the precipitation of which may play a part in the beta cell dysfunction and death associated with type 2 diabetes. Pramlintide is an analogue of IAPP that is non-precipitating and modifies glucoregulation by the hypothalamus, acting mostly through the area postrema in the brain stem (18).

Bromocriptine, a dopamine receptor agonist, has been used for some time to treat pituitary tumors and Parkinson's disease. A side effect of lowering glucose was known for decades, and was finally approved for diabetes treatment in 2009. This drug improves glucose tolerance but does not cause an increase in insulin release (18).

Dopamine D2 receptor agonist bromocriptine inhibits serotonin turnover in the central nervous system. Although the exact mechanism is uncertain, it has been proposed that it resets hypothalamic circadian organization of monoamine neuronal activities, reestablishing a normal glucoregulatory cycle. This results in neural suppression of glucose production by the liver, enhanced insulin-mediated peripheral glucose disposal, and overall improved glucose tolerance (18,26).

Another glucose-lowering treatment that was not approved until 2008 is colesevelam, a bile acid sequestrant. Its main action is to remove bile acids that are produced in the intestines from the breakdown of cholesterol by binding to them, which increases blood flow. The mechanism by which it controls blood glucose levels is uncertain. It may increase hepatic glucose metabolism by interrupting the circulation of bile acids in the liver, reducing their effects on the bile acid receptor-1 and the farnesoid X receptor systems. Another possibility is that sequestrant-bound colesevelam may encourage the secretion of glucagon-like peptide-1 (GLP-1) by interacting with bile acid receptor-1 on L-cells along the gut (18,27).

Conclusion and Future Treatment Possibilities.

Along with these that have already been approved, new diabetes treatments are being researched. Just within the last few months, new discoveries have been introduced that could potentially aid in treating diabetes.

An enzyme, glycerol 3-phosphate phosphatase (G3PP), has been identified as being able to directly hydrolyze glycerol-3-phosphate (which is present in excess when glucose levels are high) to glycerol. High levels of glycerol-3-phosphate can damage tissues, including the beta cells of the pancreas. Acting as a G3PP, newly discovered mammalian phosphoglycolate phosphatase is reportedly able to control insulin secretion in response to glucose in addition to gluconeogenesis in hepatocytes (28,29). New research also indicates that use of verapamil, a calcium channel blocker, decreases beta cell death and enhances insulin levels, resulting in lower blood glucose levels (30).

Preventing the dysfunction and death of beta cells that is characteristic of type 2 diabetes seems to be a major goal in developing and discovering new treatments for the

disease. Another aim may be to find a way to enhance the effects of insulin or improve insulin receptors. Other treatments may strive to control glucose production or how quickly it is metabolized. Just as there are a number of factors that play a role in the pathogenesis of type 2 diabetes, there are a number of potential methods of treating it (1,18).

As more people are newly diagnosed with type 2 diabetes each year while others continue to suffer from it, much attention has been focused on how to prevent its progression or control the symptoms. In addition, health initiatives aim at lowering the risk of developing the disease through weight management, physical activity, and other lifestyle changes. New treatments continue to be introduced and tested, and the research and development of more effective drugs will no doubt rely on a better understanding of the disease itself.

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