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Pathogenesis and pharmacological treatment options for patients suffering with type 2 diabetes mellitus

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PATHOGENESIS AND PHARMACOLOGICAL TREATMENT OPTIONS FOR PATIENTS SUFFERING WITH TYPE 2 DIABETES MELLITUS

by

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ABSTRACT

Type 2 diabetes mellitus is an endocrine disorder characterized by chronic hyperglycemia and insulin resistance. The mechanism of action is beta cell dysfunction in the pancreatic Islets of Langerhans where there is a combination of less than normal insulin secretion and a problem in the way the body responds to insulin. Diabetes is a multifactorial disease: there are genetic, environmental, and other lifestyle factors that contribute to its pathogenesis. The major risk factors for diabetes include obesity, a sedentary lifestyle, and physical inactivity. Smoking and alcohol consumption, environment, stress and anxiety, and race and socioeconomic status also play a role. Type 2 diabetes presents with many clinical manifestations such as microvascular and macrovascular diseases which include diabetic nephropathy, diabetic retinopathy, diabetic neuropathy, cardiovascular disease, stroke, and peripheral artery disease. Currently, there are no treatments for diabetes, but lifestyle interventions can help with the prevention and further progression of this disease. Such interventions include a healthier diet, increased levels of physical activities, and obesity management. With people who need more effective management of diabetes, anti-diabetic medications such a Biguanides and sulfonylureas, or insulin therapy can be used. Research continues to focus on the development of new therapeutic strategies to better manage type 2 diabetes.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

AGE	Advanced glycation end productions
BMI	Body Mass Index
DASH	Dietary Approaches to Stop Hypertension
DSM	Diagnostic and Statistical Manual of Mental Disorders
GI	Glycemic Index
GL	Glycemic Load
GLP	Glucagon-like peptide
HPA	Hypothalamus-pituitary-adrenal axis
IDDM	Insulin-dependent diabetes mellitus
LDL	Low-density lipoprotein
NDDM	Non-insulin-dependent diabetes mellitus
OGTT	Oral Glucose Tolerance Test
SGLT2	Sodium-glucose cotransporter 2
VEGF	Vascular Endothelial Growth Factor

INTRODUCTION

Diabetes mellitus is a disorder that is characterized by chronic hyperglycemia (prolonged elevation of blood glucose) which leads to long term clinical complications (DeFronzo, 2004). There are two major types of diabetes mellitus that are recognized clinically: Type 1 diabetes mellitus, known as insulin-dependent diabetes mellitus (IDDM), and Type 2 diabetes mellitus known as non-insulin dependent diabetes mellitus (NIDDM). Diabetes can occur when the pancreas does not make any insulin (Type 1), also known as insulin deficiency, or when the pancreas makes very little insulin and/or the body does not respond to insulin in the proper manner (Type 2) also known as insulin resistance (DeFronzo, 2004). Of the two, type 2 diabetes appears to be the most prevalent form and according to the World Health Organization, it accounts for 90% of all diabetes cases (Olokoba et al., 2012).

Glucose Metabolism

In diabetes mellitus type 2, there is a problem with insulin secretion and failure of insulin to complete its necessary actions (Fujimoto, 2000). Insulin is a critical hormone in the body responsible for a variety of things, but its main role is to maintain appropriate glucose levels and control metabolism. Glucose is produced from three sources: intestinal absorption following ingestion of carbohydrates during a meal, glycogenolysis, and gluconeogenesis (Giugliano et al, 2008). Following glucose production, the secretion of insulin allows cells in the muscles, adipocytes, and liver to absorb glucose in the bloodstream and convert it into energy (Giugliano et al, 2008).

Insulin is produced by the pancreas. The pancreas is made up of a cluster of cells known as the Islets of Langerhans, and within it there are various types of cells that work together to maintain proper blood glucose levels. The two most important are the alpha cells which secretes glucagon, and the beta cells which secrete insulin (Giugliano et al, 2008). In Type 2 diabetes, there is a combination of beta cell malfunction in the Islets of Langerhans and insulin resistance (Fujimoto, 2000).

Normally, the alpha and beta cells act as glucose sensors and they modulate their secretion based on changes in glucose concentrations in the body (Giugliano et al, 2008). The key regulator, however, is insulin. Throughout the day, the body switches between the fed state and the post-absorptive state. During the fed state, after the ingestion of carbohydrates, plasma glucose concentrations rise. The rise in glucose concentrations is the signal for the secretion of insulin, an anabolic hormone (Giugliano et al, 2008). Increased rates of plasma insulin promote the utilization of glucose in metabolic pathways such as glycolysis (the breakdown of glucose) and glycogenesis (formation of glycogen) (Giugliano et al, 2008). The goal of these reactions is to promote glucose uptake into cells and create glycogen to store energy for later use. In this way, insulin works to lower blood glucose concentrations. On the other hand, when in the post-absorptive state, insulin secretion is less and glucagon secretion, a catabolic hormone, increases (Giugliano et al, 2008). Glucagon acts primarily on the liver to promote gluconeogenesis (the formation of new glucose) and glycogenolysis (breakdown of glycogen to glucose) (Giugliano et al, 2008).

The upregulation of the secretion of insulin and glucagon in the body maintains blood glucose homeostasis. As mentioned previously, Type 2 diabetes mellitus is caused by little to no secretion of insulin by the beta cells and/or insulin resistance. As a result of insulin deficiency, glucagon concentrations rise. With little insulin around to promote the storage of glucose and the addition of glucose concentration rising, this causes increased production of glucose by the liver (Giugliano et al, 2008). This explains why the pathogenesis of diabetes mellitus results in hyperglycemia (Figure 1).

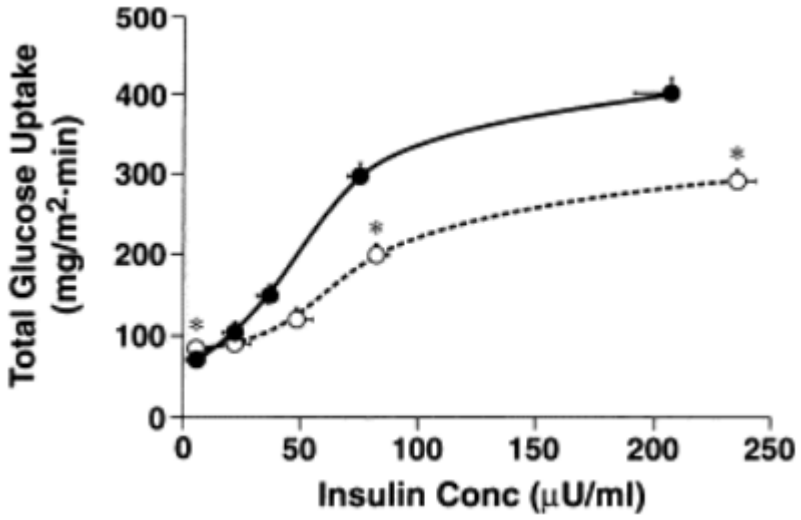

Figure 1. Relationship between Insulin Concentrations and Glucose Uptake in Control (·) and Type 2 diabetic (○) subjects. As plasma insulin concentrations rise in control patients, total glucose uptake increases. In type 2 diabetic patients, total glucose uptake is at a much slower rate. (Taken from DeFronzo 2004)

Hyperglycemia Effects

Hyperglycemia can have detrimental effects on the body. Some acute problems that may arise include glycosuria (sugar in urine), polyuria (excessive urination),

polydipsia (excessive thirst), and polyphagia (excessive eating) (Singleton et al., 2003). Additionally, chronic issues may also arise. Some examples of chronic microvascular diseases that may arise because of hyperglycemia include retinopathy, renal disease, and neuropathy (Singleton et al., 2003). Chronic macrovascular disease may also arise such as cardiovascular, stroke, and lower limb amputations. Hyperglycemia evidently affects multiple systems in the body, which is a major issue because it shows that people with Type 2 diabetes mellitus are more vulnerable to both short-term and long-term complications which often lead to premature death (Singleton et al., 2003).

Prevalence

Diabetes mellitus is a major public health challenge in which prevalence has been steadily increasing worldwide, both in developed and developing nations. In 2015, the prevalence of diabetes in the United States was 8.8% (415 million people). This number is double the amount from 2000, and this number is expected to increase to 10.4% by 2040 (Koye, 2018). Most diabetes cases are Type 2 diabetes mellitus and these cases account for 87 to 91% of all diabetes cases (Olokoba et al, 2012). In most developed countries, it is currently the leading cause of end-stage renal disease and cardiovascular disease (Koye, 2018). In developing counties, type 2 diabetes is replacing communicable diseases as a leading cause of kidney disease (Koye, 2018). In addition, this disease increases with age and is increasing in some ethnic groups. Most people with type 2 diabetes live in urban areas and low/middle income countries (Koye, 2018). The prevalence is highest in North America, the Caribbean, Western Pacific, Middle East, and

North and sub-Saharan Africa (Scobie, 2006) (Figure 2). The highest pattern of growth is seen in the African American, Latino, and Asian American populations in the United States (Olokoba, 2012).

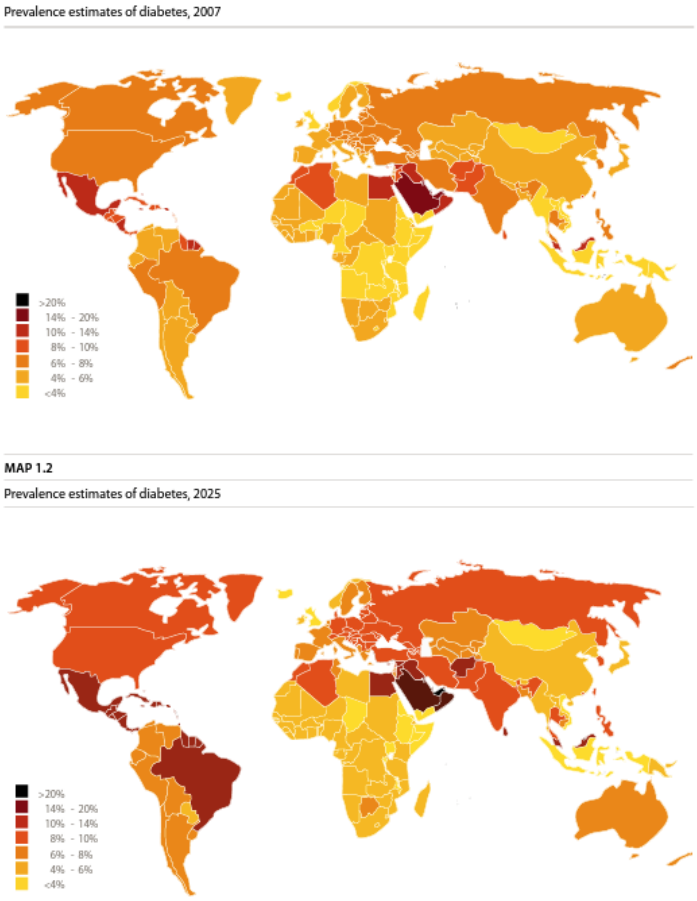

Figure 2. Prevalence Estimates of Diabetes by Country in 2007 and 2025. The incidence of type 2 diabetes is estimated to increase in all countries by 2025 **(**Taken from Scobie 2006).

Preventative Measures and Treatment

Currently, there is no cure for diabetes type 2. There are several factors that make this disease difficult to cure. One factor is that the onset of type 2 diabetes often goes

undetected; this is unlike type 1 diabetes (Giugliano, 2008). Therefore, prevalence rates are usually higher. In addition, diabetes mellitus is a multifactorial disease. The exact cause of diabetes is unknown but instead, it is usually the result of a combination of genetic and environmental factors that predispose someone to this disease. There is one test that is commonly used to screen for type 2 diabetes: the oral glucose tolerance test (OGTT) (Fujimoto, 2000). It is a blood test that checks blood glucose levels in the body. Although little can be done to prevent genetic disposition to type 2 diabetes, screening, lifestyle modifications such as diet changes, treatment of obesity, regular physical activity, current medications such as insulin sensitizers and oral hypoglycemic agents, and new treatments can be used to improve insulin and glucose balance and reduce the prevalence of type 2 diabetes (Giugliano et al., 2008).

RISK FACTORS

There are genetic, environmental, and other risk factors that contribute to the increased risk of developing type 2 diabetes.

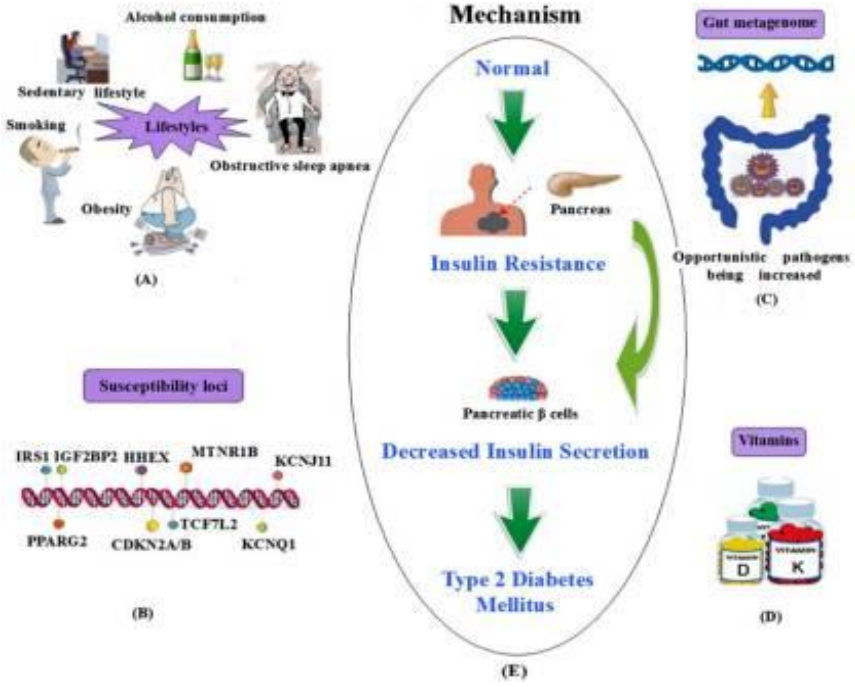

Figure 3. Summary of the Various Risk factors and Mechanism of Type 2 Diabetes. These risk factors include lifestyle habits such as having a sedentary lifestyle and obesity, social factors such as alcohol consumption and smoking, genetic markers, vitamins, and gut metagenome. The mechanism of type 2 diabetes involves pancreatic insulin resistance leading to decreased insulin secretion in the body (Taken from Wu et al., 2014).

Genetic Factors

Type 2 diabetes has a major genetic component. Evidence is found in twin studies in which higher incidence rates are found in monozygotic twins (96%) versus dizygotic twins (Wu et al., 2014). Additionally, a first degree relative of someone with type 2

diabetes has a 40% increased chance of developing diabetes as well. This is compared to the risk of the general population (6%) (Wu et al., 2014).

Susceptibility Loci

In addition to various genetic factors contributing to the increased risk of type 2 diabetes, segregation analysis has shown that this disease has polygenic nature (Wu et al., 2014). This means that multiple genes are responsible for the development of this disease. Segregation analysis has shown the presence of susceptibility loci, alleles that increases the risk for gene expression, in people with type 2 diabetes. While it increases susceptibility, it is not necessary for gene expression. Genome wide analysis studies have identified susceptibility loci in people of different countries and ethnic groups.

Table 1: Susceptibility Loci associated with Type 2 Diabetes Mellitus

KCNQ1	11p15.4	rs2237897	Japanese	6.8×10^{-13}	24
	11p15.4	rs2237895	Chinese	9.7×10^{-10}	25
	11p15.4	rs231362	European	2.8×10^{-13}	26
	11p15.4	rs2237892	Japanese	1.7×10^{-42}	27
TCF7L2	10q25.2	rs7903146	European	2.0×10^{-31}	18
KCNJ11	11p15.1	rs5219	European	6.7×10^{-11}	17
	11p15.1	rs5215	UK	5.0×10^{-11}	19
IRS1	2q36.3	rs7578326	European	5.4×10^{-20}	26
MTNR1B	11q14.3	rs1387153	European	7.8×10^{-15}	26
IGF2BP2	3q27.2	rs4402960	European	8.9×10^{-16}	17
	3q27.2	rs6769511	European	9.0×10^{-16}	19, 24
CDKN2A/B	9p21.3	rs564398	UK	1.3×10^{-6}	19
	9p21.3	rs2383208	Japanese	1.6×10^{-7}	28
	9p21.3	rs10811661	European	7.8×10^{-15}	17
HHEX	10q23.33	rs1111875	European	5.7×10^{-10}	17
	10q23.33	rs5015480	European	1.0×10^{-15}	29
PPARG2	3p25.2	rs1801282	European	1.7×10^{-6}	17
	3p25.2	rs17036101	European	7.5×10^{-6}	30

(Table taken from Wu et al., 2014)

KCNJ11 is one of the more common genes that can acquire mutations in people with diabetes. This locus encodes the gene for the potassium channel for the beta cell of the Islets of Langerhans (Wu et al., 2014). This channel is ATP-sensitive, and it senses metabolic changes in the pancreas and allows for a relationship between electrical activity and insulin secretion (Koster, 2005). Diabetic patients tend to have K channel "overactivity", which causes the potassium channels to open, the beta cells to hyperpolarize and suppress insulin secretion (Koster, 2005). This mutation is so common that it is the target of sulfonylureas, one of the medications used to treat type 2 diabetes (Wu et al., 2014)

The strongest type 2 diabetes locus found to date, however, is TCF7L2 (Wu et al., 2014). This gene encodes a transcription factor involved in regulating proglucagon gene expression and GLP (glucagon-like peptide) (Lyssenko et al., 2007). Proglucagon is the precursor to glucagon and undergoes post-translational cleavage to form GLP (Lyssenko et al., 2007). GLP promotes insulin secretion, and this hormone is impaired in type 2 diabetes (Lyssenko et al., 2007). Therefore, there is less insulin secretion which promotes hyperglycemia.

The locus for IRS1 influences insulin actin, rather than insulin secretion. IRS1 is a protein that is one of the targets of the insulin receptor tyrosine kinase (Copps & White, 2012). In type 2 diabetic patients, there are defects in IRS-dependent signaling, so there is dysregulation in the initiation of insulin secretion.

There are also defects in the MTNR1B gene (Wu et al., 2015). Melatonin is a hormone secreted by the pineal gland that is responsible for the regulation of circadian rhythms. The levels of melatonin increase during the night and decrease during the day. Melatonin regulates the secretion of insulin via the melatonin receptors. Melatonin has both an inhibitory and stimulatory effect on insulin: it decreases insulin secretion at night by inhibiting the cAMP and cGMP pathways and increases insulin secretion during the day by activating the phospholipase C/IP3 pathway (Sharma et al., 2015). Diabetes type 2 patients have a reduction in melatonin levels which disturbs circadian levels.

Aside from transcription factors that regulate insulin action or secretion, there are other transcription factors that function to preserve energy. PPARG2 encodes a gene for adipocyte differentiation (Wu et al., 2014) Adipocytes play a critical role in lipid metabolism and energy homeostasis. Their role is to store fat in times of caloric excess to provide the body with energy in times of nutrient deprivation (Wu et al., 2014). Loss of function mutations in the PPARG2 gene are what contribute to type 2 diabetes (Gouda et al., 2012) IGF2BP2 belongs to a family of three mRNA binding proteins: the growth hormone gene and insulin like growth factor genes (Gouda et al., 2012). The IGF2BP2 gene is involved in developing the pancreas and making sure that insulin develops properly and execute its necessary actions (Gouda et al., 2012)

The HHEX transcription factor affects Beta cell development, which is responsible for the secretion of insulin (Wu et al., 2014). The HHEX gene is expressed in the Delta cell of the pancreas, which produce Somatostatin (Zhang et al., 2014) This

hormone has an inhibitory effect on multiple systems. Regarding the endocrine system, somatostatin inhibits growth hormone, prolactin, gastrin, thyroid-stimulating hormone (TSH) (Zhang et al., 2014). Most importantly, somatostatin inhibits insulin and glucagon. Decreased somatostatin levels cause there to be less inhibition of the release of insulin from the beta cells in the pancreas, leading to hyperglycemia.

Another gene that affects the physiological function in the pancreas is CDKN2A (Wu et al., 2014). The CDKN2A/B genes are a family of proteins responsible for various functions on different tissues of the body. They are cyclin dependent kinase inhibitors; they block cell cycle progression and can promote tumorigenesis (Kong et al., 2017).

Table 2: Effects of CDKN2A/B on Metabolic Tissues

Tissue	Protein	Effects
Islets	$p16^{INK4A}$	Restricts beta cell proliferation in ageing, restricts beta cell regeneration, mediates overnutrition-related senescence, reduces insulin secretory function
	CDK4	Required for postnatal beta cell mass expansion
	Cyclin D1, D2	Required for postnatal beta cell mass expansion
Adipose	$p15^{INK4B}$	Inhibits adipocyte differentiation
	$p16^{INK4A}$	Modulates adipose macrophage activation and polarisation
	CDK4	Promotes adipocyte differentiation
Liver	$p16^{INK4A}$	Restrains hepatic gluconeogenesis
	Cyclin D1/CDK4	Regulates fasted–fed transition
Muscle	CDK4	Impacts mitochondrial oxidative metabolism via E2F1

(Taken from Kong et al., 2017)

The CDKN2A locus relates to diabetes because it is associated with rapid decline in beta cell function by restricting beta cell proliferation and regeneration due to aging (Kong et al., 2017). The overall effect is reducing insulin secretion.

Environmental and Lifestyle Factors for Type 2 Diabetes Mellitus

There is a wide range of lifestyle factors that contribute the development of type 2 diabetes mellitus such as diet, sedentary lifestyle, physical inactivity, smoking and alcohol consumption (Wu et al., 2014). Of these factors, a combination of diet and a

sedentary lifestyle are the leading causes; they contribute to the global epidemic of obesity (Wu et al., 2014). This is important because there is much evidence pointing to obesity as the most important risk factor of type 2 diabetes mellitus.

Changes in epidemiological trends show that there are numerous factors that contribute to the overall consumption of more unhealthy foods. Things such as urbanization, work changes from heavy labor to sedentary occupations, transportation, computerization, a better economy, and changes in food production have made it easier for unhealthy habits to take place (Ley et al., 2016). For example, fast food restaurants have expanded and having more access to these unhealthy foods results in diets consisting of a high calorie content and large portion sizes (Ley et al., 2016). Additionally, the displacement of farmers markets and fresh food with large chain supermarkets allows for the distribution of more processed foods, sugary beverages, and unhealthy snacks (Ley et al., 2016).

Besides changes in establishments, there are some parts of the world that are experiencing a livestock revolution (Ley et al., 2016). Places such as Asia have witnessed this, which leads to increased production of animal and dairy products and poultry. Furthermore, some places have witnessed increased refinement of grain products in foods such as white rice and flour (Ley et al., 2016). Refinement of things that are supposed to be healthy such as whole grains and wheat flour reduce their nutritional contents.

Due to the above-mentioned trends, this has led to an obesity epidemic. Weight gain in both men and women has led to increased deposition of adipose tissue, leading to a higher body mass index (BMI) which is the strongest risk factor for diabetes (Ley et al.,

2016). However, several studies show that there are other measurements that are a better indicator of an increased risk of developing type 2 diabetes mellitus. For example, some Asians tend to develop diabetes at a lower BMI than those of European ancestry (Ley et al., 2016). This demonstrates that there might be other, more important variables at play. One measurement that seems to be a better indicator than BMI is the presence of visceral and/or ectopic (liver) fat (Kolb & Martin, 2017). Another measurement is waist circumference; meta-analysis suggests that this has a stronger risk associated with diabetes than does a higher BMI (Kolb & Martin, 2017). Knowing this information, it is important to assess and monitor multiple factors as a physician.

Diet

There are a wide range of diet types that exist in different regions of the world. Epidemiological studies show varying evidence towards certain food groups having an association with type 2 diabetes. However, it seems that there is a consensus that certain food groups and diets are better for managing diabetes.

Nutrition and dietary trends that are better for preventing type 2 diabetes can be discussed at a macro and micro level. Overall, lifestyle intervention that involves calorie restriction and better diets can reduce the conversion to diabetes.

On a macro level, we can consider what diabetics or people who are at risk for diabetes should be consuming. The macronutrients to be discussed are carbohydrates, proteins, and fats.

Carbohydrates do not play a significant role in the development of diabetes. However, one can determine if certain foods are carbohydrate rich by looking at the glycemic index (GI) or glycemic load (GL) (Ley et al., 2016). While the proportion of carbohydrates in a diet does not significantly influence diabetes risk, low GI and GL diets are associated with lower risk of diabetes (Ley et al., 2016). A type of carbohydrate whose importance is oftentimes underestimated, is fiber. Studies show a high fiber diet may reduce the risk of diabetes. Fiber can be obtained through various sources such as fruits and cereal, but fiber from cereal has a stronger association with lowering the risk than fruits does (Ley et al., 2016).

In terms of protein, there is conflicting evidence. While some associations suggest that there should be a protein restriction for diabetics, some recommend against it. Overall, however, it seems that a low protein diet is not necessary or does not show beneficial effects for diabetics (Ley et al., 2016).

Regarding fats, there are good and bad fats. Studies show that the type of fat consumed is more important than the total fat intake (Ley et al., 2016). A diet that is full of saturated fats and trans fats is not beneficial and their intake should be limited (Ley et al., 2016). Examples of saturated fats include foods such as butter, baked and fried foods, and animal sources such as meat and dairy products. Trans fats can also occur naturally in some of these products, but they are predominantly found in fried fast foods such as fried chicken, doughnuts and cakes, french fries, mozzarella sticks, battered fish, and some snack foods like chips and crackers. Studies of diabetic women serve as evidence that

greater intake of saturated and trans fats, and cholesterol are associated with higher risk of cardiovascular disease (Ley et al., 2016). Contrastingly, a diet filled with more unsaturated and healthy fats reduced the incidence of coronary heart disease. These include foods such as fatty fish like salmon, avocados, nuts and seeds, and healthy oils such as olive and peanut.

When looking at individual foods and food groups, a diet filled with whole grains has been associated with lowering the risk of developing diabetes (Ley et al., 2016). This is the opposite of a diet filled with white rice and refined grains which have been associated with a higher risk of developing diabetes (Ley et al., 2016). Certain populations will have a greater chance of being exposed to such foods because it is their main source of calories. An example is Asia where they mostly eat white rice, and it is a staple food. In addition to grains, another food group that diabetics should stay away from is processed red meats such as hot dogs and sausages and bacon. This was strongly associated with higher diabetes risk (Ley et al., 2016).

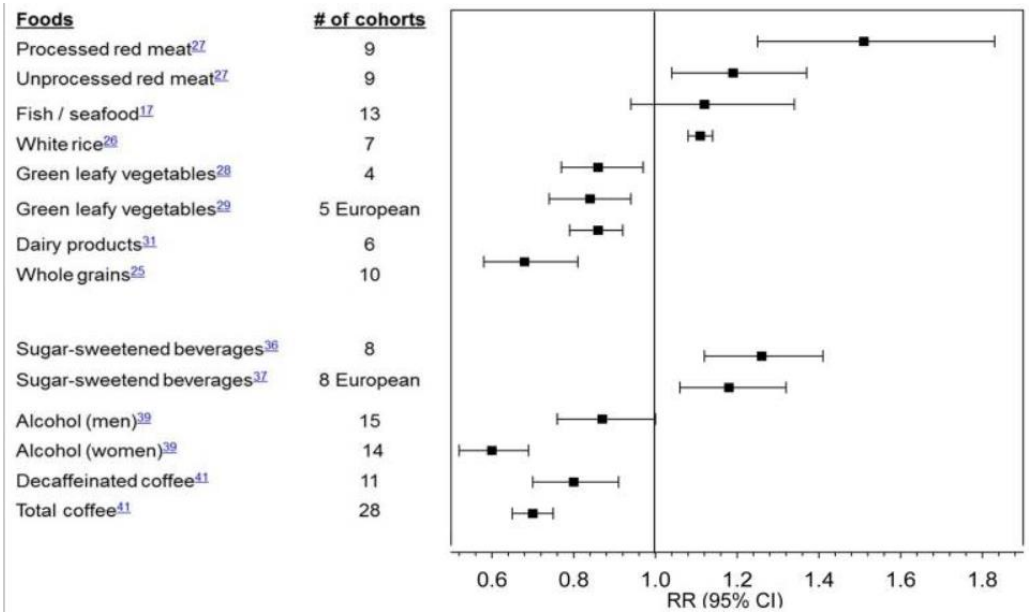

Figure 4: Cohort Studies Indicating Relative Risk of Various Foods and Beverages. Foods such as sugar-sweetened beverages and processed red meats have high relative risks of type 2 diabetes, while foods such as whole grains and green leafy vegetables have low risk (Taken from Ley et al., 2016)

Interestingly, the consumption of fish and seafood was associated with higher diabetes risk, but only in certain parts of the world such as in North America and Europe (Ley et al., 2016). In places like Asia, there is a lower risk. While the reason for this remains unknown, it may be due to the way the fish and seafood is prepared and if the fish has been exposed to pollutants (Ley et al., 2016.

Fresh fruits and vegetables are advantageous to include in the diet of a diabetic person. More specifically, leafy green vegetables such as kale, spinach, and lettuce and specific fruits like blueberries and apples are significantly associated with lower diabetes risk

(Ley et al., 2016). Lastly, the consumption of dairy products, especially yogurt, and the consumption of nuts is linked to lower incidences of diabetes.

While it is important to be cautious of the distributions of the macronutrients being consumed and the food groups, in 2014, the American Diabetes Association recommended that it is more important to focus on having healthy eating patterns and personalized goals (Ley et al., 2016). Such diets include the US-style eating pattern, a Mediterranean diet, and a vegetarian/vegan diet.

Table 3: Dietary Patterns for Type 2 Diabetes Management

	Main components	Diabetes prevention	Diabetes management
Mediterranean diet	high consumption of minimally processed plant based foods; olive oil as the principal source of fat; low- to-moderate consumption of dairy products, fish, and poultry; low consumption of red meat; and low-to-moderate consumption of wine with meals	Mediterranean dietary patterns were associated with lower risk of type 2 diabetes in prospective cohort studies and RCTs.[34, 35, 42, 43]	Mediterranean diets compared to a conventional diet for diabetes management improved glycemic control and insulin sensitivity, and reduced risk of CVD.[43, 74, 80, 81]
Dietary Approaches to Stop Hypertension (DASH)	rich in vegetables, fruits, and low-fat dairy products, including whole grains, poultry, fish, and nuts; lower in saturated fat, red meat, sweets, and sugar containing beverages; and often reduced in sodium	Adherence to the DASH diet was associated with lower risk of diabetes.[46, 47]	The DASH diet with 2 400mg/d sodium restriction had beneficial effects on glycemic control and CVD risk factors.[86, 87]
Vegetarian and vegan	vegan, diets devoid all animal-derived products; vegetarian diets, diets devoid of some animal products including lacto- ovo (consuming dairy and/or eggs), pesco (consuming fish, eggs, and/or dairy), semi (consuming all but no red meat and poultry)	Vegan, lacto-ovo and semi-vegetarian diets were associated with lower risk of type 2 diabetes.[47]	Improved glycemic control or CVD risk was not consistently reported,[87, 88] and the effect of vegetarian diets was difficult to isolate because calorie-restriction was often implemented.
Dietary guidelines - Alternative Healthy Eating Index (AHEI)	indices of the diet quality created based on foods and nutrients predictive of chronic disease risk, including greater intake of vegetables and fruits, whole grains, nuts and legumes, long-chain omega-3 fatty acids, PUFAs; lower intake of sugar-sweetened beverages and fruit juice, red/processed meat, trans fat, sodium; and moderate alcohol consumption	Adherence to high quality diet assessed by AHEI was strongly associated with lower risk of diabetes.[44]	NA
Prudent pattern	dietary patterns higher in fruits, vegetables, whole grains, and vegetable fats and lower in red meats, refined grains, and sugared soft drinks	Prudent dietary patterns over Western dietary patterns were associated with lower type 2 diabetes risk.[48-53]	NA

(Taken from Hey et al., 2016)

There are numerous diets that have been recommended by various organizations to treat and prevent diabetes. However, in several randomized controlled trials among people with type 2 diabetes, the Mediterranean diet showed the most improvement in glycemic control and insulin sensitivity (Ley et al., 2016).

The Mediterranean diet is a special diet because it is not considered to be the ordinary "diet"; it is a way of life. People usually think of a diet as a plan that involves cutting out food groups, making strict calorie restrictions, and sometimes even bland foods. The Mediterranean diet, however, does not require any of these things. Instead, it promotes seasoned cooking, freshly cooked meals, and use of extra-virgin olive oil (Milenkovic, 2021). In addition to food, this diet also encourages people to socialize with each other over fresh and healthy food. The Mediterranean diet mainly consists of consuming more fruits and vegetables, more fish and seafood while minimizing red meats, nuts, and legumes (Milenkovic, 2021).

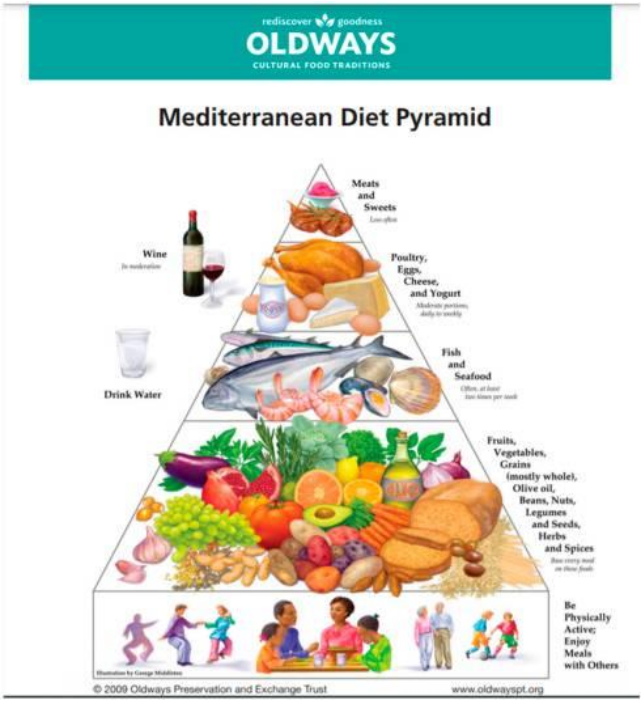

Figure 5: Mediterranean Diet Pyramid. This diet consists of eating more fruits, vegetables, nuts, and seeds. An olive while eating minimal amounts of red meats and sweets (Taken from Milenkovic 2021)

Another diet that has shown improvements in diabetic patients is the DASH (Dietary Approaches to Stop Hypertension) diet. It is very similar to the Mediterranean diet in which whole grains, vegetables, and fruits are at the forefront. The main difference between the two is that the Mediterranean diet focuses more on consuming seafood, while the DASH diet is less restrictive and allows for more consumption of lean meats, poultry, and fish (Ley et al., 2016). An additional benefit of this diet is that it has favorable effects on lowering low-density lipoprotein (LDL) cholesterol and blood pressure (Ley et al., 2016).

Lastly, vegan (a diet consisting of no animal-derived products) and vegetarian (a diet consisting of partial animal-derived products) diets have also been tested in diabetic people, but these diets have not consistently shown improvement regarding glycemic control like the other diets have (Ley et al., 2016). These diets did have on an effect on weight loss, however, and improved triglyceride and cholesterol levels (Ley et al., 2016).

Beverages

The beverage that has a significant effect on the risk of type 2 diabetes is sugar-sweetened beverages. Greater intake of sugar-sweetened beverages is associated with a higher risk of type 2 diabetes (Ley et al., 2016).

One drink that has an inverse relationship with the risk of developing type 2 diabetes is coffee. Several studies show that both caffeinated and decaffeinated coffee intake lowers the risk of diabetes (ley et al., 2016). In addition to coffee, drinking tea, especially green tea, has beneficial effects by decreasing fasting blood glucose.

The effects of alcohol seem to be dose dependent (Ley et al., 2016). Its effects become more harmful with increasing dosage. While more alcohol consumption is associated with increased risk, moderate consumption has improved insulin sensitivity (Ley et al., 2016).

Exposure to cigarette smoking, whether via first-hand or second-hand smoke, also increases type 2 diabetes risk (Ley et al., 2016). Furthermore, heavy smokers are more susceptible than light smokers.

Vitamins and Minerals

Other lifestyle factors that play a role in the susceptibility of developing Type 2 diabetes include vitamins and minerals. Vitamins such as Vitamin D and Vitamin K have beneficial effects on reducing diabetes risk (Wu et al., 2014).

One mineral that has been found to have an inverse association with diabetes risk is higher magnesium intake (Ley et al., 2016). Magnesium is a major component of many healthy foods that should be a part of the diet of a diabetic person. It is widely distributed in foods such as whole grains, green leafy vegetables like spinach, nuts, and seeds, and it is even added to some breakfast cereals (Schwalfenberg & Genius, 2017). Magnesium is an abundant mineral in the body and is a necessary cofactor in various metabolic reactions. Magnesium is required for biochemical reactions such as energy production, glycolysis, and oxidative phosphorylation (Schwalfenberg & Genius, 2017). It also regulates protein synthesis, glucose control, blood pressure, and muscle and nerve function (Schwalfenberg & Genius, 2017). It plays a role in maintaining the integrity of bone, is required for DNA and RNA synthesis, and plays a role in maintaining ion balance across the cell membrane (Schwalfenberg & Genius, 2017). Regulating ions is important because it is important for nerve muscle contraction and normal heart rhythm.

Vitamin D concentrations has an inverse association with diabetes risk. Aside from taking vitamin D supplements, plasma Vitamin D is a good indicator of having a healthy lifestyle as it is an indicator of frequent outdoor physical activities (Wu et al., 2014). Recent studies have shown that vitamin D deficiency can have detrimental effects on

glucose intolerance and insulin secretion (Wu et al., 2014). This is especially important because vitamin D production and insulin production are related. The vitamin D receptor and 1-alpha-hydroxylase (the enzyme that catalyzes the conversion of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D (the active form of vitamin D)) are both present in pancreatic B cells, which shows that vitamin D plays a significant role in insulin release, synthesis, and sensitivity (Sung et al., 2012)Vitamin D also plays a role in regulating the absorption of calcium and proper growth and development of bones and teeth. The role that Vitamin D plays in lowering blood sugar levels makes it a good form of therapy for diabetics.

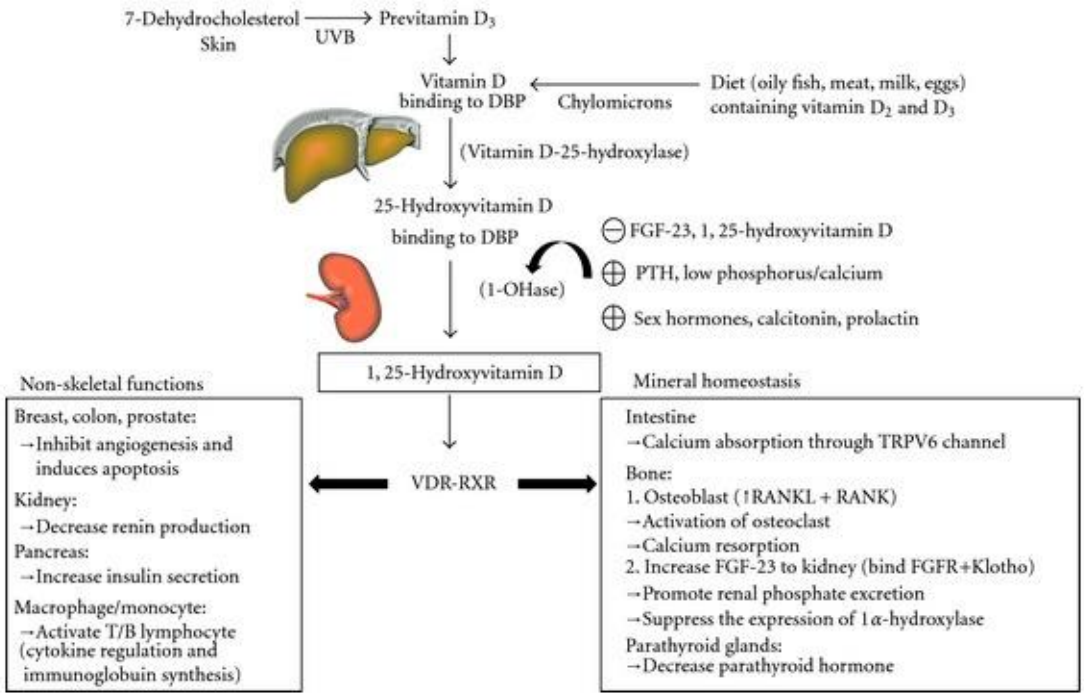

Figure 6: Synthesis and Metabolism of Vitamin D. Vitamin D functions in maintaining homeostasis within the body by affecting multiple organs (Taken from Sung et al., 2012)

Vitamin K plays several roles in maintaining homeostasis in the human body. Its main function is to maintain bone quality by promoting expression of osteoblasts, which are cells that synthesize bone. Increased levels of Vitamin K contribute to decreased risk of type 2 diabetes by providing glucose homeostasis (Wu et al., 2014).

Leisure Time and Physical Activity

In addition to diet, another key determining factor that can predispose someone to developing type 2 diabetes is the level of physical activity. The activities one chooses to do for their leisure time, or even the type of occupation one has can determine how much physical activity one will get throughout the day. Low levels of physical activity are inversely associated with diabetes risk. Epidemiological studies show that levels of physical activity reduce the risk of diabetes by approximately 30% (Kolb & Martin, 2017). Various experiments also show that by reallocating 30 minutes of sedentary time and changing it to any sort of moderate to vigorous physical activity, insulin sensitivity can be improved by 15% (Kolb & Martin, 2017).

Closely related to the level of physical activity one has is the amount of sedentary time. Sedentary time refers to any time spent doing activities that involve sitting or in a reclining or lying posture (but not sleeping). People can spend a lot of time being sedentary at work, home, or school depending on the lifestyle. Studies show that increased sedentary time doubles diabetes risk and is strongly associated with obesity as well (Kolb & Martin, 2017). There was one study that illustrates that for every one hour of television, the risk of developing diabetes increased by 3.4% over 3.2 years (Kolb &

Martin, 2017). The reason why this is especially dangerous is because a sedentary lifestyle promotes obesity and vice versa, so the situation never gets better. Diabetic patients should try to make sure that some form of movement is a part of their daily routine because reports have shown beneficial metabolic effects from moving such as obtaining less body fat over time and increasing energy expenditure levels (Kolb & Martin, 2017).

Figure 8 shows that there is a dose-response association between sedentary time and diabetes occurrence.

One factor that can be overlooked when considering someone's health status is the duration and quality of sleep. Some things that can diminish the quality of one's sleep include if someone has extended working hours or night-time exposure to noise or light. Increased exposure to noise, traffic on a busy road, or pollution may cause sleep disturbances, and this is associated with a higher risk of type 2 diabetes by 20-40% (Kolb & Martin, 2017). While diminished sleep is a risk factor for diabetes, it is important to have the optimal amount of sleep. Extra hours of sleep above the optimal amount increases chances of getting type 2 diabetes (Kolb & Martin, 2017). There is a meta-analysis that shows that the lowest risk of developing diabetes is when someone receives 7-8 hours of sleep per day (Shan, 2015). For every 1 hour shorter or longer sleep duration, the risk is increase by 9% (Shan, 2015).

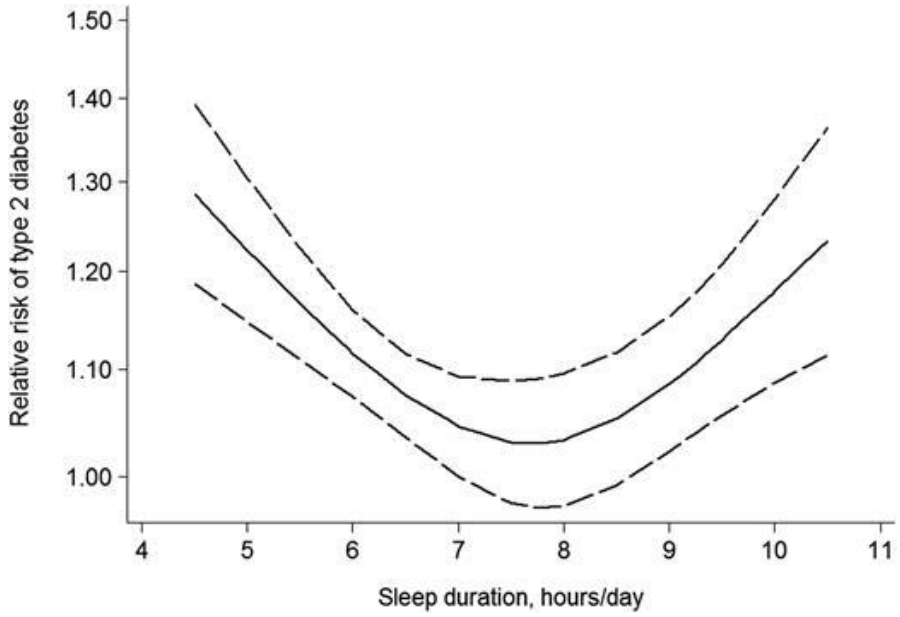

Figure 7: Relationship Between Sleep Duration and Type 2 Diabetes Risk. The lowest risk of developing type 2 diabetes is at 7-8 hours of sleep. (Taken from Shan 2015)

Psychological Factors

Two very important risk factors to consider that affects diabetes patients or prediabetics are stress/anxiety and depression. Depression is a very serious medical condition that is present in both low and high-income countries but is more prevalent in high income countries (Kolb & Martin, 2017). According to the DSM-5, depression disturbs emptions, cognition, and behaviors and is characterized by symptoms such as irritability, anhedonia, loss of self-esteem, fatigue, difficulty concentrating, suicidal thoughts, weight changes, changes in activity, and sleep changes (Badescu et al., 2016). Depression rates are two times higher in patients with diabetes type 2 compared to the

general population and anxiety is prevalent in about 40% of patients with type 2 diabetes (Badescu et al., 2016). Both risk factors are dangerous, and their presence worsens the prognosis in addition to increasing non-compliance to medical treatment and increasing the mortality rate. Like obesity and diabetes, depression and diabetes also have a bidirectional association (Badescu et al., 2016). Some people are more prone to becoming depressed due to certain epigenetic factors that activate specific pathways (Kolb & Martin, 2017). Some of these epigenetic factors include previously mentioned risk factors such as poor quality of sleep, poor diet, lack of physical exercises, and low socioeconomic status (Kolb & Martin, 2017). The main pathway that causes stress to affect the body is through the activation and disturbance of the stress system. Two systems are activated: the hypothalamus-pituitary-adrenal (HPA) axis and the

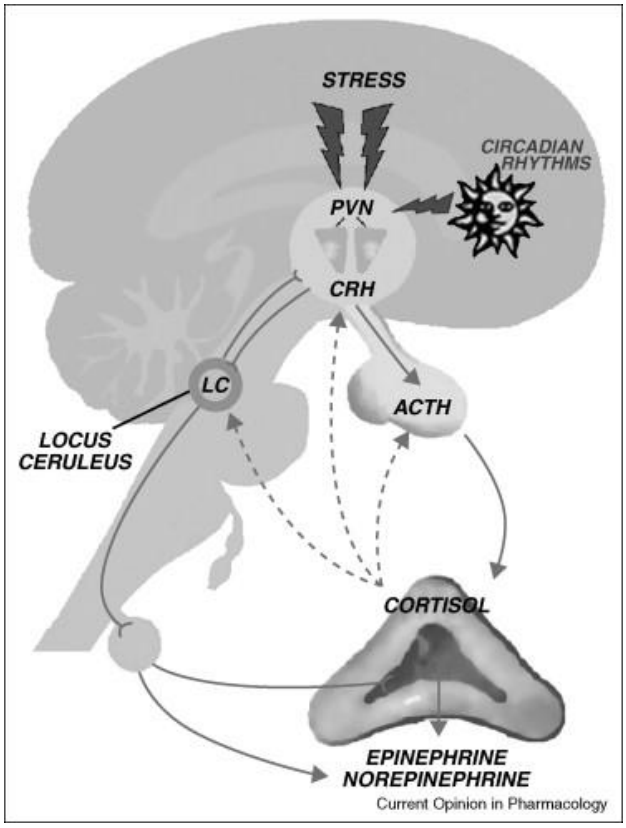

Figure 8: Stress-Induced Activation of the HPA Axis. (Taken from Kyrou & Tsigos, 2009)

sympathetic nervous system (Badescu et al., 2016). Through this system, there are increases in cortisol and adrenaline, and prolonged activation causes hypercortisolemia and increased production of these hormones promote insulin resistance, obesity, metabolic syndrome, and type 2 diabetes mellitus (Badescu et al., 2016).

Chronic stress also affects the immune system by promoting the production of inflammatory cytokines (Kolb & Martin, 2017). These inflammatory cytokines interfere

with the normal function of the pancreatic beta-cells of the Islets of Langerhans. This also results in insulin resistance and contributes to the development of depression.

Socioeconomic Status and Race

Most of the above-mentioned risk factors are modifiable. However, there are also non-modifiable risk factors that contribute to the development of type 2 diabetes. Such factors include socioeconomic status and minority status. Socioeconomic status is a major determinant of type 2 diabetes mellitus. Research from various countries indicate that diabetes type 2 is more prevalent in people with lower education and income (Assari et al., 2017). Along a social gradient, the highest prevalence of diabetes is in the people with the lowest socioeconomic status (Assari et al., 2017).

Another non-modifiable risk factor is minority status. Black people have a higher risk of type 2 diabetes, lower socioeconomic status, and worse outcomes if they have diabetes (Assari et al., 2017). The prognosis is especially worse in black people because the other risk factors mentioned before are all more common among the Black population such as obesity, poor nutrition, and not enough exercise (Assari et al., 2017).

These risk factors are especially more common among blacks who live in urban areas (Assari et al. 2017). Some more uncontrollable risk factors include physician care. Blacks suffer worse health outcomes and are more prone to further complications and a higher rate of mortality (Assari et al., 2017). Poorer quality and less frequent care further potentiate such statistics.

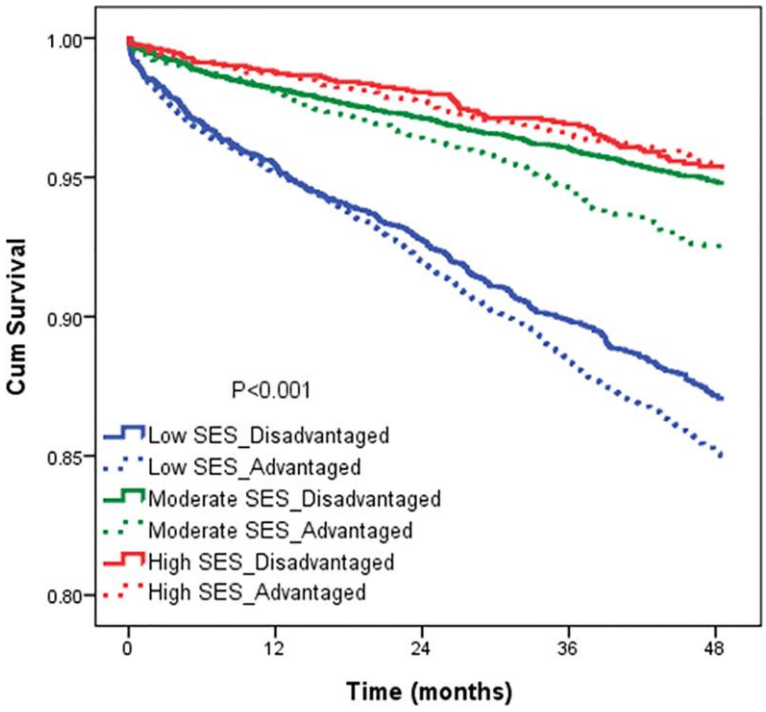

Figure 9: Survival Levels of T2DM Patients With Different Socioeconomic Statuses. High income people have a better chance of survival than low income. (Taken from Yang et al., 2017)

Overall, there are a variety of factors that interact to increase someone's risk of developing type 2 diabetes mellitus. Some of these factors directly affect beta-cell function, while others indirectly affect beta-cells. These factors may have distant sites of action such as the immune system, adipose tissue, liver, muscle, brain, microbiome, and many other systems. These organs all influence each other and the effect on each system of the body can overlap.

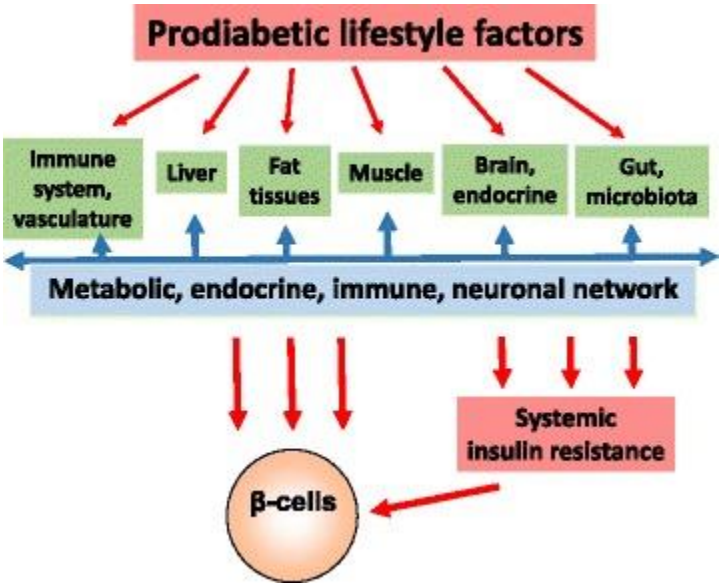

Figure 10: Prodiabetic Lifestyle Factors Effect on Organ Systems. Various factors interact with multiple organ systems to promote Beta-cell dysfunction (Kolb & Martin, 2017)

COMPLICATIONS OF DIABETES

Complications of type 2 diabetes mellitus include both microvascular and macrovascular diseases. Examples of macrovascular diseases include hypertension, coronary artery disease, strokes, vascular diseases, and heart attacks. Microvascular diseases include retinopathy, nephropathy, and neuropathy (Wu et al., 2014). Chronic hyperglycemia plays a role in the initiation of these vascular complications via abnormal activation of signaling cascades, increased production of reactive oxygen species, and stimulation of various regulation systems (Singleton et al., 2003). Cancers such as liver, kidney, bladder, and colorectal can also occur as a result (Wu et al., 2014).

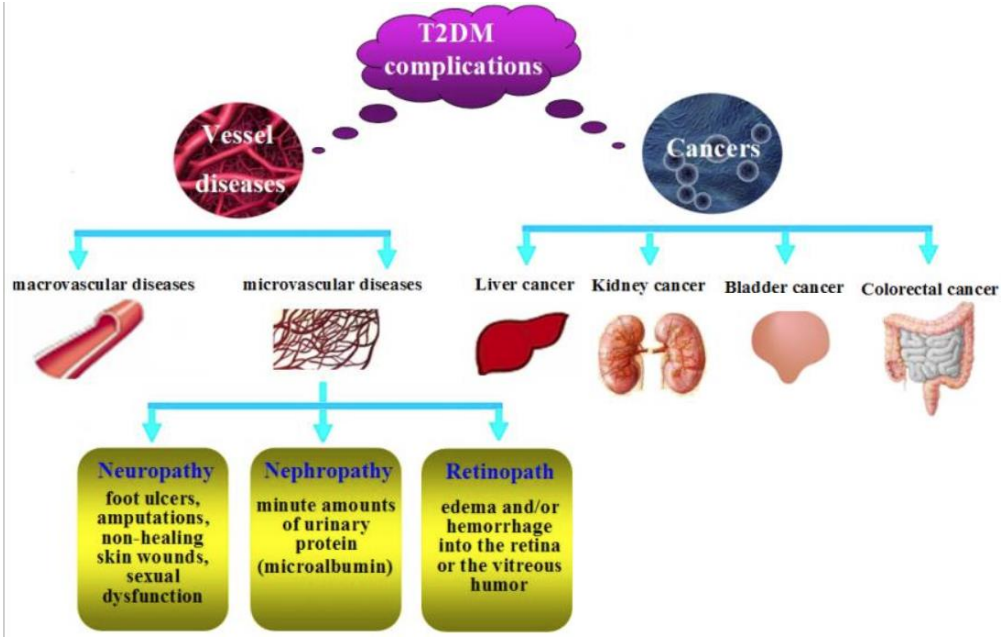

Figure 11: Complications of Type 2 Diabetes Mellitus. The 3 main -pathies of diabetes include diabetic neuropathy, nephropathy, and retinopathy. Some cancers may also arise such as liver, kidney, bladder, and colorectal. (Taken from Wu et al., 2014)

Microvascular Complications

The three microvascular complications of diabetes include diabetic retinopathy, neuropathy, and nephropathy.

Diabetic retinopathy can affect many parts of the eye, but it especially affects the retina or the macula or both. The retina is one of the most important parts of the eye because its job is to convert the light that enters the eye to signals that can be sent to the brain to create images for people to see (Cade, 2008). It is also the most vascular region in the body, which means it requires a lot of oxygen (Wu et al., 2014). There are two categories of retinopathy: proliferative and non-proliferative. Proliferative retinopathy refers to the

abnormal growth of blood vessels and is more dangerous than non-proliferative (Cade, 2008).

Retinopathy may cause partial, total, or central vision loss. The mechanism of action is via hyperglycemia. Chronic hyperglycemia causes microvascular damage to the vessels in the retina, causing macular edema and/or hemorrhage into the retina due to vascular permeability (Cade, 2008). Macular edema is diagnosed by the observation of thickening of the retina and/or hard exudates (Cade, 2008). Diabetic retinopathy is the leading cause of blindness in people with diabetes.

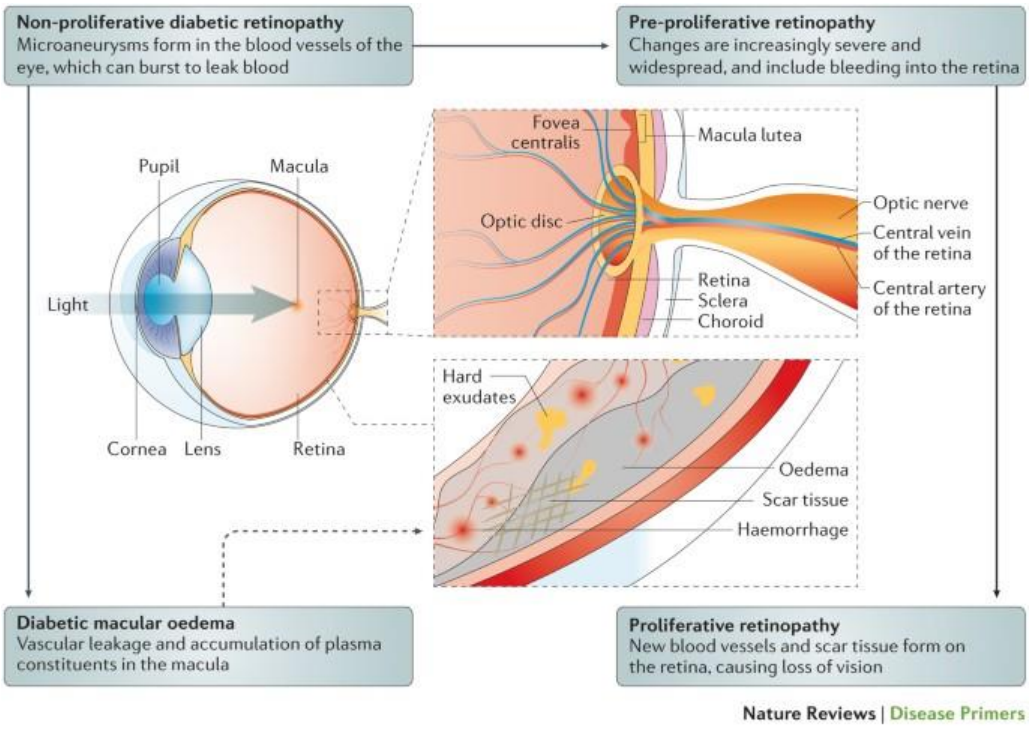

Figure 12: Stages and Clinical Manifestations of Diabetic Retinopathy. The main states include non-proliferative to pre-proliferative to proliferative retinopathy which can lead to macular edema. (Taken from Wong 2016)

Hyperglycemia is the most significant factor in the progression of retinopathy because it impairs retinal blood flow and causes hypoxia which damages the blood vessel. A physician would see common symptoms such as blurred vision, vision loss, fluctuating vision, or blind spots in one's vision (Cade, 2008).

The chance of developing retinopathy increases the longer one has diabetes, and studies show that people with both type 1 and type 2 diabetes will eventually develop some form of retinopathy, especially the proliferative kind (Cade, 2008). Furthermore, type 1 diabetic patients have the highest prevalence of retinopathy and type 2 diabetics patients have the lowest (Cade, 2008). Other confounding variables can increase the chances of retinopathy even in people with prediabetes such as hypertension and a higher body mass index.

One important transcription factor that plays an important role in the development of proliferative diabetic retinopathy is VEGF. Proliferative retinopathy refers to the proliferation of blood vessels, known as angiogenesis. The function of VEGF is to create new blood vessels during embryonic development, after injury, and following exercise (Shibuya, 2011). It plays a role in both vasculogenesis and angiogenesis (Shibuya, 2011). Excess proliferation of blood vessels can lead to disease and the promotion of tumorigenesis.

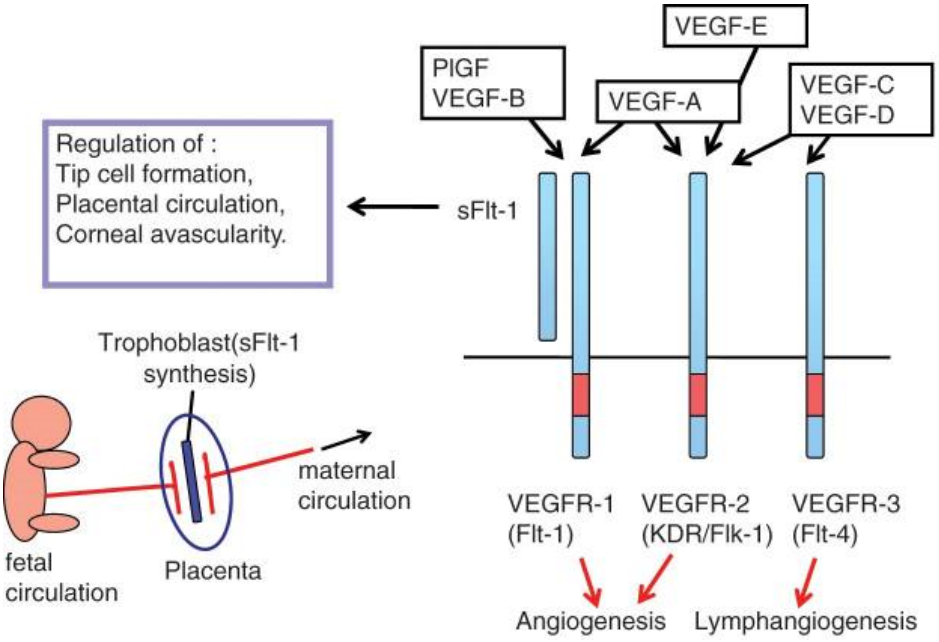

Figure 13: The VEGF and VEGF Receptor. VEGF plays a major role in angiogenesis and vasculogenesis, which is especially important in regulating blood vessel growth in the retina. (Taken from Shibuya 2011).

One of the major histological markers of diabetic retinopathy is the loss of pericytes (Cade, 2008). Pericytes are cells that surround endothelial cells that serve a protective role in maintaining capillary tone and growth (Cade, 2008). The effect that the loss of pericytes has on the eyes is the inability of the capillaries to constrict, causing vessels that are always dilated and loss of protection from reactive oxygen species (Cade, 2008). Another histological marker is the presence of microaneurysms in the eye.

Neuropathy is another microvascular complication associated with type 2 diabetes. Neuropathy refers to damage or dysfunction of nerves that can result in various uncomfortable sensations such as numbness, tingling, muscle weakness, and pain in affected areas (Cade, 2008). The most affected areas are the arms and legs. Some effects

of neuropathy include foot ulcers, wounds, amputations, and even sexual dysfunction (Wu et al., 2014). If the neuropathy gets worse, it can eventually lead to loss of sensation in the feet, callus formation, infection and then gangrene (Wu et al., 2014). Aside from the neuropathy affecting the upper and lower extremities, one might also experience axonal thickening, loss of microfilaments, and decreased capillary blood flow (Cade, 2008).

Of the three most common diabetic microvascular complications, diabetic nephropathy is one of the most important. The first clinical manifestation of nephropathy is microalbuminuria, which refers to increased albumin levels in the urine (Cade, 2008). Albumin is a protein that is not filtered in the blood under normal conditions. However, a damaged kidney allows albumin to be filtered and for it to pass from the blood into the urine (Koye et al., 2017). Albumin in the urine is an indicator of a non-functional kidney. Some other characteristic features of nephropathy include thickening of the glomerular basement membranes as well as hyperfiltration (Koye et al., 2017).

Another kidney-related condition that can arise in diabetic patients is CKD (chronic kidney disease). It is characterized by albuminuria and reduced glomerular filtration rate (GFR) (Usherwood & Lee, 2021). The reduced glomerular filtration rate is a problem because it decreases the ability of the kidney to get rid of the wastes that the body's wastes.

With chronic kidney disease, there are many further complications that affect different areas of the body. One common complication that can arise is anemia. Anemia develops

because patients with chronic kidney disease have a deficiency in erythropoietin production due to the destruction of interstitial cells in the kidney, which are the main source of erythropoietin (Usherwood & Lee, 2021). Furthermore, because iron deficiency is also common in patients with this disease, and erythropoiesis depends on sufficient ion stores, it is easier for anemia to persist (Usherwood & Lee, 2021). Another complication arising from chronic kidney disease are bone disorders because of a disturbance in mineral homeostasis. Levels of calcium, phosphate, parathyroid hormone, and vitamin D are altered, and this causes diminished bone strength and soft tissues (Usherwood & Lee, 2021). It is expected to find lower levels of 1,25-(OH)2 D3 (the active form of Vitamin D) and elevated serum phosphate due to reduced excretion (Usherwood & Lee, 2021).

There is a common mechanism in which both the microvascular diseases affect various parts the body. This involves the production of AGE (advanced glycation end products) which are proteins that re exposed to sugars and become glycated (Cade, 2008). This is often used as a marker of when a degenerative disease is getting worse.

For example, if AGE is present in retinopathy, it can induce apoptosis of retinal pericytes, overproduction of endothelial growth factors such as VEGF, increase neovascularization and inflammation (Cade, 2008). These effects combined can led to worse outcomes such as retinal ischemia which can then lead to retinal fibrosis and/or detachment and vision loss (Cade, 2008). Ultimately, AGE can cause a cascade of events to occur which can lead to endothelial cell dysfunction.

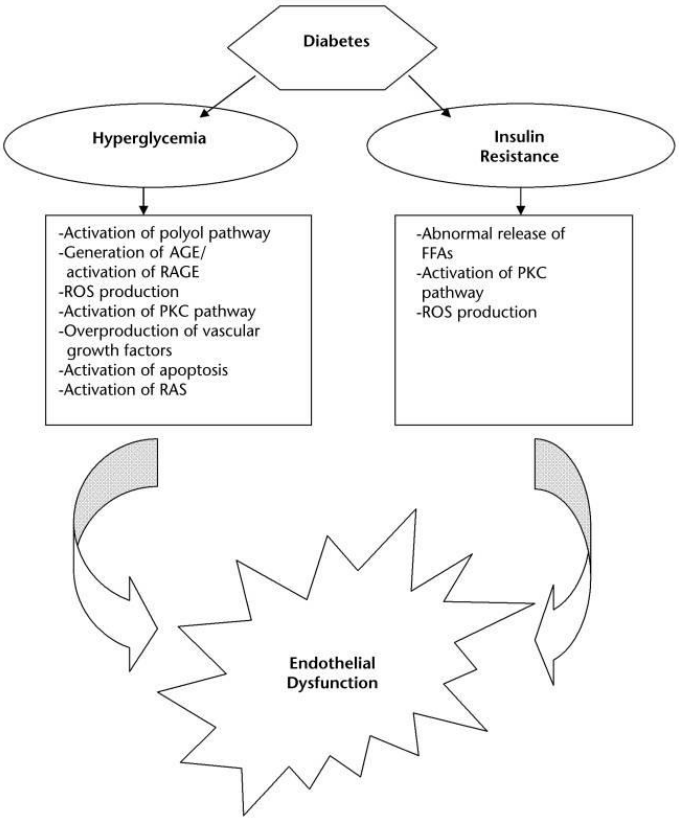

Figure 14: Diabetes Pathway for Endothelial Dysfunction. The path towards endothelial dysfunction stems from hyperglycemia and insulin resistance which triggers the activation of various pathways. (Taken from Cade 2008)

If AGE is present in nephropathy, it can contribute to death of mesangial cells, which play a role in removing debris from the glomerulus, as well as the over secretion of growth factors which decrease the glomerular surface area for filtration (Cade, 2008).

Macrovascular Complications

In addition to microvascular diseases, there are also macrovascular complications of type 2 diabetes. Examples include cardiovascular disease, cerebrovascular disease, and peripheral artery disease.

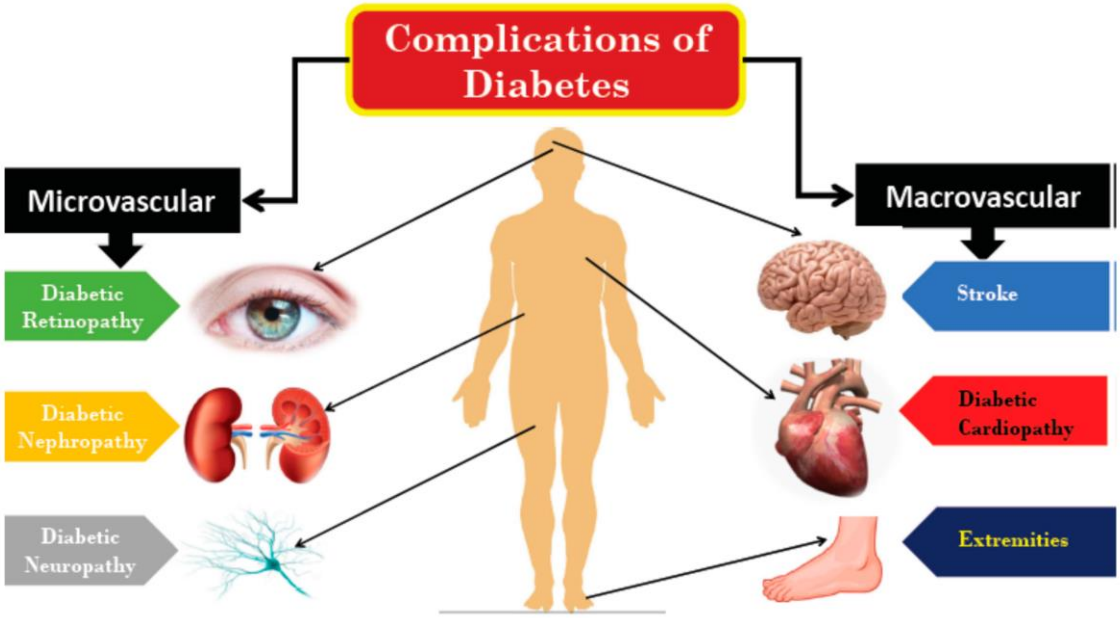

Figure 15: Two Categories of Diabetes-Based Complications. Complications fall into microvascular and macrovascular complications which affect various organs such as the brain, heart, kidneys, lungs, feet, and eyes. (Taken from Oh et al., 2020)

Cardiovascular disease is the leading cause of death in people with type 2 diabetes (Cade, 2008). In addition to being susceptible to cardiovascular disease, diabetics are also at a greater risk for a myocardial infarction and congestive heart failure (Cade, 2008). Stroke is the third leading cause of death (Wu et al., 2014). In people with diabetes, the cerebrovascular circulation is interfered with, and there is an increased risk of intracranial, and extracranial atherosclerosis (Cade, 2008).

Another macrovascular complication that is like one of the microvascular complications spoken about is peripheral artery disease. This disease refers to narrowing or blockage of

the vessels that supply the lower extremities, which can cause pain and functional impairments such as difficulty walking (Cade, 2008).

The mechanism for the way macrovascular disease causes effects on the body is not singular; it is multifactorial. The basic mechanism is via injury to the vascular endothelium, which impairs its ability to vasodilate by inhibiting nitric oxide production (Cade, 2008). The result is the production of reactive oxygen species.

With the many complications that can arise with diabetes, there should be some treatment to help manage the symptoms. Currently, type 2 diabetes is not a curable disease but there are some treatments to be used as well as prevention options.

PREVENTION AND TREATMENT OF TYPE 2 DIABETES

There is no cure for diabetes, but to manage symptoms, physicians recommend lifestyle modifications such as obesity management, improving diet, and physical activity changes.

Physical inactivity is an issue that contributes to the development of type 2 diabetes and the obesity epidemic. Types of physical activity that have proven to be effective include walking for at least 150 minutes per week, cycling, swimming, or gym-based activities (Wu et al., 2014). Studies show that increasing levels of physical activity can reduce diabetes risk by 30-50% (Wu et al., 2014).

Diet is another important factor in preventing/managing the development of type 2 diabetes. A diet rich in whole grains, fruits and vegetables, dairy, and nuts and legumes are what is best to maintain a healthy lifestyle (Wu et al., 2014).

Treatments: Pharmacological Agents

If diet and exercise are not enough to manage type 2 diabetes, diabetic medications or forms of insulin might be needed.

Table 4: Antidiabetic Agents for Managing Type 2 Diabetes Mellitus

Class	Drug (s)	Target	Action (s)	Disadvantages
Biguanides	Metformin	AMP-kinase	blood glucose↓ insulin sensitivity↑ cardiovascular risk↓ hypoglycemia risk↓	GI side effects lactic acidosis Vitamin B12 and folate deficiency
Sulfonylureas	Glyburide/ Glipizide/ Gliclazide/ Glimepiride	ATP-sensitive, K+ channels	insulin secretion↑	hypoglycemia weight gain
TZDs	Troglitazone/ Roziglitazone/ Pioglitazone	PPAR-γ	insulin sensitivity↑ hypoglycemia risk↓ glycemic control↑	bladder cancer risk↑ weight gain edema
AGIs	Acarbose/ Miglitol/ Voglibose	α-glucosidase	carbohydrate absorption↓	GI side effects dosing frequency
GLP-1 receptor agonists	Exenatide/ Liraglutide	GLP-1 receptors	insulin secretion↑ glucagon secretion↓ satiety↑ hypoglycemia risk↓	GI side effects acute pancreatitis renal dysfunction thyroid C-cell tumors in rodents

(Table taken from Wu et al., 2014)

The most common antidiabetic drug used in the treatment of type 2 diabetes is Metformin which is under a class of drugs known as Biguanides (Wu et al., 2014). Metformin is a first line therapy for diabetic patients, so it is the medicines doctors first resort to for diabetes. It has an effective role in lowering blood glucose levels while reducing the risk of hypoglycemia and improving insulin sensitivity (Wu et al., 2014). Metformin lowers blood glucose by reducing metabolic reactions such as gluconeogenesis and glycogenolysis and upregulating metabolic reactions such as glycogenesis in skeletal muscle (Olokoba et al., 2012). Furthermore, Metformin activates AMPK which acts on hepatic glucose stores to manage glucose tolerance (Wu et al., 2014). The special effect that Metformin has on diabetic patients is that it is the only drug that improves the above-mentioned macrovascular outcomes and reduces mortality rates (Wu et al., 2014).

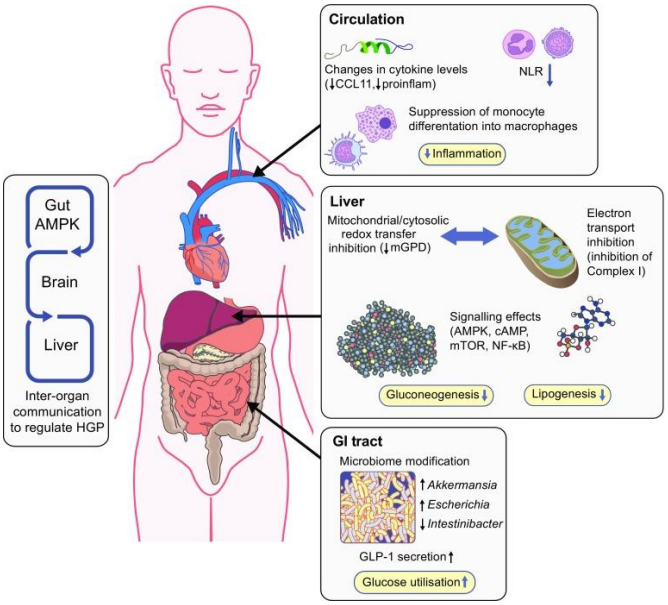

Figure 16: Metformin Effects on Metabolism and Inflammation. Of most importance, Metformin reduces gluconeogenesis in the liver and increases glucose utilization in the GI tract. (Taken from Rena et al., 2017)

Another class of drugs commonly used to treat type 2 diabetics are sulfonylureas. This is different from Biguanides because sulfonylureas are second line agents. They are specifically used for patients who are not severely obese, but in general, second line agents are used when the first-line treatment is not producing the necessary results that need to be seen in the patient. Sulfonylureas work by acting directly on the beta cells of the Islets of Langerhans to close the potassium channels for insulin secretion to occur (Wu et al., 2014). The caveat to the efficacy of sulfonylureas is that they require the presence of enough functional beta cells to work. Unlike Metformin, sulfonylureas have a higher rate of hypoglycemia because they also stimulate endogenous insulin secretion (Olokoba et al., 2012). Due to this fact, sulfonylureas should be monitored in patients who have impaired renal or hepatic function.

In addition to first- and second-line agents, another type of therapy used in the treatment of type 2 diabetes is thiazolidinediones. They are a class of insulin sensitizers, which are drugs that improve the sensitivity of cells to the effects of insulin (Wu et al., 2014). Thiazolidinediones work by increasing the skeletal muscle, adipocytes, and liver's sensitivity to insulin (Wu et al., 2014). They are known as euglycemics, drugs that return blood sugar levels back to normal. They work by activating PPAR, which controls insulin sensitivity (Olokoba et al., 2012). These drugs are most effectively used when in combination with other antidiabetic agents but especially insulin (Wu et al., 2014). This

combination provides the ability to lower blood glucose levels without causing hypoglycemia as well as to lower the high insulin dosage. These drugs are the first drugs to address the problem of insulin resistance.

The fourth class of drugs used in the treatment of type 2 diabetes are alpha-glucosidase inhibitors (AGIs). These drugs are unique because they specifically focus on affecting postprandial hyperglycemia (Olokoba et al., 2012). They exhibit their effects on the body by inhibiting the intestinal enzyme, alpha-glucosidase, which converts complex polysaccharides into simple monosaccharides (Wu et al., 2014). Essentially, alpha-glucosidase inhibitors inhibit the absorption of carbohydrates from the small intestine. These drugs work by competitively inhibiting drugs such as maltase, sucrase, alpha-amylase etc. By delaying carbohydrate absorption, it delays the spike in blood sugar levels that usually occurs after ingestion of a meal. Gastrointestinal side effects can occur with this drug.

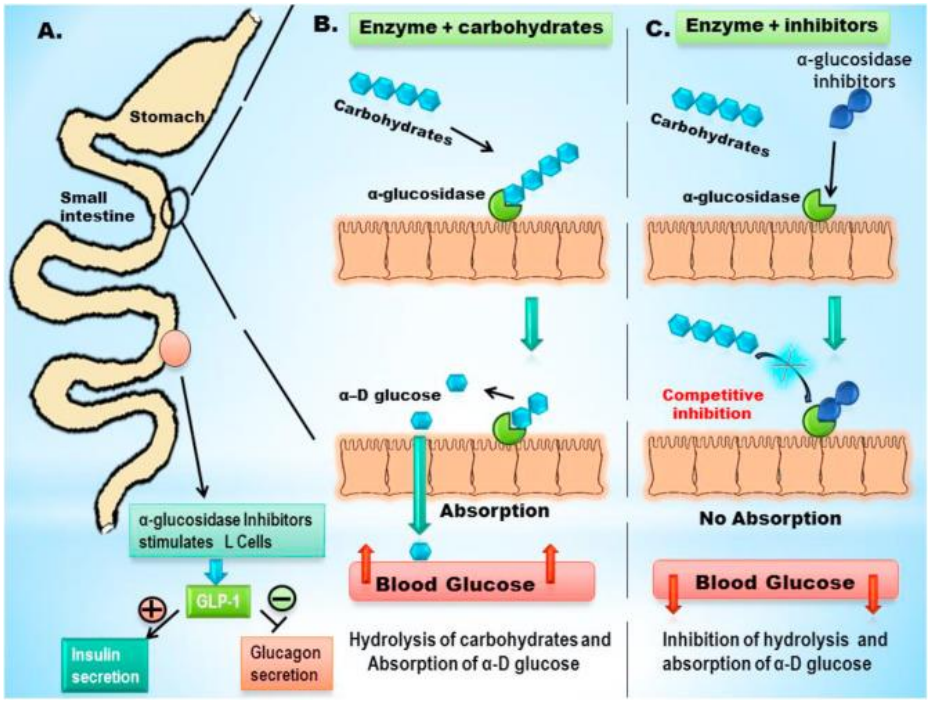

Figure 17: Mechanism of Action of Alpha-glucosidase Inhibitors. Alpha-glucosidase inhibitors controls postprandial hyperglycemia by preventing the absorption of carbohydrates via competitive inhibition (Taken from Hossain et al., 2020)

The last class of drugs that are used in the treatment of type 2 diabetes are incretin-based therapies. Incretin is a hormone responsible for stimulating insulin secretion while suppressing glucagon secretion after meals (Wu et al., 2014). These drugs tie in with another class of drugs known as GLP-1 receptor agonists. They relate to each other because incretins are secreted from intestinal cells such as GLP-1 or GIP (Wu et al., 2014). GLP-1 receptor agonists have the same mechanism of action as incretin-based therapies. They are especially effective at reducing HbA1c levels by up to 1.5% (Olokoba et al., 2012).

When people with type 2 diabetes have not achieved their target blood glucose levels after changes in exercise, diet, or anti-diabetic drugs, they may require insulin. Insulin is the most effective anti-hyperglycemic agent and can manage glucose levels even when other anti-diabetics did not prove to be effective (Wu et al., 2014). Insulin works by suppressing hepatic glucose production and allowing better utilization of glucose after eating (Wu et al., 2014). Furthermore, insulin therapy can decrease the effects of glucose toxicity on the body by improving beta cell function and the way tissues in the body respond to insulin (Wu et al., 2014).

Insulin analogues are like insulin; these drugs mimic the effect of the natural insulin that is made in the body (Olokoba et al., 2012). Insulin analogues have various injectable forms, ranging from rapid acting to long acting, and the long-acting insulin analogues have proven to be the most effective (Wu et al., 2014).

In addition to oral hypoglycemic agents and insulin therapies, which are more standard forms of medications, there are also new therapeutic strategies being examined for future use. Examples of such medications SGLT2 inhibitors, DPP-4 inhibitors, stem cell educator therapy, and antioxidant therapy (Wu et al., 2012).

CONCLUSION

Type 2 diabetes mellitus is a chronic disease that results from elevated blood sugar levels. It is an impairment in the way the body responds to insulin due to beta cell malfunction. Diabetes leads to major disorders of the renal, nervous, immune, cardiovascular, and circulatory systems. This disease is caused by an interaction between genetic and environmental factors, as well as other lifestyle factors. Currently, the best way to prevent diabetes is obesity management, having a healthy diet, and increasing levels of physical activity. There is no cure for this disease, but there are many pharmacological treatment options that help to manage the symptoms. These drugs include first-line agents such as Biguanides (Metformin), which are the first resort physicians use to manage diabetes, and second-line agents such as sulfonylureas which are used for when the disease is not being managed well. These drugs have proven to be effective by suppressing hepatic glucose output and gluconeogenesis and increasing glycogen stores. Most antidiabetic agents used to treat type 2 diabetes have shown beneficial effects when used as the only treatment or in combination therapy with insulin. Researchers have made it a priority to find an ideal therapy and are currently working on new therapeutic treatments in response to increasing incidence of this disease. Further research should consider treatments that are both effective and have minimal adverse side effects, better prevention measures, and earlier diagnosis for earlier treatment to reduce the prevalence of type 2 diabetes and improve the quality of life.

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