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Comparing and Contrasting Therapeutic Drugs Vs. Lifestyle Changes That CombatType-II Diabetes

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Evaluation of Therapeutic Treatments for Type-II Diabetes

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Type-II diabetes is considered to be one of the most common metabolic disorders world-wide which is characterized by hyperglycemia, elevated blood glucose levels. Epidemiological studies of this chronic disorder identify two major problems in the body that lead to this increase in glucose which include a deficiency in insulin secretion by pancreatic beta-cells along with decreased insulin response from insulin-sensitive tissues.[1] Currently there are two distinct categories of strategies that are used to treat, manage, and prevent this disorder. This paper discusses both therapeutic drug targets and lifestyle change as a means to combat this disease along with placing emphasis on the preventative aspect for developing type-II diabetes.

Pathophysiology of Type-II Diabetes

The development of type-II diabetes is primarily caused by 2 pathophysiological features happening in the body which include impaired insulin secretion from pancreatic beta-cells along with decreased insulin sensitivity which is commonly referred to as insulin resistance due to the inability of insulin-sensitive tissues being able to respond to insulin. Essentially, the type-II diabetic outcome can be viewed as a malfunction between feedback loops that are involved in both insulin secretion and insulin resistance promoting the amplification of hyperglycemia resulting in the diagnoses of type-II diabetes.[1] Studies have shown that the impaired insulin secretion can be linked to genetic pre-dispositions in the development of type-II diabetes. Specifically, with type-II diabetic patients, other late pathophysiological features can affect various organs in the body including the eyes, kidneys, and nerves.[2]

Pancreatic Beta-Cell Physiology

Impaired insulin secretion is the lack of response to glucose from insulin caused by the dysfunction of pancreatic beta-cells which limits the regulation the body has on maintaining physiological glucose levels. The role of pancreatic-beta cells is the production of insulin which

is then synthesized as pre-proinsulin. Proinsulin is then produced by proteins from the Endoplasmic Reticulum which travels to the Golgi Apparatus where it is cleaved into both insulin and C-peptide. From here, matured insulin is released in response to high glucose concentrations. The signaling pathway of insulin secretion from pancreatic beta-cells in humans without type-II diabetes can be observed in **Figure. 1**. [1] In a patient without type-II diabetes, an

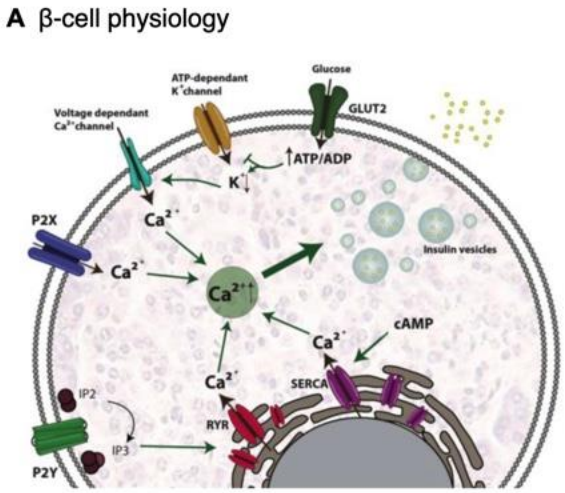

Figure 1. Pancreatic Beta-Cell Physiology

increase in glucose levels will prompt pancreatic beta-cells to take in glucose molecules via GLUT2 transporter which activates glucose catabolism causing the increase in the intracellular ATP/ADP ratio. This closes the ATP-dependent K+ channel, leading to depolarization of the cell, and ultimately openes the voltage dependent Ca^{2+} channel allowing for triggering insulin secretory vesicles to secrete insulin promoting insulin exocytosis.[1]

Regarding the mechanism leading to pancreatic beta-cell dysfunction, there are a variety of factors that can lead to this decrease in insulin secretion. Patients with obesity, hyperlipidemia, and hyperglycemia display an excessive nutritional state which causes pancreatic beta-cells to lose their islet integrity. It results from inflammatory stress on the Endoplasmic Reticulum causing metabolic and oxidative stress. [1] Other studies have evaluated

the relationship between size and pancreatic beta-cell function; however, there is no confirmed data that the lack of insulin secretion is due to the decrease in beta-cell mass.[2]

Insulin Resistance

The second contributing pathophysiological feature that contributes to hyperglycemia in the body and development of type-II diabetes is insulin resistance. This feature refers to the metabolic response of insulin-responsive cells to become impaired or have a reduced response to insulin in the bloodstream due to presence of increased glucose levels. Insulin resistance can also be expanded into 3 categories including decreased insulin secretion by pancreatic beta cells, presence of insulin antagonists in the plasma impairing insulin receptors, and impaired insulin response to target tissues. [1] There are multiple insulin resistant sites in the body which include skeletal muscle, liver, and adipose tissue which potentially causes a type-II diabetic diagnosis. Specifically, in the liver, the effect of insulin resistance will increase glucose production, hepatic glucose-6-phosphatase in the glucose cycle pathway, and enhance the gluconeogenesis process.[2] In addition to these outcomes, insulin resistance in the liver will also contribute to the decrease in glucose uptake in insulin-sensitive tissues such as skeletal muscle and adipose tissue. The presence of insulin resistance in skeletal muscle can be explained by either mutations that ultimately reduce the expression of GLUT4, the insulin receptor, or malfunctioning to either downstream or upstream signaling pathways. In addition to these, other mutations affecting phosphorylation sites can hinder INSR tyrosine kinase activity which is foundational to the use of insulin for glucose metabolism. Adipose tissue insulin resistance can also lead to impaired glucose uptake and impaired suppression of lipolysis. Due to the presence of insulin resistance on adipose tissue, the enhancement of glucose uptake, triglyceride uptake, and the induction of FFA uptake via the suppression of triglyceride hydrolysis becomes decreased. [1]

Prevalence and Severity of Type-II Diabetes

As stated previously, the two pathophysiological features responsible for hyperglycemia and diagnosis of type-II diabetes include both decreased insulin secretion via pancreatic beta-cells and insulin resistance of insulin-sensitive target tissue. The severity of these outcomes in the body are quite extensive and should be taken seriously. Common symptoms of hyperglycemia include headache, blurred vision, frequent urination, fatigue, increased thirst, and dry mouth. [3] Other notable reported symptoms also include extremity numbness and tingling, dry skin, unintentional weight loss, and skin infections. The severity of concerns are vast and extensive due to type-II diabetes both affecting and causing damage to major organs in the body including the heart, liver, kidneys, blood vessels, nerves, and eyes. These encompass nerve damage, heart and blood vessel disease, kidney disease leading to renal failure, eye damage that can lead to blindness, skin conditions leading to amputations, and more. [3]

Further complications for the development of type-II diabetes has the potential to lead variety of other chronic illnesses with the most severe complication being cardiovascular disease, CVD. This disease is both the most severe and most prevalent cause of morbidity and mortality in type-II diabetic patients. And in the United States alone, the death rates are 1.7 times higher among adults >18 years of age having diabetes than those who are not diagnosed with diabetes due to placing individuals at an increased risk for myocardial infarctions and strokes. In addition to CVD, a type-II diabetes diagnoses can also result in the development of hypertension, dyslipidemia, cardiovascular autonomic neuropathy, and diabetic cardiomyopathy.[4]

The prevalence of type-II diabetes worldwide is evidence by the increase in type-II diabetes diagnoses increasing from 30 million to 382 million from 1985 to 2014 with an estimate of 592 million people being diagnosed by 2035. [4] The CDC reports that nationwide, more than

37 million Americans, 1 in 10 citizens, have diabetes with 90-95% of people having type-II diabetes.[5]

Developmental Risk Factors for Type-II Diabetes

A multitude of risk factors lead to the development of type-II diabetes. The 4 major risk factors include: genetic predispositions, obesity, sedentary lifestyle, and maintaining an unhealthy diet. Globally, evidence suggest that the prevalence of type-II diabetes is highest among ethnicities that include Japanese, Native Americans, and Hispanic populations having the highest risk for developing type-II diabetes.[1] Strictly speaking about hereditary genetics, studies have shown this only contributes to approximately 5-10% of a type-II diabetic onset.[2] The same study also concluded that 70-75% of type-II diabetic patients were diagnosed due to environmental factors that relate to lifestyle. These include obesity, unhealthy eating habits, and sedentary lifestyle with obesity being considered as the strongest risk factor in developing type-II. Other risk factors that are involved with a type-II diagnosis include age, fat distribution, familial history, blood lipid levels, and polycystic ovary syndrome. [5]

Testing of Type-II Diabetes

There are different types of testing that can be performed to identify hyperglycemia, elevated blood glucose levels in the body, and the most common evaluation used is the A1C test. This test measures your blood glucose levels over the past 2-3 months with $< 5.7\%$ indicating a normal level, between 5.7 and 6.5% indicating prediabetes, and $> 6.5\%$ indicating diabetes. Other forms of testing include a fasting blood sugar test, glucose tolerance test, and random blood sugar tests which are all measured in mg/dL.[5]

After a diagnosis of prediabetes or type-II diabetes, there are a variety of ways in which a medical provider can help treat, manage, and prevent further advancement of this chronic

disorder. The first broad category of combatting type-II diabetes includes the implementation of therapeutic drug targets.

History of Drug Treatment for Type-II Diabetes

Regarding the history of Type-II diabetes, there was no effective pharmacological agents that were used to treat this chronic disease prior to the 1920s. In 1918, there were early studies conducted with guanidine; however, this study stopped in the 1920s. Charles Best and collogues researched pharmacological agents using ground up beef parts along with an acidic alcohol, filtered with toluene, and sterilized which formed insulin in 1921. The first bottle of insulin was both produced and commercialized by Eli Lilly and Company in July 1922 which led to the official commercialization of insulin in 1923. In the same year of 1922, the first exogenous insulin was administered to a human being. Other major developments of diabetic medications include the first GLP-1 receptor agonist presented in 2005 and first DPP-4 inhibitor along with the first SGLT-2 inhibitor presented in 2006. Even with the 11 various drug categories present on the drug market today specifically targeting hyperglycemic patients, insulin is still considered to be one of the most effective therapeutic drug treatments for both type-I and type-II diabetes.[6]

Common Drug Therapeutic Treatments for Type-II Diabetes

Metformin

Metformin is deemed on the first, if not the first, medication that is prescribed for type-II diabetic patients. [3] This medication belongs to the biguanide drug classification, was first introduced in the United States in 1959, formally accepted by the FDA in the 1990s, and is the only clinically significant and available drug on the market in this biguanide classification still being used today. [6] The aim of metformin is to lower hepatic glucose levels in the liver in addition to the improvement of the body's sensitivity to insulin.[3] Generally, it can be concluded

that patients taking this medication will tolerate it well along with displaying a decrease in one's A1C levels by approximately 1.5%.[6] Advantages of Metformin also include its efficacy, low cost, oral intake, and application in treating other chronic issues that encompass certain lipid improvement and reduction in cardiovascular events.[7]

The mechanism of action for Metformin is still considered to be a controversial debate regarding what the drug targets that results in decreased hepatic glucose levels. It has been shown that on a molecular scale in rat hepatocytes that Metformin targets the activation of AMP-activated protein kinase, AMPK. The activation of this enzyme is due to increased ratios between AMP:ADP and ADP:ATP. This results in a decrease in cAMP levels leading to a decreased rate in the expression of gluconeogenic enzymes.[8] One study also explains that metformin ultimately causes a reduction in gluconeogenesis. This study implemented ^{13}C NMR spectroscopy to measure the rates of glycogenolysis along with measuring the rate of glucose administration to overserve the rate of endogenous glucose production over the span of 2 months with 7 patients that had poorly controlled type-II diabetes. Subtracting these two values provided the rate of gluconeogenesis. After the use of Metformin for 2 months, the glucose production of gluconeogenesis decreased by 24%, plasma glucose concentration decreased by 30%, and the rate of gluconeogenesis decreased by 36% which led the study to draw conclusions that metformin lowers the rate of glucose production due to targeting gluconeogenesis since type-II diabetic patients display in increased rate in gluconeogenesis before Metformin use and a decreased rate in gluconeogenesis after Metformin use. [9] In addition, the diabetes prevention project concluded that the use of Metformin, 850mg twice a day, reduced the cumulative incidence of type-II diabetes from 29 to 22% over 3 years; however, it was noted that even with these results being significant, it was not as much compared to the intervention of lifestyle

change.[10] Further studies are still researching the effects of Metformin and its ability to reduce glucose levels, and current studies are targeting the effects of Metformin on the intestines rather than the liver due to Metformin displaying a delayed release that remains in the gut resulting in minimal absorption.[8]

Even though Metformin is deemed a tolerable oral medication, various side-effects from this drug have been documented and further explored. These side effects can include: vitamin B-12 deficiency, abdominal pain, nausea, vomiting, diarrhea, and bloating.[3] 20-30% of patients taking Metformin have reported gastrointestinal symptoms with 5% of patients having to discontinue the use of this drug treatment due to severe adverse side effects.[8] Another potential side effect from Metformin use includes lactic acidosis in which patients with chronic kidney disease should not be taking Metformin.[7]

Sulfonylureas

In addition to Metformin, sulfonylureas, SUs, are another type of major therapeutic drug target in treating type-II diabetes. The history behind this type of drug was understood in 1946 with evidence that aryl SU compounds actually stimulate the release of insulin which displayed the effect from pancreatic beta-cell function. [6] SUs can be classified by first, second and third generation agents in which the United States has recognized and approved the second and third generation drug targets in 1984 and in 1995 which points to the success of SUs in lowering diabetic patients' A1C levels by 1-2% .[6] This decreased A1C value is relative to the progression of type-II diabetes in patients due the efficacy of SUs decreasing in later stages of pancreatic beta-cell function which is why SUs are typically used to manage early stages of type-II diabetes. Regarding the second generation of SUs, these agents are typically more potent on a weight basis and include common names such as glipizide, gliclazide, glimepiride, and glyburide.[11] These

different generations also differ with respect to dosage, rate of absorption, elimination route and binding site action on target pancreatic beta-cell receptors, and duration of action.[12]

SUs ultimately combats a type-II diabetic patient's inability to secrete insulin by specifically targeting pancreatic beta-cells. The major effect with this drug is increasing plasma

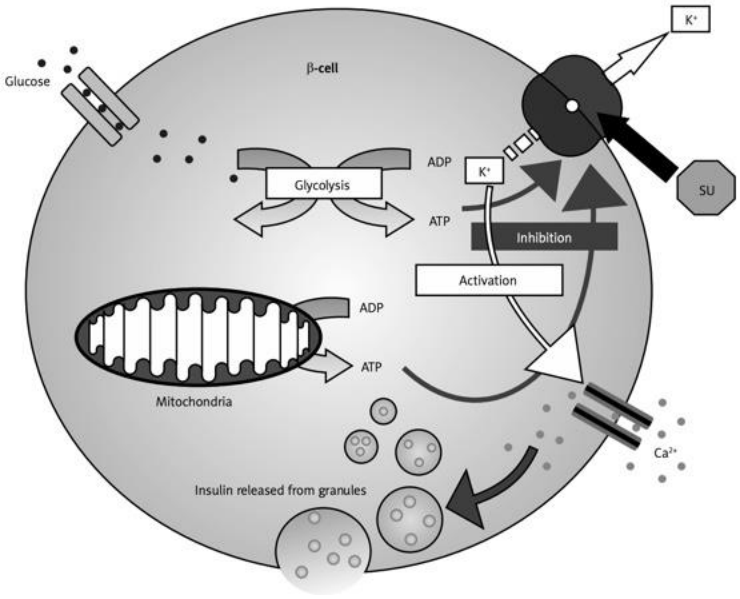

Figure 2. Sulfonylureas Mechanism of Action

insulin concentrations due to the presence of residual pancreatic beta-cells. The mechanism of action for SUs can be seen in **Figure 2**. There is a specific receptor on pancreatic beta-cells, an ATP-sensitive K^+ channel, that SUs bind to such as SUR1, and this causes blockage to the K^+ ion channel which stimulates the increase of Ca^{2+} ions. The increased concentration of K^+ causes depolarization to the pancreatic-beta cell membrane which allows for Ca^{2+} ions to enter into the cell via the voltage-gated Ca^{2+} channel and enter into the pancreatic beta-cells. Due to K^+ depolarization, Ca^{2+} do not excrete into the cytosol which this allows for actomyosin filaments to contract and prompt the exocytosis of insulin. This is due to the Ca^{2+} ions moving into the cell causing the movement of insulin-containing secretory granules to the cell surface and get released by the pancreatic beta-cell.[1211]

In addition to SUs main mechanism of action, there are additional extra pancreatic actions performed by SUs which include the enhancement of insulin stimulation of carbohydrate transport in skeletal muscle, inhibiting triglyceride lipase and glucose output in the liver, and increasing the oxidation and uptake of glucose in adipose tissue.[12]

Common side effects of SUs include hypoglycemia along with weight gain. The side effects of weight gain can additionally place type-II diabetics at an even greater risk for developing other chronic diseases.[6] In addition to these common side effects, severe adverse side effects from taking SUs include skin rash, hemolytic anemia, thrombocytopenia, agranulocytosis, flushing, hyponatremia, and cholestatic jaundice.[11]

Alternative Approaches to Type-II Diabetes Treatment and Prevention

As previously stated, there are 2 major categories regarding the treatment, management, and prevention of type-II diabetes including both therapeutic drug targets and lifestyle changes. Various therapeutic drug targets are on the market and implemented in type-II diabetic treatment with Metformin and SUs serving as both the first and second line of agents used to treat type-II diabetic patients due to low cost, oral ingestion, absorption factors, efficacy, and minimal adverse side effects in comparison to other type-II diabetes medication.[13] However, there are multiple other approaches to both treating type-II diabetes and to prevent a type-II diabetes and other chronic illness diagnosis. An emphasis will be placed on 3 major sections of lifestyle change that can be targeted in treating type-II diabetes which include: obesity, unhealthy eating, and sedentary activity.

Obesity is considered to be one of the most significant risk factors an individual can have regarding developing a type-II diagnosis. A person is deemed obese if their BMI is considered to be $\leq$30 kg/m^2, and there is an inverse linear relationship between BMI and age of diagnosis for

type-II. However, the exact mechanism by which obesity increases type-II diabetes along with insulin resistance is still being studied on the understanding that it deals with cell-autonomous mechanisms along with inter-organ communication.[1] In managing or losing weight, the focus is placed on increasing physical activity and healthy nutritional eating habits.[3] When combatting obesity to prevent the onset of type-II diabetes, it has been shown that moderate amounts of weight loss can ultimately lead to an increase in HDLs along with a reduction in triglycerides. Both Finnish studies and the Diabetes Prevention Project obtained similar results that weight loss, no matter how it was accomplished, decreases an individual's risk for developing type-II diabetes in comparison to those who are obese and have not lost weight.[4] Even though this approach does not fit into the category of lifestyle change, bariatric surgery has also been used for a variety of reasons to combat obesity developing type-II diabetes. It has been shown that bariatric surgery has reduced the incidence of type-II diabetes by 83% after 15 years of having the surgery along with improving insulin resistance in these individuals.[14]

Sedentary lifestyles have also been shown and proven to be a risk factor for type-II diabetes due to the reduced ability for the body to secrete insulin along with tissues becoming insulin resistant. On a molecular level, these outcomes occur due to proinflammatory molecules being released into the bloodstream with specific tissues causing an inflammatory state in the body called metabolic inflammation. This also leads to pancreatic beta-cell dysfunction. If weight loss becomes an outcome in individuals participating in physical activity, this will ultimately improve insulin sensitivity and enhance the production of anti-inflammatory cytokines. In addition to weight loss being a positive outcome combatting the obesity risk factor for type-II diabetes, there are multiple other benefits that physical activity can either prevent or delay the onset of a type-II diabetes diagnosis. These benefits include reducing abdominal fat

which promotes insulin resistance, improving glucose uptake and insulin sensitivity by reversing oxidative stress, and increasing blood flow into the muscles which enhances glucose uptake from plasma by contracting skeletal muscle cells.[1] The skeletal muscles accounts for approximately 80% of insulin stimulated glucose uptake; however, total body glucose metabolism is decreased by 40% with normal-weight subjects having either insulin resistance or type-II diabetes. Conclusions can be drawn from this that increased physical activity aiding in skeletal muscle function provides benefits to individuals as skeletal muscles are most important site for insulin resistance in type-II diabetes in addition to physical activity having the ability to induce an increase in skeletal muscle mitochondria with the enhanced expression of mitochondrial proteins present in mitochondrial biogenesis .[15]

The American Diabetes Association conducted two randomized trials that implemented a lifestyle intervention of 150 minutes of physical activity a week, approximately 21.4 minutes per day, along with diet induced weight loss of 5-7%, and the results showed a reduction in the risk of developing impaired glucose tolerance by 58%. This study was further continued to show that just diet or physical activity also reduced the risk for impaired glucose tolerance. When targeting an individual's A1C levels, it was shown that structured exercise programs emphasizing intensity have both clinically and statistically proven to benefit a type-II diabetics glycemic control along with decreasing their A1C levels.[16] To also show the dramatic effects that physical activity can have in both treating and preventing type-II diabetes, studies conducted under the British Journal of Sports Medicine have shown that a single bout of exercise can increase insulin sensitivity in the liver and muscle for up to 16 hours along with prolonged exercising producing a decrease in hyperinsulinemia and hyperglycemia. In addition, controlled intervention exercised studies have resulted in insulin sensitivity, carbohydrate oxidation, and reduction in body mass with just

training at 50-70% VO2 max along with reporting changes in total glucose disposal.[17] The Diabetes Prevention Project also conducted a randomized controlled trial of 3234 patients in the United States with prediabetes also showed that a lifestyle modification program that aimed at 7% weight loss in patients reduced the incidence of type-II diabetes over 3 years from 29 to 14%.[10] From this, the same project also concluded from similar studies that individuals who have failed in reaching the 7% weight loss goal but still managed to complete the physical activity recommendation had a 44% lower diabetes incidence than those who didn't.[18]

It is also important to note here, that increased physical activity should not be viewed solely as a means to treat and prevent chronic metabolic diseases such as type-II diabetes. In the United States alone, studies identified that at least 250,000 deaths have occurred each year that is premature to physical inactivity along with providing the statistic that between 50-70% of Americans are not receiving enough physical activity that will provide health benefit outcomes.[15]

The third major element under the umbrella of type-II diabetic treatment and prevention via lifestyle change is the incorporation of a healthy diet. One's nutrition plays a key role in either the development of type-II diabetes or the prevention and management of type-II which can easily be seen in the standard American diet. High-caloric foods that contain excessive amounts of carbohydrates and fats result in the elevation of blood glucose levels which can lead to a spike in reactive oxygen species that generate an inflammatory response to the body.[1] When specifically dealing with type-II diabetes, dietitians urge patients to implement a diet regimen that includes smaller portion sizes, regularly scheduled meals, and the implementation of foods with high-fiber content, low refined grains, low-fat meats, low-fat dairy portioning.[3]

Other herbal products and secondary metabolites incorporated in individuals' have been used for the treatment and management of type-II diabetes as well. These minerals, vitamins, and

metabolites have demonstrated abilities to elicit hypoglycemic action both *in vitro* and *in vivo.* Throughout history, botanicals have been incorporated for medicinal purposes which can especially be found in the EU. Their use is for promoting glucose management, and the major botanicals used to accomplish this includes bitter melon, fenugreek, gurmar, nopal, ivy gourd, and cinnamon. Bitter melon is the most common of the one's listed and this plant that belongs to the Cucurbitaceous family has demonstrated glucose management via the inhibition of intestinal glucose absorption, decrease hepatic gluconeogenesis, and reduce gluconeogenic enzymes. In addition to this, bitter melon has the ability to enhance the activation of AMPK pathway, just like Metformin, and reduce the expression of phosphoenolpyruvate carboxykinase, PEPCK. Further research is still being conducted on this plant to confirm these results on its ability to prevent and treat type-II diabetes. Secondary metabolites including resveratrol and flavonoids have also been studied regarding their hypoglycemic mechanisms. Clinical studies and *in vitro* animal studies have confirmed resveratrol's ability to improve insulin sensitivity, reduce oxidative stress, regulate carbohydrate-metabolizing enzymes, and activate AMPK. Flavonoids have also been studied on potentially leading to treating type-II diabetes due to it being a widely consumed dairy polyphenol that can perform antioxidant actions, increase insulin sensitivity, and promote central nervous system effects.[19] These herbal products and metabolites can also serve under the umbrella of both treating and preventing type-II from a lifestyle standpoint.

The area of study surrounding type-II diabetes has increased over the past two decades especially in the United States due to its' exponential prevalence among American citizens with type-II diabetes effecting 37 million Americans, almost 1 in 10 citizens. Personal experience working in both a health & wellness program, specifically implementing lifestyle change to combat chronic illnesses such as type-II diabetes, along with working as a medical scribe in a

level-2 emergency department at Ball Memorial developed a passion throughout my undergraduate studies to further understand the role and mechanisms of type-II diabetes. These experiences also provided a first-hand account as to how severe the effects of type-II diabetes are on the human body when there is name to a face of an individual with a type-II diabetes diagnosis. From further understanding of this chronic metabolic disorder, advances in both my jobs have been made regarding how to best serve Grant Co, Delaware Co, and surrounding towns with low socioeconomic statuses in combatting chronic illnesses. These experiences have also provided a way to further enhance my career aspirations throughout completing my undergraduate degree regarding applying to medical school and becoming a licensed physician.

By definition, there is no formal cure for type-II diabetes; however, there is a multitude of ways in which one can effectively treat, prevent, and manage this disorder. The reason as to why emphasis should be placed on treatment and prevention of this disease is due to the severe effects that both insulin resistance and sensitivity along with decreased insulin secretion has on the body. With type-II diabetes affecting the liver, heart, pancreas, kidneys, eye, nerves, and blood vessels, serious complications arise in type-II diabetic patients which can cause the most severe casualty of death. This paper explored a variety of ways in which modern medicine and treatment options have be used to combat diabetes; and from this paper, it appears that lifestyle change has been the number one choice in both treating and preventing type-II diabetes verses the use of therapeutic drug targets.

As previously stated, therapeutic drug target targets have been studied, revised, and continued to be used in treating type-II diabetes since the 1920s and the last major milestone in therapeutic drug treatment for this disease was the introduction of the first SGLT-2 inhibitor which is currently still being researched.[6] However, there is an extensive list of side effects and

disadvantages that should be considered when solely using therapeutic drug treatments as a means to manage type-II diabetes. The symptoms and side effect list also contributes to the feedback loop of potentially causing patients to be placed at even further risk for developing other chronic diseases including various forms of heart disease such as cardiovascular disease. Furthermore, diabetes medication such as Metformin and Sulfonylureas tend to be paired in conjunction with each other to most effectively manage the development of type-II diabetes which adds another element of side effects and potential drug interaction complications.[13] Since there is no cure for type-II diabetes, these medications do not have the ability to reverse the diagnosis and allow one's body to obtain a normal A1C level. In addition, these medications can truly just manage one's illness without providing the potential for a higher and healthier quality of life to be obtained by type-II diabetic patients. The final concluding disadvantage of using therapeutic drug agents in treating type-II diabetes is the cost factor. The American Diabetes Association reported that the United States spent an estimate of $327 billion in total expenses for treating both type-I and type-II diabetes which is a 26% increase from the estimated $245 billion from 2012.[20]

With the extensive list of side effects and cost disadvantages that therapeutic drug agents possess while treating type-II diabetes, the alternative approach of combating type-II diabetes via lifestyle change has proven to be more effective across numerous categories. This paper specifically analyzed the benefits that weight loss, diet change, and physical activity can have on the treatment and prevention of type-II diabetes. Other than just treating type-II diabetes with the implementation of lifestyle change, there is a wide variety of benefits that lifestyle change can have that therapeutic drug agents cannot possess. To start, the lifestyle approach when treating diabetes basically eliminates the side effect factor that therapeutic drug agents can have. The side

effects of either placing one at risk for potentially developing further chronic illnesses or reducing one's quality of daily living due to the extensive drug side effect list simply just doesn't exist when it comes to lifestyle change. In addition, the treatment of type-II diabetes from a lifestyle approach not only treats the two major pathophysiological functions that become impaired in a type-II diabetic patient, but lifestyle change also treats the other major organs involved in the disease pathology of type-II in which therapeutic drug targets tend to manage one or two organs involved. This was shown with the effects of physical activity on skeletal muscle, adipose tissue, cardiac health, etc. Finally, emphasizing implementing lifestyle change to treat type-II diabetes over therapeutic drug agents would drastically reduce the cost that the United States spends on treatment for this, in most cases, preventable chronic metabolic disorder.

When drawing final conclusions on the evaluation of treatment for type-II diabetes, the most foundational element that making lifestyle changes has over the use of therapeutic drug agents is the preventative aspect for developing chronic diseases such as type-II. The implementation of lifestyle change that combats obesity, sedentary lifestyle, and unhealthy diet habits is an opportunity for individuals at any age and health background to increase the quality of life along with promoting longevity. In addition to these benefits, individuals also significantly decrease their chances of developing an exhaustive list of chronic diseases. Even though this paper explored the physical effects and benefits of lifestyle change, other mental and emotional health benefits have been identified in which therapeutic drug targets do not provide.

Overall, there are multiple options that have been proven to treat, manage, and prevent type-II diabetes in which categories such as therapeutic drug targets and lifestyle change were explored extensively throughout this paper. Both of these categories have proven to be beneficial when combating a type-II diagnosis; however, it appears that lifestyle change has further

demonstrated its' ability to not only treat a type-II diagnosis, but also prevent individuals from the development of this disease, decrease the risk for developing other chronic diseases, and promote healthy effects throughout the body. From this research process, I was able to broaden my perspective on the importance of both the use of therapeutic drug targets and implementation lifestyle change to combat type-II. In addition, I continue to remain hopeful for the future of health and wellness programs that help facilitate the implementation of lifestyle change by walking alongside individuals in achieving their potential for a healthy lifestyle that reduce chronic disease diagnoses throughout the United States.

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