

The Effects of Exercise on Diabetes Mellitus Type 2

College of Arts and Sciences

Senior Honors Project

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## Abstract

Diagnosis of diabetes mellitus type 2 is slowly rising in the United States, with poor eating habits and sedentary lifestyles increase the number of incidences. Medications are used to treat individual symptoms of diabetes. Society ignores the positive effect exercise has on all aspects of the disease and improving quality of life. Research previously completed demonstrates: exercise decreases blood pressure, adipose tissue levels, resting blood glucose, insulin resistance, immune responses, and inflammatory factors. These changes in physiology have a direct link to alleviating symptoms and complications diabetes mellitus type 2. While medications and exercise both aim to treat this disease, exercise is a lifestyle change that the body does not become resistant to. This gathering of previous research aims to influence the increase of exercise and nutrition as a viable prescription for the management and cure of diabetes mellitus type 2.

## Introduction

According to the Center for Disease Control and Prevention in the year 1980, there were approximately 5.5 million cases of patients diagnosed with Diabetes mellitus (CDC Public Resource Statistics, 2014). Since this time, the number of diagnoses have nearly quadrupled to approximately 21 million (CDC Public Resource Statistics 2014). Lifesaving medicines have been developed and used widely all over the nation. Insulin analogs are used at increasing rates in order to improve insulin sensitivity and decrease blood glucose levels. But with the ever present rise of insulin resistance, more effective methods to improve absorption and response time were necessary. Higher dosages and more frequent intake of insulin analogs have been required to keep stable blood glucose levels. The CDC released the following data in 2011; Figure 1 represents the slow decrease in patients using alternative medications (pills) and insulin separately to battle their diabetes and a rise in the combination of medications simultaneously. The number of patients taking only insulin has decreased significantly since the year 1997 by nearly 13 percent. The number of patients taking pills has increased slowly and remained fairly constant from the year 1997; with only an eight percent increase. The percentage of patients taking both pills and medication has been slowly on the rise from about nine percent to about 13 percent.

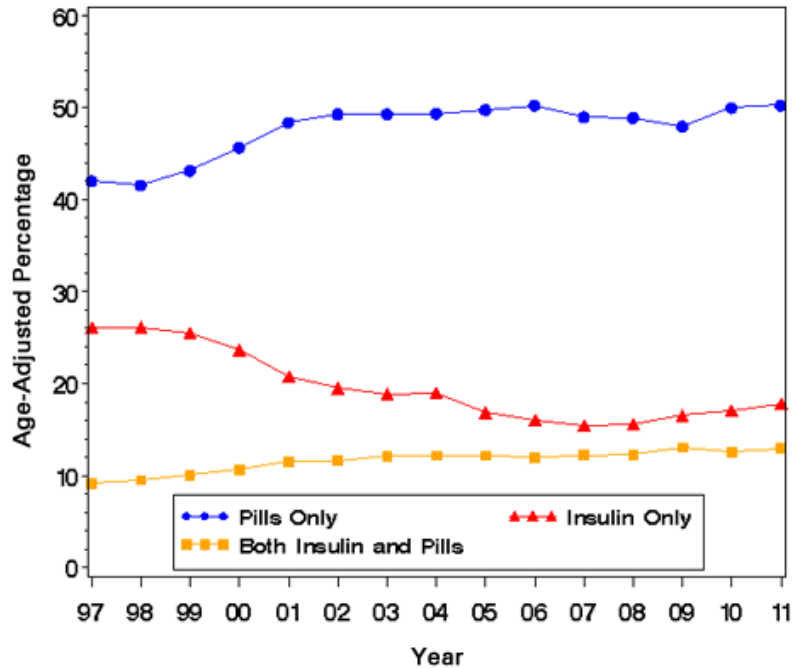


Figure 1: Evaluation of Diabetes Mellitus Type 2 Treatments (Center for Disease Control and Prevention)

As insulin resistance continues to increase without lifestyle alterations such as increased levels of exercise and changes in nutrition, the need for multi-drug treatment increases as well. The purpose of multi-drug treatment is to improve glucose levels as quickly as possible to decrease the potential cellular damage resulting from chronic hyperglycemia associated with type two diabetes mellitus. Because these cells involved in glucose uptake are damaged, due to the effects of hyperglycemia, they are no longer effected by the single treatment, glucose levels remain unnaturally high.

Insulin therapy has been shown to be an effective treatment for type 2 diabetes mellitus. However, insulin metabolism is slow. Insulin for type 2 diabetics is usually taken post meal in association with incoming rise in glucose levels. Because of the slow metabolism, insulin will not go into effect for 20 – 30 minutes after injection and does not peak for 2-3 hours. This delay brings late post-prandial hypoglycemia (Hirsh). Late post-prandial hypoglycemia or reactive

hyperglycemia occurs when our body's own insulin production plus the added insulin injection are working at the same time. Because the injected insulin does not take full effect for 2-3 hours, the body's natural production of insulin occurs leading to massive amounts of glucose uptake leaving the blood stream in a dangerous hypoglycemic state.

Rather than turning to a healthier lifestyle change, our society leans toward increased medications as a treatment. Exercise has multiple benefits to both healthy bodies and those afflicted with diabetes mellitus. The positive outward physical benefits alone are not the singular reason exercise presents such a positive change in our lives. The biochemical cascade created by the cellular stress induced during exercise leads to overall positive body effects. These effects range from biochemical and physiological changes, to large scale modulation of damaging contributors in Type 2 diabetics. These include muscle mass change, glucose receptors, inflammatory response, diabetic neuropathy, atherosclerosis, cardiovascular change, renal damage, and hypercoagulability. In conclusion, with insulin resistance and dependence on the rise, it is imperative to shift focus to exercise regimens that can positively effect and reverse diabetic symptoms.

## Background

This section details the biochemical response to glucose ingestion and regulation including: hormones and GLUT receptors, and the pathophysiology of diabetes mellitus type 1 and type 2.

## Blood Glucose Levels

Diabetes is labeled a metabolic disorder due to changes in blood glucose levels and the ability to regulate glucose absorption. This section describes the body's ability to regulate glucose and what it means to be a diabetic.

## Hormones

The following section includes an explanation of glucose transport from serum to cells (GLUT1-4).

Homeostasis of glucose levels in the body is maintained by GLUT receptors and three hormones produced by the pancreas. Insulin, glucagon and amylin all have an impact on blood glucose levels. Insulin and amylin are produced and secreted from pancreatic beta cells. The insulin signaling network contains two major pathways; PI 3-kinase, and MAPK pathway. These pathways utilize various enzymes and signaling cascades leading to: glucose uptake, glycogen synthesis, and protein and lipid metabolism.

Amylin has a variety of functions in glucose regulation. Amylin slows glucose uptake by reducing gastric emptying and promoting satiety, thereby preventing spikes in blood glucose levels. It slows the rate at which glucose appears in the blood after ingestion of nutrients by inhibition of digestive secretions including: pancreatic enzymes, gastric secretions, and bile release (Buse et al. 3). Amylin does not directly affect glucose uptake into cells; rather it slows the rate at which glucose enters the blood after a meal thereby allowing more time for the cells to respond to the insulin without causing a hyperglycemic state.

Glucagon is produced in the pancreas and released from alpha cells when blood glucose levels are low. This hormone is released from pancreatic alpha cells and signals liver cells to begin the process of glycogenolysis. The storage form of glucose, polysaccharide glycogen, gets acted upon by glycogen phosphorylase, phosphoglucomutase, glycogen debranching enzymes, alpha [1-6] glucosidase, and glucose-6-phosphate phosphorylase. Glycogen is broken down through this pathway of enzymes and released as useable glucose energy.

## GLUT Receptors

The following section describes the types of glucose receptors and their functions in the cell.

In response to insulin action, glucose is taken up into the cell via secondary active transport. Sodium-glucose symporters cotransport two sodium molecules and one glucose molecule. This mechanism derives its energy from Na<sup>+</sup>/K<sup>+</sup> ATPase transport system. These glucose transporters consist of a family of 14 transmembrane members. Here we will look at Class 1 transporters (GLUT1-4). These transporters facilitate glucose movement bidirectionally driven by the concentration gradient. This bidirectionality is limited by the organ tissue that expresses the specific transporter. Only organs that produce and store glucose release it into the bloodstream.

GLUT1 and GLUT3 are present in nearly all cells and are responsible for basal glucose uptake. These two transporters constantly transport glucose to maintain homeostasis and energy balance. GLUT1 is expressed in high levels in cells that function as barriers. It is highly expressed in fetal tissues and adult brain microvessels. It is thought to provide glucose transport in various cells that form barriers between body tissues and the blood supply. It is found in epithelial and endothelial barrier cells, such as those that constitute the blood-brain barrier, and also in the placenta. GLUT1 levels in cell membranes are increased by reduced blood glucose levels and decreased by increased glucose levels. GLUT3 is the most prominent glucose transporter isoform expressed in adult brain. There it tends to be preferentially located in neurons, rather than in other cell types, such as glia or endothelial cells. It is also widely distributed in other human tissues, having been detected in the liver, kidney and placenta. GLUT3 functions similarly to GLUT1 utilizing the concentration gradient of glucose to drive the flow in and out of the blood stream.

GLUT2 is present in hepatocytes, insulin-secreting pancreatic beta cells, and absorptive epithelial cells of the intestinal mucosa and the kidney. It functions as a low affinity, high-



turnover transport system. Together with the enzyme glucokinase, it is thought to act as a glucose-sensing apparatus that plays a role in blood glucose homeostasis, by responding to changes in blood glucose concentration and altering the rate of glucose uptake into liver cells, where it can be stored as glycogen. Unlike GLUT4, GLUT (1-3) do not rely on insulin to participate in glucose regulation. GLUT2 initiates the first step in glucose-stimulated insulin secretion, and a glucose metabolism-dependent signaling mechanism. It also participates in the sodium-glucose cotransporter in the cellular transport of glucose in the small intestine and kidney. This glucose transporter is required for glucose sensitivity in the hypothalamus and brainstem. Involved in the control of food intake and stimulation of glucose uptake by peripheral tissues.

GLUT4 is expressed in high levels in adipose tissue, and striated muscle cells. This transporter is regulated by insulin released from pancreatic beta cells. Under conditions of low insulin, most GLUT4 is sequestered in intracellular vesicles in muscle and fat cells. Insulin induces a rapid increase in the uptake of glucose by prompting the translocation of GLUT4 from these vesicles to the plasma membrane. As the vesicles fuse with the plasma membrane, GLUT4 transporters are inserted and become available for transporting glucose, and glucose absorption increases.

### Insulin and Non-Insulin Effects on GLUT4

The following section depicts insulin and noninsulin effects leading to GLUT 4 vesicle translocation.

At the cell surface, GLUT4 permits the facilitated diffusion of circulating glucose down its concentration gradient into muscle and fat cells. Once within cells, glucose is rapidly phosphorylated by glucokinase in the liver and hexokinase in other tissues to form glucose-6-

phosphate, which then enters glycolysis or is polymerized into glycogen. Glucose-6-phosphate cannot diffuse back out of cells, which also serves to maintain the concentration gradient for glucose to passively enter cells.

Figure 2 shows the effects of muscle contraction and insulin on GLUT4 receptor integration into the membrane. This is an important site for insulin uptake because muscle cell response to insulin is to break down glucose into useable energy. It does not cause storage of glucose and fat buildup rather fat and energy breakdown.

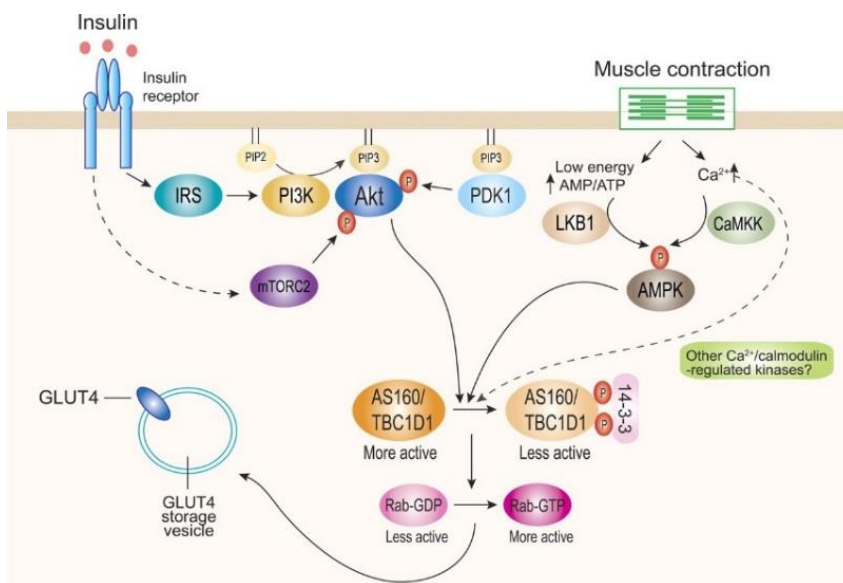


Figure 2. Insulin and Non-Insulin Mediated GLUT4 release (Sakamoto and Holman)

Muscle contraction stimulates muscle cells to translocate GLUT4 receptors to their surfaces. This is especially true in cardiac muscle, where continuous contraction can rely upon a constant source of glucose, but is observed to a lesser extent in skeletal muscle.

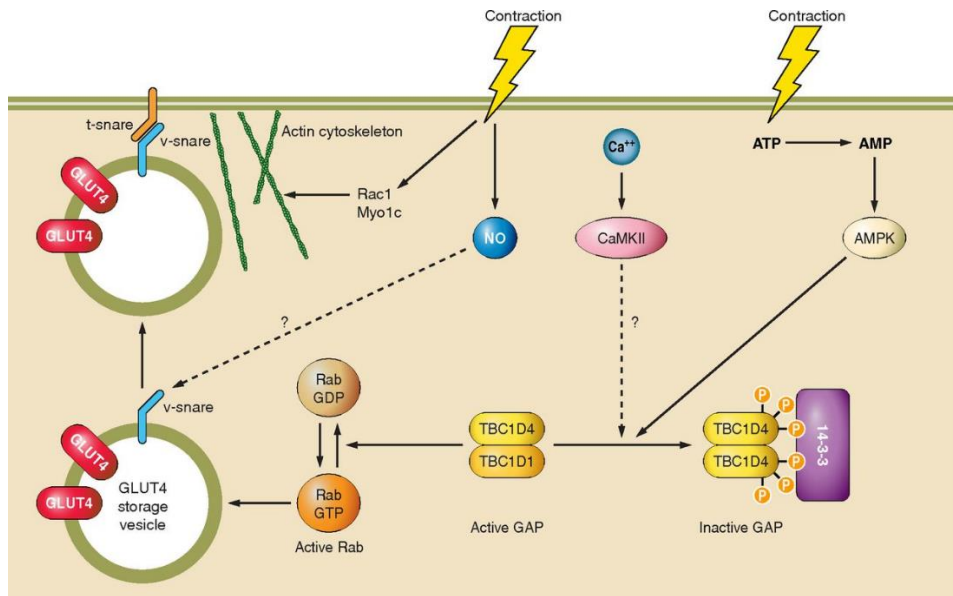


Figure 3. Exercise Induced GLUT4 Vesicle Translocation (Richter and Hargreaves)

In all muscle cell types when exercise occurs, there is recruitment of capillaries which increases the available surface area for glucose delivery and exchange. As seen in Figure 3, cellular contraction leads to the increase in AMP levels and need for more ATP to continue powering cellular functions and ultimately increases AMPk action. Nitric oxide (NO) and 5'-AMP-activated protein kinase (AMPk) are involved in glucose transport and mitochondrial biogenesis in skeletal muscle. AMPk increases GLUT4 receptor translocation to the cell surface increasing glucose uptake for more ATP production.

A variety of other cellular stress signals also enhance glucose uptake in skeletal muscle cells. Hypoxia and inhibitors of cellular metabolism (e.g., glycolysis inhibitor; electron transport inhibitors; oxidative phosphorylation uncoupler 2,4-dinitrophenol) signal at least partially through AMPK by decreasing the cellular energy supply and increasing AMP/ATP ratios as seen in Figure 3. Hyperosmolality also promotes GLUT4 translocation by activating AMPk in muscle or by activating a Gab-1 dependent signaling pathway in adipocytes

## Diabetes mellitus Type 1 and Type 2

This section describes the overall pathophysiological status of a patient with type 1 or type 2 diabetes mellitus.

Diabetes mellitus is a disease that affects the body's ability to maintain blood glucose levels through lack of glucose uptake into cells leading to a state of chronic hyperglycemia.

The classic symptoms of untreated diabetes mellitus are weight loss, polyuria (increased urination), polydipsia (increased thirst), and polyphagia (increased hunger). Symptoms may develop rapidly (weeks or months) in type 1 diabetes mellitus, while they usually develop much more slowly and may be subtle or absent in type 2 diabetes mellitus. Diagnosis of diabetes mellitus is based on the evaluation of HbA1c levels, fasting blood glucose, 2-hour plasma glucose level during oral glucose tolerance test, or random glucose level testing. Normal HbA1c levels range from 4-5.6%, those at risk of developing diabetes range from, 5.6-6.4%, and those above 6.4% are at risk or have already developed diabetes mellitus. Those at risk of diabetes mellitus have fasting glucose levels higher than 126 mg/dl. Those with 2-hour plasma glucose tests result in levels higher than 200 mg/dl are also at risk for a diagnosis of diabetes mellitus.

Diabetes mellitus Type 1 comes about through lack of insulin production or zero insulin production from the pancreas. This includes autoimmune diseases that attack pancreatic beta cells, cancer that causes pancreas failure, genetic mutations that lead to production of faulty beta cells that would otherwise normally produce insulin. Once 80-90% of functioning beta cells in the pancreas are lost, hyperglycemia occurs. Without insulin production, cells expressing insulin dependent glucose transporters fail to respond to high levels of blood glucose. Unable to take up the glucose in the blood stream, glucose overflows into the urine and is lost.

Diabetes mellitus type 2 is not a complete lack of insulin but rather, cells have become resistant to insulin signaling. This can occur because of constantly high levels of blood glucose

(hyperglycemia) which in turn leads to constantly high levels of insulin. The cells no longer respond to the insulin despite its high production levels in the pancreatic beta cells. This resistance primarily occurs in myocytes, adipocytes, and hepatocytes. Other potentially important mechanisms associated with type 2 diabetes mellitus and insulin resistance include: increased breakdown of lipids within adipocytes, resistance to and lack of incretin, high glucagon levels in the blood, increased retention of salt and water by the kidneys, and inappropriate regulation of metabolism by the central nervous system. Type 2 diabetes mellitus is very closely associated with obesity and high fat content.

### Insulin sensitivity

The purpose of insulin in healthy bodies is to signal the cells to take glucose from the blood into the cells for energy utilization or storage. In type 2 diabetes mellitus, cells do not respond to insulin effectively. The receptors may not bind the insulin that is being produced by the pancreas or the receptors simply do not respond to the insulin because the concentration is not high enough to instigate a cellular response. Insulin resistance is very important in both hepatocytes and myocytes. Figure 4 demonstrates the insulin resistance mechanisms in myocytes. A chronic hyperglycemic state induces insulin resistance. If the cells no longer respond to insulin, glucose is not taken into the hepatocytes for glycogen storage in myocytes or energy utilization.

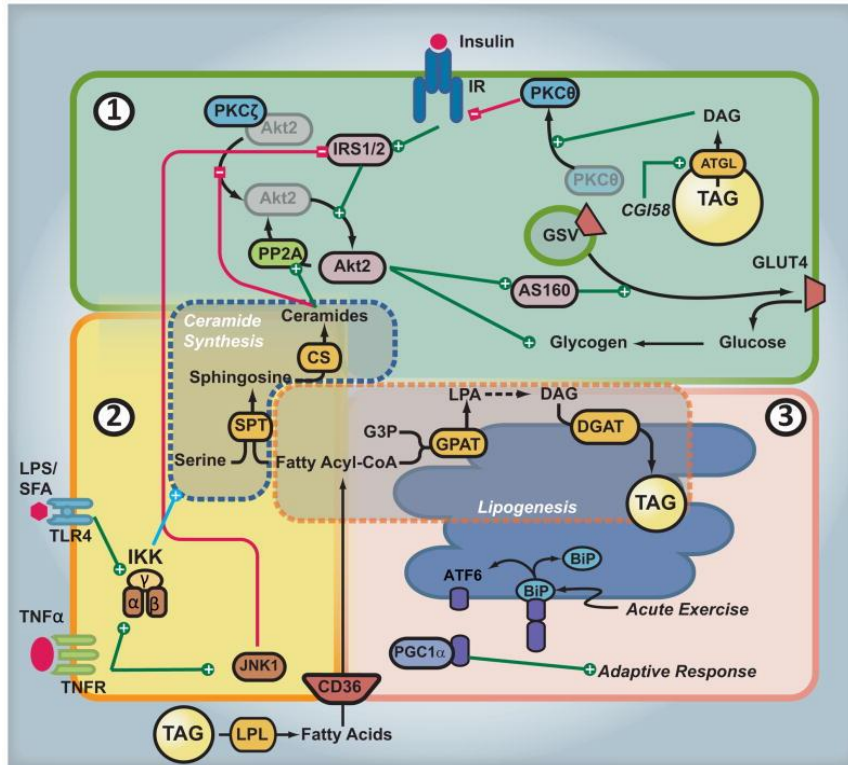


Figure 4 Insulin Resistance Biological Mechanism (Samuel and Sulman)

Insulin activates the insulin receptor tyrosine kinase which in turn activates tyrosine phosphorylation of IRS1. Through a series of intermediate steps, this leads to activation of Akt2. Akt2 activation, promotes the translocation of GLUT4 containing storage vesicles (GSV) to the plasma membrane. This translocation allows the entry of glucose into the cell and initiates glycogen synthesis. This central signaling pathway is connected to multiple other cellular pathways. Area one of Figure 4 represent mechanisms for lipid induced insulin resistance, notably diacylglycerol mediated activation of PKCθ and in succession, impairment of insulin signaling, as well as ceramide mediated increases in PP2A and increased reuptake of Akt2 by PKCζ. Impaired Akt2 activation limits translocation of GSV's to the plasma membrane resulting in impaired glucose uptake. Impaired Akt2 activity also decreases insulin mediated glycogen synthesis. Area two of Figure 4 depict several intracellular inflammatory pathways, notably the activation of IKK, which may impact ceramide synthesis and the activation of JNK1, which may

impair insulin signaling via serine phosphorylation of IRS1. This phosphorylation inhibits use of IRS1. Area 3 of Figure 4 illustrates that activation of the UPR (unfolded protein response) which under some instances may lead to activation of ATF6 and a PGC1 $\alpha$  (peroxisome proliferators-activator receptor gamma coactivator-1 alpha) mediated adaptive response. The ER membranes also contain key lipogenic enzymes and give rise to lipid droplets. Proteins that regulate the release from these droplets may alter the concentration of important lipid intermediates in cell compartments. Insulin sensitivity plays a key role in the treatment of diabetes mellitus.

### Oxidative Damage (Unifying Hypothesis)

Chronic hyperglycemia in type 2 diabetes mellitus leads to various consequences due to oxidative damage. The Unifying Hypothesis most effectively describes the oxidative damage due to chronic hyperglycemia from diabetes. Figure 5 depicts a step by step cause and effect pathway stimulated by a hyperglycemic state which will be explained here.

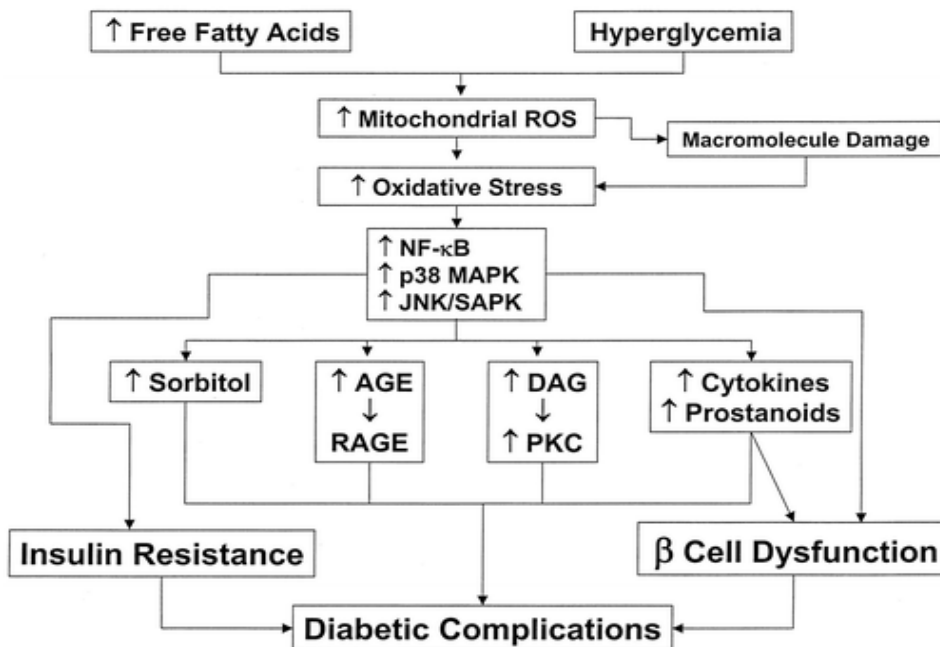


Figure 5 Unifying Hypothesis (Evan et al. 5)

Excess glucose leads to negative feedback all throughout the glycolysis pathway resulting in inhibition of glucose uptake and negative total body physiological effects. Electron leakage from CoQ of the electron transport chain leads to superoxide production and inhibition of GAPDH. Inhibition of GAPDH causes buildup of glyceraldehyde 3-phosphate. Glyceraldehyde 3-phosphate activates protein glycation and DHAP and further negative feedback inhibition in glycolysis. DHAP leads to PKC activation, smooth muscle growth and vessel wall thickening. Protein glycation leads to production of AGEs, RAGEs and other inflammatory responses. Inflammation inhibits proper cellular function; for example, energy utilization (glycolysis, electron transport chain etc.). Inhibition of conversion of fructose-6-phosphate to glyceraldehyde-3-phosphate causes inhibition of plasminogen activator, decreased clot dissolution, and increased vascular occlusion. Continued inhibition of glycolysis leads to increased activation of the polyol pathway. Increased sorbitol from the pathway decreases NADPH, and glutathione. Glutathione is an important antioxidant. Decreased production of antioxidants increases damage done by electron leakage from the electron transport chain and increasing the negative effects of superoxides left to roam in the body.

The stress from sorbitol accumulation has been associated with an underlying mechanism in the development of diabetic microvascular complications, diabetic retinopathy. Cells are also thought to be injured by glycoprotein buildups. High glucose concentrations can promote the nonenzymatic formation of advanced glycosylated end products (AGEs). In animal models, these substances have also been associated with formation of microaneurysms and pericyte loss. Growth factors, including vascular endothelial growth factor (VEGF), growth hormone, and transforming growth factor  $\beta$ , have also been postulated to play important roles in the development of diabetic retinopathy. VEGF production is increased in diabetic retinopathy,



possibly in response to hypoxia. In animal models, suppressing VEGF production is associated with less progression of retinopathy (Samuels et al. 2012).

### Pathological Consequences

Changes to the kidney include increased glomerular basement membrane thickness, microaneurysm formation, mesangial nodule formation (Kimmelsteil-Wilson bodies), and other changes. The underlying mechanism of injury may also involve some or all of the same mechanisms as diabetic retinopathy. The precise origin of injury to the peripheral nerves from hyperglycemia is not entirely known, but it has been associated with mechanisms such as polyol accumulation, injury from AGEs, and oxidative stress. Peripheral neuropathy in diabetes may manifest in several different forms, including sensory, multifocal, and autonomic neuropathies. Several other forms of neuropathy may mimic the findings in diabetic sensory neuropathy and mononeuropathy. Chronic inflammatory polyneuropathy, vitamin B12 deficiency, hypothyroidism, and uremia should be ruled out in the process of evaluating diabetic peripheral neuropathy. Diabetic autonomic neuropathy also causes significant morbidity in patients with diabetes. Neurological dysfunction may occur in most organ systems and can be manifest by gastroparesis, constipation, diarrhea, anhidrosis, bladder dysfunction, erectile dysfunction, exercise intolerance, resting tachycardia, silent ischemia, and even sudden cardiac death. Cardiovascular autonomic dysfunction is associated with increased risk of silent myocardial ischemia and mortality (Konhordi et al. 11 2015).

The central pathological mechanism in macrovascular disease is the process of atherosclerosis, which leads to narrowing of arterial walls throughout the body. Atherosclerosis is thought to result from chronic inflammation and injury to the arterial wall in the peripheral or coronary vascular system. In response to endothelial injury and inflammation, oxidized lipids from

LDL particles accumulate in the endothelial wall of arteries. Angiotensin II may promote the oxidation of such particles. Monocytes then infiltrate the arterial wall and differentiate into macrophages, which accumulate oxidized lipids to form foam cells. Once formed, foam cells stimulate macrophage proliferation and attraction of T-lymphocytes. T-lymphocytes, in turn, induce smooth muscle proliferation in the arterial walls and collagen accumulation. The net result of the process is the formation of a lipid-rich atherosclerotic lesion with a fibrous cap. Rupture of this lesion leads to acute vascular infarction (Konhordi et al. 11 2015).

Type 2 diabetes typically occurs in the setting of the metabolic syndrome, which also includes abdominal obesity, hypertension, hyperlipidemia, and increased coagulability. These other factors can also act to promote CVD. Even in this setting of multiple risk factors, type 2 diabetes acts as an independent risk factor for the development of ischemic disease, stroke, and death. Among those with type 2 diabetes, women may be at higher risk for coronary heart disease than men. The presence of microvascular disease is also a predictor of coronary heart events

Hearing loss can also be associated with diabetes. The mechanism related to this symptom is still unclear. Various skin conditions also come to light after long term hyperglycemia. These conditions come about through damage to microvessels and macrovesicles leading to decreased circulation to epithelial tissue. Bacterial infections, fungal infections, poor circulation, acanthosis nigricans, diabetic dermopathy, Necrobiosis Lipoidica Diabeticorum, Bullosis Diabeticorum (diabetic blisters), eruptive xanthomatosis, digital sclerosis, and possibly disseminated granuloma annular (Konhordi et al. 11 2015).

Both Type 1 and Type 2 diabetes mellitus can be altered by exercise. This literature review specifically examines the physiological alterations made by exercise on type 2 diabetes

mellitus. Many studies have been done to evaluate these effects and will be examined below. These studies include both physiological and biochemical changes in Type 2 Diabetics, and modulation of damaging contributors in type 2 diabetes mellitus.

### Research Articles

These studies exhibit both biochemical and pathophysiological consequences of diabetes in patients entering an exercise regimen.

### Biochemical Effects

These initial studies demonstrate biochemical alterations during exercise on type 2 diabetes mellitus.

#### Study 1 - Muscle Mass Changes

Aerobic and resistance training are similarly effective in reducing blood glucose levels as both types of exercise efficiently burn calories as well as build muscle. Aerobic exercise training has become a pillar in prevention of type 2 diabetes mellitus. However, resistance training increases the amount of skeletal muscle and can account for up to 40 percent of total body weight, and approximately 75 percent of body insulin-stimulated glucose uptake. Resistance training has been shown to induce muscle fiber hypertrophy and an increase in muscle mass and strength. Hypertrophy exercises consist of heavy loads for less repetitions. Among cardiac and respiratory improvement, blood glucose levels and insulin sensitivity improved with increased muscle mass. Endurance training has been shown to decrease fasting blood glucose levels, HbA1c, weight and waist circumference, an increase in oxidative enzyme activity, increased capacity of skeletal muscle, a gain in muscle mass and strength and a shift to type 1 fibers (Egger et al. 10).

The study below describes improved mRNA expression from a specific gene in skeletal muscle with expression of: AdipoR1, AdipoR2, Glut4, IL-6, eNOS, PGC-1alpha, showing a linear increase during the course of the study, whereas oxidative stress-related genes p22, gp91, heme oxygenase, PPARalpha and PPARgamma, showed a transient increase during a further five months of training. This study compares the effects of hypertrophy training, endurance resistance training and aerobic exercise training on body composition, glycemic control, muscle mass and strength (Egger et al. 10).

This study compared 32 patients, 13 men and 19 women, with type 2 diabetes mellitus. The participants were randomly assigned into two groups: either hypertrophy resistance training or endurance resistance training, both groups participated in aerobic exercise activity. Body composition tests, hematology and blood tests, work capacity tests and maximum strength tests were performed to assess initial fat content, blood glucose levels, and strength capacity (Egger et al. 10).

Each participant performed supervised aerobic exercise training for eight weeks on cycle ergometers. The endurance portion of the study was completed on two non-consecutive days during the week to avoid excessive muscular fatigue. Heart rate goals were set and monitored during each training session based on the Karvonen-Formula. The endurance portion of the workout included five minutes of warm-up, 60 minutes of cycling at a goal heart rate, and five minutes of cool down time. Resistance training was implemented for 50 minutes per session as well. Exercises included: chest press, latissimus pulldowns biceps curl, seated rowing, and upright rowing. Heart rate was monitored for optimal fat burning. The goal of this program was to increase cardiovascular functioning and improve muscle mass and strength (Egger et al. 10).

All but one of the patients completed the study. At baseline there were no significant difference between the groups except for abdominal adipose measurements and arm strength in back pull. Both groups showed significant reduction in waist circumference, weight loss and BMI. After this 8-week program, both groups showed reductions in fasting glucose levels, and fructosamine levels. Neither group showed change in HbA1c levels but showed trends to decrease with more training over time. At baseline resting and maximal heart rate, systolic and diastolic blood pressure were fully comparable between groups and showed significant decrease but no significant difference between the different types of exercise. Resting heart rate remained unchanged in both groups (Egger et al. 10).

These results indicate the positive ramifications of exercise. The fat loss alone gives suggestion of reduction of inflammatory activity, increased blood flow, decreased blood pressure, improved blood glucose regulation and insulin sensitivity (Egger et al. 10).

#### Study 2 - GLUT 4 Receptor Concentration Changes

Previously mentioned in the background section, GLUT receptors are responsible for glucose uptake into the cells. GLUT 4 is specifically responsible for glucose uptake in muscle cells and is important for glucose homeostasis. Resistance training effectively builds muscle, by increasing number of cells, in order to more efficiently regulate blood glucose levels.

Theoretically more muscle cells contribute to increased opportunity for glucose uptake into the cells for energy utilization. An effective way to build muscle cells is through resistance training. Exercise in the form of resistance training can be done a couple of ways, isotonic or isometric. Isotonic exercise is when the contracting muscle shortens against a constant load, for example lifting heavy loads. The load changes position as the angle of the limb changes as well. Isometric muscular contractions occur without movement of the involved parts of the body. The load

bearing limb does not have an angle change and the load remains motionless. It is more likely that those who are obese will begin a training program that consists of low intensity resistance training rather than a plan designed for endurance training (Holten et al. 9).

A study done in 2003 evaluated the increased levels of GLUT4 receptors in skeletal muscle after a training regimen of 30 minutes a day, three times a week for six weeks. The results indicate that in the lower limb that was active during the resistance training increased muscle mass, and therefore increased GLUT4 receptors. Each participant had one leg sampled to test for original GLUT 4 receptor levels. The participants performed 10-12 repetitions using 50 percent of their one rep max equivalent on a single leg and resting for 90 seconds between sets. The exercises consisted of leg press, knee extension, and hamstring curls. Between training sessions, a catheter was inserted in the median cubital vein for addition of insulin and glucose. Other catheters were inserted and used to evaluate blood pressure, and blood sampling. Euglycemic hyperinsulinemic clamps were started and plasma glucose levels were evaluated for a 120-minute duration of glucose and insulin infusion. Muscle samples were taken and analyzed for significant analyte changes. All of the subjects had increased muscle mass in the leg participating in the strength training program. Those who participated in the trial and were type 2 diabetics, showed significant decrease in insulin resistance with whole body glucose clearance rates. Glucose clearance rates in the leg showed no significant change from the initial testing values. The levels of glucose, C-peptide and insulin were high in the plasma of type 2 diabetics compared to the control individuals. The level of GLUT4 receptors in muscles for both type 2 diabetics and control individuals were similar in the leg that received muscular training. The study stated there was a 40% increase of GLUT4 receptors in trained muscle in Type 2 diabetics. For control subjects there was a 13% increase in GLUT4 receptors. For both the control group

and the Type 2 Diabetics there was no significant change in level of insulin signaling. There were no significant changes in the level of insulin receptor proteins on the cell surface of the trained muscle compared to untrained muscle (Holten et al. 9).

This study is very effective in examining the direct effects of exercise on GLUT 4 receptors. Unfortunately, there is very minimal research of this type done in diabetic populations. This study represents a healthy population that clearly demonstrates the positive effect of exercise on GLUT 4 receptors. These are very important in glucose regulation as muscle cells do not store large amounts of glucose rather uses most of the glucose absorbed right away for cellular energy (Holten et al. 9).

### Study 3 - Insulin Sensitivity

During exercise our body exhibits a state of hypoxia, which is defined as a deficiency in the amount of oxygen reaching the tissues. This lack of oxygen hinders the cells' ability to utilize energy during the acute stressed state. This state creates a need for maximum glucose uptake. Hypoxia increases the cells' ability to uptake glucose using skeletal muscle contraction stimulated by a pathway independent of insulin. As the short effects of glucose increased uptake due to exercise wears off, insulin sensitivity begins to increase in order to maintain energy levels. Myocytes are most affected by this increased insulin sensitivity. The increase in insulin sensitivity is mediated by translocation of GLUT4 glucose transporters to the cell surface in response to an insulin stimulus. Although the post exercise increase in muscle insulin sensitivity has been characterized in considerable detail, the basic mechanisms underlying this phenomenon remain a mystery (Mackenzie et al. 7).

The following study evaluates the effect of hypoxia during exercise on the sensitivity of the cells to insulin. Eight type 2 diabetics completed 60 minutes of normoxic rest, hypoxic rest,

normoxic exercise, and hypoxic exercise, at their 90% lactate threshold. Glucose testing occurred after each conditioning period. Body fat percentages were taken prior to the five laboratory visits and again after the five visits were completed (Mackenzie et al. 7).

Nutritional intake was not different between conditions for both total caloric and carbohydrate intake. This suggests all changes in glycemic control may be largely attributed to the experimental conditions. Other than improved cardiac and respiratory function, which occurs through regular physical activity, this study suggests insulin sensitivity and first-phase insulin secretion are improved immediately following hypoxic exposure. Also an increase in glucose uptake in the four hours following exercise were enhanced when exercise was combined with hypoxia in individuals with type 2 diabetes. Circulating blood glucose concentrations were reduced during acute exposure to hypoxia. There was no change in insulin concentrations from baseline values, which was aligned with a decrease in blood glucose concentration during hypoxic exposure. This study leads to the assumption that moderate hypoxia may have up-regulated body glycolytic energy pathways to compensate for the possible reduction in mitochondrial respiration. Stimulation of the sympathoadrenal system during hypoxia is associated with up-regulation in glucose disappearance rates, reduced fatty acid uptake and an inhibition of insulin secretion (Mackenzie et al. 7).

Aerobic exercise increases insulin action in skeletal muscle in sedentary obese and type 2 diabetics. Hypoxia and exercise have an additive effect on insulin sensitivity. Blood glucose concentration was lower in hypoxic exercise when compared to the exercise only trial. This increase in insulin sensitivity suggests that insulin signaling, and so insulin-dependent-glucose transport may have been up-regulated following hypoxic exercise. The changes in glucose



concentration during hypoxic exercise can be attributed to the increase in insulin sensitivity (Mackenzie et al. 7).

#### Study 4 – Mitochondrial Capacity

High intensity interval training leads to a physiological remodeling that differs from moderate intensity continuous endurance training. A change in exercise in a few as six high intensity interval training sessions over a two-week span, increase muscle mitochondrial capacity, as well as glucose tolerance and improving insulin sensitivity in healthy adults. The purpose of this study is to examine the effects of low-volume high intensity training on glucose regulation on skeletal muscle and metabolic capacity in individuals with type 2 diabetes mellitus (Little et al 8).

Prior to beginning the training sessions, a muscle biopsy was taken from each participant and evaluated. The muscle was tested for citrate synthase enzymic activity, and continuous glucose monitoring was performed by all participants. The study involved evaluating participants over a two-week span of low volume high intensity interval training. The patients performed three training sessions a week for two weeks. They involved cycling intervals, of high intensity short bursts of work with low intensity resting periods (Little et al 8).

The blood glucose concentrations over a 24-hour period after the last training session were reduced. The maximum activity of citrate synthase was elevated after the training sessions and skeletal muscle mitochondrial protein content was increased (Little et al 8).

The conclusions of this study lead to the suggestion that low-volume high intensity interval training can rapidly reduce hyperglycemia and increase skeletal muscle oxidative capacity in patients with type 2 diabetes mellitus. Those with insulin resistance and type 2

diabetes have been shown to have reduced mitochondrial content and weakened mitochondrial function (Little et al 8).

These two weeks of low-volume high intensity interval training lowered average blood glucose concentrations and increased mitochondrial capacity in individuals with type 2 diabetes mellitus. In general, aerobic exercise is recommended for increasing cardiorespiratory fitness; however, some studies have shown that resistance exercise may also increase cardiorespiratory fitness. In this study, the aerobic exercise group (moderate intensity walking, five times per week, for 60 minutes) showed significant improvements in oxygen uptake at the anaerobic ventilation threshold, and the resistance exercise group (40% to 50% 1RM, 10 to 15 exercises, using a resistance band, three sets, five days per week, for 60 minutes) showed an increasing trend, although it was not statistically significant, which is consistent with the results of previous studies. Plasma volume in muscle increases during exercise. The nitric oxide produced in endothelial cells plays an important role in vasodilation. Leukocytes and monocytes prevent foreign particles from attaching to the blood vessel walls and interfering with the interaction between platelets and the blood vessel walls. The permeability of endothelial cells is then reduced, and the proliferation of vascular smooth muscle cells is blocked, causing a reduction in tension from the blocked vessels (Little et al 8).

#### Study 5 – TLR2 and TLR4

Associated with the need for more energy vasodilation is caused by exercise in order to increase transport of glucose and other indicators of cellular stress. Inflammation and increased circulation of inflammatory factors are an example of these indicators.

An increase in basal circulating proinflammatory cytokines is common in the pathogenesis of obesity, insulin resistance, and type two diabetes mellitus. Toll like receptors

(TLR) play an important role in our immune system. Toll like receptors will often elicit a response such as activation of cytokines, and other inflammatory responses. This study specifically evaluates the effects of toll like receptor 2 and 4. TLR2 are located on the cell surface of neutrophils, monocytes, macrophages, and dendritic cells. TLR4 are present on the surface of monocyte derived dendritic cells and use the Myd88-dependent pathway to produce interleukins 12 and 18 which signal naive T-cells to mature into type 1 helper T cells. Interleukins that are activated by TLR4 and TLR2 induce natural killer cell proliferation, production of interferons, and subsequently leads to increased macrophage activity. Increased inflammatory response can be irritating, and painful. Increased TLR2 and TLR4 expression and the resulting proinflammatory environment are associated with a cluster of cardio metabolic risk factors including insulin resistance, type 2 diabetes and atherosclerosis. Exercise improves metabolic health and decreases the risk of type 2 diabetes and its associated metabolic disruptions. If the anti-inflammatory effects of regular exercise are likely to attributable to a reduction of adipose tissue but there is growing evidence that exercise in the absence of weight loss can also directly impact immune cell phenotype and alter systemic inflammatory mediators (Robinson et al. 8).

The purpose of this study is to examine the impact of high intensity interval training and moderate intensity continuous training on inflammatory markers of cardio metabolic health of those at risk for developing type two diabetes. Researchers studied circulating pro- and anti-inflammatory cytokines, leukocyte TLR2 and TLR4 expression, ex vivo cytokine secretion and standard cardio metabolic health. These were measured before and again after a two-week program of high intensity interval training or moderate intensity interval training in overweight and obese adults at risk of developing type 2 diabetes.

These participants agreed to be randomized into two groups. Three men and 17 women in the group participating in high intensity interval training and four men and 15 women in the moderate intensity interval training group. The protocol for this program consisted of 10 sessions of training over a two-week period. The exercises were determined based on individual scores of VO<sub>2</sub>max. The moderate intensity continuous training sessions were comprised of three minute warm up and cool down with 20 to 25 minutes of interval training in between. These individuals worked at 60% of their maximum heart rate. At the end of 10 sessions these individuals had increased their cardiovascular health and were able to participate in 50 minutes of interval training. Those participating in high intensity interval training, worked at their 80 percent maximum heart rate during four intervals made up of one minute of work and one minute of resting. By their tenth training session, they had increased their intervals to ten intervals per training session. This improvement was made from the participants initial four intervals per session baseline programming (Robinson et al. 8).

Blood samples were taken to evaluate fasting glucose, fasting nonesterified fatty acids, and fasting insulin. Using flow cytometry, TLR2 and TLR4 expression on CD14+ on monocytes, CD15+ neutrophils and lymphocytes was measured. The following plasma cytokines were analyzed; tumor necrosis factor alpha, IL-1beta, IL-6 and IL-10(Robinson et al. 8).

TLR4 expression on lymphocytes was reduced in both high intensity and moderate intensity groups with no significant difference between groups. TLR2 on monocytes and neutrophils was not affected by either training program and there was no significant change in plasma cytokines expect for an interaction effect of IL-29 with post hoc tests showing a reduction after moderate intensity continuous training. The significant reduction in immune cell TLR2 and TLR4 occurred without a change in basal circulating proinflammatory cytokines.

There was a reduction of plasma fructosamine after both high intensity interval training and moderate intensity continuous training (Robinson et al. 8).

Short-term high intensity interval training and moderate intensity circuit training significantly improved VO<sub>2</sub>max and reduced monocyte and lymphocyte TLR4 expression and lymphocyte TLR2 expression in a group of inactive adults at risk of developing type two diabetes. Moderate intensity continuous training showed a significant reduction in fasting plasma glucose, which was not seen after high intensity interval training sessions. There was also a greater reduction in neutrophil TLR4, which may be linked to longer-duration exercise in moderate intensity training sessions (Robinson et al. 8).

Decrease in these inflammatory factors can improve quality of life. There is a decrease in outward symptoms of inflammation. These can include: pain, swelling, redness and skin irritations. Exercise may cause acute discomfort but this study shows it also relieves some inflammatory responses elicited by these TLR's.

#### Study 6 – Epigenetic Effects

The creation of proteins is a very intricate process that begins in the nucleus. DNA is stored within the nucleus and when needed, is transcribed into RNA fragments. These RNA fragments will then leave the nucleus, and are transcribed into amino acid chains in the cytoplasm. Amino acids are formed into proteins in the cytoplasm and modified in the rough endoplasmic reticulum. From there these proteins are transported within the cell or transported out of the cell via exocytosis. Acetylation and methylation can affect the number of proteins produced by inhibiting transcription.

Epigenetics is the study, in the field of genetics, of cellular and physiological phenotypic trait variations that are caused by external or environmental factors that switch genes on and off and affect how cells read genes instead of being caused by changes in the DNA sequence. Hence,

epigenetic research seeks to describe dynamic alterations in the transcriptional potential of a cell. For those suffering with type 2 diabetes mellitus, several epigenetic modifications have been evaluated. DNA methylation of PPARGC1A is elevated in pancreatic islets compared to those not suffering with type 2 diabetes. This methylation and gene silencing of GLUT4 transcription leads to decrease in GLUT4 expression in cells (Santos et al. 5).

Researchers have been relating the changes on the epi-genome with insulin resistance and mitochondrial dysfunction in skeletal muscle. At rest, studies suggest that activation of AMPK induced by phosphorylation HDAC5, causing dissociation from MEF2. This results in chromatin structure condensing. This part of the chromatin structure allows for expression of GLUT4. Upon condensing of the chromatin, decreased expression of GLUT4 occurs. After exercise and cellular stress, HDAC5 is phosphorylated and dissociates from MEF2. GLUT4 expression begins to increase again and glucose levels begin to slowly restore. MEF2 has also been shown to interact with the coactivator for protein PPAR gamma coactivator 1-alpha (PPARGC1A) during and shortly after exercise. This binding leads to enhanced transcriptional activity of GLUT4 gene expression (Santos et al. 5).

Other genetic testing includes sequences related to leptin production which is predominately expressed in mature adipocytes. Leptin is a hormone that is secreted to regulate appetite and energy. The expression of leptin is dependent on a CG-rich region called CpG island. High fat diets lead to increased methylation of this CpG site, suggesting that as more methylation occurs, increasing uncontrollable hunger affects those with this passed on methylated site (Santos et al. 5).

To conduct this study, preadipocytes were taken from human samples by collagenase digestion and were cultured. These cells were analyzed by using DNA isolation and PCR to maximize available DNA for testing (Santos et al. 5).

The use of genetic testing in patients with type 2 diabetes has been increasingly more popular. These predispositions suggest development of type 2 diabetes, but do not ensure that the person with these genetic factors will specifically develop type 2 diabetes.

### Pathophysiological Effects

The following studies are related to modulation of damaging contributors to type two diabetes mellitus and how exercise can improve the quality of life for patients suffering with these symptoms.

### Study 7 - Peripheral Neuropathy

Symptoms of type 2 diabetes associated with hyperglycemia may include Peripheral Neuropathy; also known as diabetic nerve pain. It can cause weakness, numbness, and pain in the extremities. This symptom of type two diabetes mellitus can be a result of poor circulation, or imbalance in metabolites. Long periods of elevated blood glucose can injure the vessels that supply the body's nerves with adequate nutrition and oxygen. Peripheral neuropathy can cause muscle weakness and the loss of reflexes, which often leads to changes in a person's mobility, gait, and balance. Changes in pressure distribution during walking may lead foot deformities and foot injuries. Risks from foot wounds are especially dangerous to diabetics. The combination of neuropathy and poor blood circulation leads to longer clotting time, and decreased reproduction of epithelial cells and overall slowed healing around the area of injury. Exercise has been theorized to improve blood circulation and slow the effects of peripheral neuropathy by providing nutrients to extremities more so than an immobile patient (Turtle et al.4).

This study completed at the University of California, San Diego, evaluates a 76-year-old man's response to a 12-week moderate-intensity progressive exercise program. This program involved walking on a treadmill, balance exercise and strengthening exercises. To properly evaluate the damage of diabetes caused to the patient's peripheral nerves, the program was specifically designed to increase circulation, and muscle control in the patient's lower limbs and feet. The program consisted of ankle mobility tests and walking for distance. The patient used a StepWatch activity monitor to calculate the amount of steps they took. A visual evaluation was completed after each exercise to ensure the safety of the footwear and status of the skin. After 12 weeks, the patient was able to walk further and had a larger range of mobility in their ankles and toes. Weight loss and increased circulation can be attributed to this improved function. The patient's HbA1c dropped by 0.5%, from 6.9% to 6.4%. Temperature measurements were taken from the plantar side of the foot to identify areas at risk for skin breakdown or tearing. Low temperature indicating poor circulation and temperature closer to body temperature indicating healthy circulation. Poor circulation is highly associated with increased risk for skin tearing. These false positives and his improved circulation due to increased levels of exercise lead to decreased risk of skin tearing (Turtle et al. 4).

The overall decrease in HBA1c levels indicate balancing glucose levels and therefore less risk of developing or leading to declining symptoms of diabetic neuropathy. Unfortunately, this study only involved a single individual at risk of developing peripheral neuropathy. Many patients who have already developed diabetic nerve pain and peripheral neuropathy do not want to participate in a study like this for fear that the exercise may cause their pain to increase or last for longer periods of time. A much larger study with more participants and over a longer



duration of time could produce results that have more authority in the scientific community (Turtle et al. 4).

#### Study 8 - Endothelial Function

Associated with peripheral neuropathy and poor circulation, diabetes affects the endothelium. Endothelium is thin layer of cells at the internal surface of blood vessels, and regulates vascular tension and maintains structure. The endothelium plays an important role in the body's physiology and ability to regulate blood pressure. Regular exercise increases the number of smooth muscle cells and endothelial cells, expands aortic vessels and increases arterial diameter. Smooth muscle cells and endothelial cells promote differentiation and increases in the number of capillaries contributing to favorable outcomes in vasculature. Improved nitric oxide bioavailability occurs with training as a result of enhanced synthesis and reduced oxidative stress-mediated destruction (Kwon et al. 8).

A study was constructed to evaluate these effects of exercise on this breakdown of endothelial cells that occurs often in diabetic patients. Those included were 40 female patients with type 2 diabetes mellitus ages 45 to 65 years old. They participated in a two-week trial to evaluate activity levels and track caloric intake. These women were randomly assigned to one of three groups: moderately intense exercise, resistance exercise, or a control group. Those in the moderate intensity training group performed aerobic exercises. This included walking for 60 minutes five times a week. During the first four weeks, the patients visited the hospital once a week for checkups. During the last eight weeks, they visited the hospital every two weeks. The group participating in resistance training used resistance bands throughout their exercise program. The amount of resistance increased as their strength increased during the 12-week trial. The participants performed upper body exercises including bicep curls, triceps extensions, upright rows, shoulder chest press and seated rows. They also participated in core exercises that

consist of trunk side bends and lower body exercises including: leg press, hip flexions, leg flexions and leg extensions. The control group was told to perform normal activities and were not required to exercise (Kwon et al. 8).

To evaluate the effects of exercise, blood samples were taken to acquire initial blood analyte levels. These analytes included glucose, total cholesterol, triglycerides, high density lipoprotein levels and fasting insulin levels. The following non-invasive tests were performed; waist circumference, body mass index, and blood pressure. Exercise tests and endothelial cell function tests were performed (Kwon et al. 8).

The results of the study indicate the two groups who participated in the exercise programs showed improved endothelial function. Endothelial-independent vasodilation in the aerobic exercise group increased significantly from baseline, but there were no significant differences between active groups. The resistance training group and the control group showed no statistically significant changes in endothelial-independent vasodilation. This study concludes that to improve endothelial cell function through exercise, aerobic exercise that increases cardiovascular fitness appears to be necessary. To improve endothelial cell function, continued weight loss is recommended for all those involved in the study to decrease risk of cardiovascular disease. High blood glucose levels have been shown to suppress endothelial cell dependent vasodilation. This hinders blood flow and may cause pain if not addressed. If chronic hyperglycemia is not addressed endothelial cell function will continue to decline putting the patient for very high risk for developing cardiovascular disease, and atherosclerosis. With poor diet the risk of plaque buildup is significantly higher than in a patient who eats a more controlled healthy diet. If plaque buildup occurs and the endothelial cell wall is compromised, the patient

may be at risk for cardiac arrest or limb loss if circulation continues to be compromised (Kwon et al. 8).

#### Study 9 - Cardiovascular Risk

Decreased circulatory function of type 2 diabetics plays a large roll in endothelial function as mentioned above as well as cardiovascular function. Cardiovascular disease develops through lack of exercise and poor diet. Together this combination leads to high blood pressure and high cholesterol. These predispositions associated with cardiovascular disease are often symptoms of those suffering with type 2 diabetes and is an associated risk (Balducci et al. 12).

In order to evaluate the effects of exercise on cardiovascular function associated with type 2 diabetes, this study evaluated the potential changes made to VO<sub>2</sub>max and muscular endurance levels. A study completed in 2012 compared the effects of low training exercise and high training exercise in 22 outpatient diabetics. These supervised programs occurred twice a week, with various exercises such as aerobic and resistance/strength training. Examples of aerobic training include, use of a treadmill, stairs, elliptical, and cycle-ergometer. Resistance training exercises include: chest presses, lateral pulldowns, squats and abdominal training. Both of these programs also include stretching exercises. Those participating in low intensity exercise training performed 55% of their VO<sub>2</sub>max and resistance training at 60% of their assumed one repetition maximum load. Subjects participating in moderate to high intensity exercise training program performed at 70% of their VO<sub>2</sub> max and resistance training of their predicted one repetition maximum of the given lift. The duration of these exercises were varied in order to obtain the same caloric expenditure. The intensity of each training program was adjusted based on the physical improvement of the participants in order to maintain the same amount of oxygen

consumption throughout the study. Over the 12-month study, 12 subjects dropped out; the results include only those who fully completed the programs (Balducci et al. 12).

The results of this study indicate that during the 12-month period, cardiovascular functioning of both groups improved significantly. The duration of exercise increased from 46 minutes during month one to 53 minutes per training session during month 12 in the low intensity exercise training group. The high intensity training group improved their sessions from 34 minutes per session to 40 minutes per session in month 12. There was an overall reduction in the endpoint HbA1c. This change was significantly higher in the high intensity training group than the low intensity training group. In regard to risk for cardiovascular disease, the changes over baseline were significantly more marked in high intensity than in low intensity groups for triglycerides and total cholesterol but not for fasting blood glucose and insulin. With respect to cholesterol levels, those training at low intensity levels showed more improvement with decreased low density lipoprotein ratios than those training at high intensity levels. The study discussion states that training at high intensity levels does not provide significant incremental benefits as compared with isometric low intensity training in terms of improving cardiovascular disease risk factors. Both high intensity and low intensity exercise decrease HbA1c levels and affect cholesterol levels, and triglyceride levels. Patients with type 2 diabetes showed significant improvements in these areas but the intensity of the activity matters less than the type of exercise and volume. These factors are more important in glycemic control for the type 2 diabetics. The issue with using high intensity exercise in patients with type 2 diabetes is their weight. More subjects dropped out of the study who participated in high intensity workouts despite its benefits on glycemic control (Balducci et al. 12).

Although this study compared different levels of exercise intensity there were only marginal changes between the two groups in terms of cardiovascular disease risk factors. Their results indicate type and volume of exercise is more important than intensity in targeting glycemic control and reduction of cardiovascular risk. In retrospect, because low intensity training or high intensity training will be effective in reducing cardiovascular risk factors, it is important to focus on volume and type of exercise. Longer duration and weight bearing exercise programs are most efficient (Balducci et al. 12).

#### Study 10 - Plasma Lipocalin-2

Plasma lipocalin-2 is an adipocyte derived acute phase protein that has been positively correlated with obesity, insulin resistance, type 2 diabetes and cardiovascular disease. Those with diabetes often develop kidney disease or injury. Plasma lipocalin-2, also known as neutrophil gelatinase associated lipocalin (NGAL), is a marker of kidney injury. NGAL is protease resistant and small. Therefore, it is excreted and can be measured in urine. This protein has been associated with apoptosis and innate immunity. The binding of NGAL to bacterial siderophores is important in the innate immune response to bacterial infection. Upon encountering invading bacteria, the toll-like receptors on immune cells stimulate the synthesis and secretion of NGAL. Secreted NGAL then limits bacterial growth by sequestering iron-containing siderophores. Lipocalin-2 binds, next to bacterial siderophores, also to the mammalian siderophore 2,5-dihydroxybenzoic acid (2,5-DHBA). This complex ensures that excess free iron does not accumulate in the cytoplasm. Lipocalin-2 also functions as a growth factor. It has also been shown to have high association with the inflammatory factor, high sensitivity C-reactive protein (hs-CRP). These are all associated with inflammation responses due to high levels of adipose tissue. A great strategy for battling obesity and diabetes is decreasing inflammation responses and therefore Lcn2 and hs-CRP levels (Moghadasli et al. 3).

The biochemical responses to resistance training are different from the responses experienced during endurance training. The purpose of this study was to examine the effects of resistance training versus endurance training on plasma lipocalin-2, body composition, insulin resistance, and hs-CRP in healthy sedentary men. The results of this study are to be used for furthering research in the positive correlation of exercise and improving diabetic status (Moghadasi et al. 3).

This study evaluated 30 healthy, sedentary men. These men had not engaged in exercise programs at least six months prior to completion of the study. These men completed an 8-week strength training program involving both upper and lower extremity exercises. The program was designed much like an interval training program, with ten minutes of warm up followed by 50 to 60 minutes of resistance training. The participants in this study were active three days a week for eight weeks. Each circuit and set was separated by three minutes of rest time. The endurance training portion of this study included running at 65-80% of maximal heart rate for 20-34 minutes per day, three days a week for eight weeks. Each participant began the program running at 20 minutes per session, increasing their cardiovascular fitness to 34 minutes of running per training session at the end of eight weeks. The participants used heart rate monitors to ensure their heart rate stayed within the 65-80% range during their training sessions. The participants were randomly assigned into three groups; resistance training, endurance training or control. (Moghadasi et al. 3).

Several tests were completed during the study including: body composition measurements, maximal oxygen consumption measurements, energy intake and energy expenditure controls, and a biochemical analysis consisting of: plasma Lcn2 levels, hs-CRP levels, plasma glucose, and serum insulin levels (Moghadasi et al. 3).

The results of the study indicate; that between the resistance training group and the endurance training group there was no significant variation in body mass, BMI, or body fat percentages. After eight weeks the participants' VO<sub>2</sub>max increased in both the resistance training and the endurance training groups. In both groups, the plasma concentration of Lcn2 decreased as well as hs-CRP levels. There was no significant difference in plasma concentration of Lcn2 and hs-CRP levels between resistance training and endurance training groups. Between there control groups and the groups that were active, the active groups showed significant improvement relative to the baseline control group (Moghadasi et al. 3).

Plasma levels of Lcn2 decreased in both resistance training and endurance training after eight weeks in the young men who participated in this study. There was a significant positive relationship with body mass, body fat percentage and hip to waist ratio, suggesting that increased fat mass might account for elevated blood levels of these adipokines in these individuals. These results indicate improved quality of life and decreased level of kidney injury in those who have type 2 diabetes if regular participation in an exercise program occurs (Moghadasi et al. 3). The comparison between the two types of exercise is less relevant due to the low level of differences in results between the two. Rather it is imperative to perform exercise of any type in order to alleviate the damage done to the kidneys.

#### Study 11 - MMP and TIMP, Hypercoagulability

Diabetes mellitus is highly associated with endothelial cells proliferation. Research has narrowed the variable to several analytes that are active during this cellular proliferation. TIMP-2 or TIMP metalloproteinase inhibitor 2 is a gene in the TIMP family. The proteins encoded by this gene are natural inhibitors of matrix metalloproteinases. Metalloproteinases are directly involved in the destruction of the extracellular matrix. MMPS and TIMPS have been linked to vascular remodeling atherosclerotic plaque instability, because of poor MMP/TIMP ratio. Dangerous

degradation can occur if MMP activity is too much for TIMP activity to control. MMP-9 is referred to as a gelatinase, which readily digests the denatured collagens, gelatins. MMP-9 is important for its role in degradation, type IV collagen, gelatin, and elastin. When specific cleavage of MMP-9 occurs, the following biological effects can be seen: generation of angiostatin like fragments, and proinflammatory responses. TIMPS are natural inhibitors of MMPs (Kadoglou et al. 9).

This study investigated the effects of a 16-week exercise intervention on cardiovascular risk factors, such as inflammatory agents and the MMP/TIMP system in patients with type 2 diabetes mellitus. Until now, little attention has been paid to the anti-inflammatory effects of self-controlled exercise training. In this study, fifty inactive, overweight, Caucasian patients were recruited for the 16-week program. 17 men and 33 women, ages ranging from 50 to 65 years, were following a diet and taking oral antidiabetic drugs for at least four months. Despite their efforts, their glycemic control remained slightly out of their control, with slightly higher HbA1c levels than recommended for type 2 diabetics (Kadoglou et al. 9).

Body mass index, waist-to-hip-ratio, and blood pressure were measured at baseline and again after the program was completed. 25 patients were assigned to a control group and 25 were assigned to the exercise group. From there the patients underwent blood sampling, and ergospirometry at baseline and again after 16 weeks. The 25 patients assigned to the exercise group participated in 30 to 60 minutes of brisk walking distributed over four days a week. This could be performed throughout the week but with no more than two consecutive days without physical activity. They were encouraged to increase their daily lifestyle activities as well. The main goal for each patient was to accumulate more than 150 minutes per week of self-controlled, moderate-intensity physical activity. The intensity of the workout was self-determined by the



patient. This could include walking on a treadmill, cycling or calisthenics. Within the first four weeks, their workout intensity increased to 50 to 70% of their VO<sub>2</sub>max for 60 minutes (Kadoglou et al. 9).

At baseline all parameters were similar in both groups. Exercise treated patients were highly compliant to treatment and 86.96% of the patients achieved their target of 150 minutes per week of exercise. Body mass index, waist to hip ratio, and insulin resistance surrogate indices changed only slightly throughout the study in both patient groups. The exercise group improved their VO<sub>2</sub>mx compared with the control group. Despite the absence of significant alterations in body weight and insulin resistance, the 16-week moderate intensity intervention of self-controlled exercise significantly reduced the inflammatory factors. Those who followed the exercise program had a reduction in hs-CRP and fibrinogen; they also showed a reduction in MMP-9 and an increase in TIMP-2 levels (Kadoglou et al. 9).

MMP-9 shows a significant link to proatherogenesis by promoting a fibrous cap degradation and plaque destabilization. Reducing MMP-9 levels is associated with favorable long term cardiovascular improvement. This study suggests with exercise comes a reduction in circulating MMP-9 (Kadoglou et al. 9).

Due to the association of MMP-9 with plaque formation and fibrous tissue, as MMP-9 levels decrease, the risk of Coronary Artery Disease also decreases. In addition, subjects exhibited improved circulation and lower blood pressure. Many conclusions can be drawn from this study, including; a moderately intense, physical activity program significantly improved the levels of inflammatory, proatherogenic and anti-atherogenic markers together with an overall metabolic improvement (Kadoglou et al. 9).

## Conclusion

Exercise is not a new medicine; it is an old medicine. Exercise of any type, high intensity or low intensity, shows a positive correlation in alleviating the symptoms of type 2 diabetes. Studies show that duration is more important when taking into consideration intensity levels of exercise. Short term high intensity bursts are effective for example: weightlifting circuit workouts, as well as long duration low intensity exercise for example; long distance running. Exercise has shown to; increase VO<sub>2</sub>max, blood flow and travel of nutrients, muscle mass. Exercise also decreases blood pressure, resting glucose levels, inflammatory responses, adipose tissue levels, and plaque formation. Exercise is more effective than taking a medication for each symptom. Modifying the patient's entire lifestyle is a difficult route. Making diet changes from high amounts of processed foods and high sugar diets to a more stable diet balanced with proper protein, carbohydrates, and fats is often a shock and many patients cannot complete this process on their own. Adding in nutrition changes and exercise regimens to a longitudinal study would likely show much more impressive results across the board.

Results seen from adding exercise and changing nutritional intake will not be seen overnight. Medications can be used to treat sudden spikes in glucose, but exercise improves the body's natural response to glucose spikes and insulin resistance begins to slowly decrease. Hyperglycemia is the beginning of nearly all symptoms of type 2 diabetes, and these studies highlight that blood sugar levels decrease after only two weeks of an exercise program. Unfortunately, symptoms of type two diabetes that get in the way of some patients starting an exercise program include obesity, high blood pressure, and peripheral neuropathy. The short term discomfort associated with exercise is a wall some patients are not willing to work through in order to experience the long term improvements by exercise. These results take longer to achieve, which stacks the bricks on the wall that much higher. Society is looking for the quickest

way solve their problem. Increasing dosages, and frequency of synthetic insulin will continue to aid in managing the disease. Exercise gives these same patients an opportunity to not only manage their disease but reverse it completely.

Society knows improved diet and more frequent exercise is the answer we just don't take the time to make these life changes. Living a sedentary life with a poor diet is addictive. Eating good nutrients and exercising frequently improves overall body function and can be just as addictive. Exercise can improve mental state of participants as well. Exercise improves mood, reduced stress as well as promotes an improved ability to cope with stress, improved self-esteem, pride in physical accomplishments, increased satisfaction with oneself, improved body image, and increased feelings of energy.

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