Heart Disease in Patients with Type 1 Diabetes and the Effects of Exercise

An Honors Thesis (HONR 499)

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Abstract

In the modern society there has been such a focus placed on exercise and type 2 diabetes, but the same focus is not placed on the connection between type 1 diabetes and exercise. The risk of cardiovascular disease with type 1 diabetes has also been brushed to the side in favor of discussing other heart disease risk factors. The culmination of research in the topics of diabetes, heart disease, and exercise have been combined into one research paper to portray the interwoven connection between the three more accurately.

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Process Analysis

The idea for this research paper was born from four years of exercise science classes in which we discussed the effects of exercise in various forms. It found a more concrete form when I began meeting with my advisor, Dr. Fleenor, to discuss the project. I have always had an interest in type 1 diabetes, most likely because it is less discussed in the general population than type 2 diabetes. During my semester immediately prior to this project, I became interested in the connection between type 1 diabetes and exercise through Dr. Fleenor's advanced exercise physiology class, and from there we decided to narrow the discussion to heart disease. This includes how type 1 diabetic individuals are at risk for heart disease, and how exercise can play a role in decreasing this risk.

For this project, I relied on published research articles rather than conducting my own research. At this point in my schooling this was the more realistic option, and it allowed me to practice reading scientific research articles. Through the process of finding articles related to my topic, I quickly discovered that it is very difficult to find articles that discuss type 1 diabetes, heart disease, and exercise in the same article. I knew that this would be the case, but it was even more extreme than I imagined. I assumed I would find one article from which to branch off, but my starting point ended up being an article that only included two of my three main topics of interest. Through this process I also learned how to maximize my time when reading these scientific articles. I realized quickly that it would be impossible to read every single sentence of each article, so I began scanning section headers and dividers to find where the critical information was. This is not to say that the information was not important, but rather that it was not needed for my research.

The purpose of this research is to identify the effects of exercise on heart disease in people with type 1 diabetes. In order to understand the complex relationship between type 1 diabetes, heart disease, and exercise, it is important to understand each component individually first. The first major component is the difference between type 1 and type 2 diabetes, which is one that is greatly misunderstood among the general public. Next, it is critical to understand that heart disease is a blanket term which encompasses several different conditions. Each condition has different causes, treatments, and effects on the body, and thus should be treated separately. In this, the relationship between heart disease and exercise will be examined in seemingly healthy individuals without type 1 diabetes. Finally, the exercise component must be addressed. Appropriate exercise for type 1 diabetic people should be determined, and then the effects of various exercises should be examined in people with type 1 diabetes and heart disease. There is much talk among both researchers and the general public about the correlation between exercise and type 2 diabetes, but not as much is said about exercise and type 1 diabetes. Specifically, many people do not realize that type 1 diabetes can be linked to heart disease, and how these conditions can be prevented or managed with exercise.

Diabetes

Before it is possible to examine these relationships, one must first know the difference between type 1 and type 2 diabetes. Both type 1 and type 2 diabetes are chronic conditions, but the causes of the two are different. Type 2 diabetes is much more common, and in this form of the condition there are two interrelated primary causes. The first is that "cells in muscle, fat, and liver become resistant to insulin," (1) which causes these cells to take in inadequate amounts of sugar. The second problem that leads to type 2 diabetes is that "the pancreas is unable to produce enough insulin to manage blood sugar levels," (1). Individuals who are overweight and inactive are generally at a higher risk for type 2 diabetes, but these factors are not indicative of type 1 diabetes prevalence.

Type 1 diabetes is the much less common form, with only about 5-10% of people with diabetes having type 1, according to the CDC (2, 3). This form of diabetes "is characterized by an absolute insulin deficiency caused by T-cell-mediated autoimmune destruction of the pancreatic ß-cells," (4). Type 1 diabetes usually presents at younger ages due to the rapid rate of ß-cell destruction in younger adults, but it can also present in adults (4). People with type 1 diabetes require insulin injections to make up for the lack of natural insulin production within their bodies, whereas type 2 diabetes patients do not require insulin via injections. Type 1 diabetes is known as insulin-dependent diabetes mellitus, and type 2 diabetes is known as insulin-independent diabetes mellitus. While type 1 is generally diagnosed in younger individuals and type 2 in older individuals, people of any age can be diagnosed with either form of the disease.

Heart Disease

Next it is important to understand what is meant by heart disease. Heart disease is not, in fact, one singular disease; instead, the term refers to several types of heart conditions, the most common of which in the United States is coronary artery disease—commonly referred to as CAD. Heart disease is the leading cause of death in the United States, and is often referred to as "silent", meaning that it is not diagnosed until a person has experienced signs or symptoms of a heart attack, heart failure, or an arrhythmia. A heart attack is the most serious of the three, and it includes several telling signs and symptoms. These include chest pain, upper back or neck pain, upper body discomfort, indigestion, heartburn, nausea or vomiting, extreme fatigue, dizziness, and shortness of breath. Shortness of breath and fatigue can also indicate heart failure, as well as swelling of the feet, ankles, legs, abdomen, or neck veins. Heart palpitations—fluttering feelings in the chest—are the main telling symptom of an arrhythmia (2, 3). The Centers for Disease Control and Prevention also lists diabetes as a factor putting people at higher risk for heart disease, along with overweight and obesity, unhealthy diet, physical inactivity, and excessive alcohol use. This is important because it identifies the direct link between diabetes—type 1 and type 2—and heart disease. It also directly mentions physical inactivity as a risk factor, meaning that all individuals should stay physically active, regardless of whether or not they have diabetes.

As previously mentioned, coronary artery disease is the most common type of heart disease in the United States, and it is sometimes referred to as coronary heart disease or ischemic heart disease. CAD is caused by "plaque buildup in the walls of the arteries that supply blood to the heart and other parts of the body," (2, 3). A process known as atherosclerosis occurs when this plaque buildup narrows the arteries and leads to a blockage in blood flow. A heart attack is often many peoples' first clue that they have coronary artery disease. Over time CAD can weaken the heart muscle, potentially leading to a heart attack and subsequent heart failure (2, 3).

Exercise and Cardiovascular Disease

According to Bove et al., exercise is often listed as an essential component of lifestyle advice for cardiovascular diseases (5). It is now known that exercise is more beneficial to heart failure patients than extended periods of bed rest (6). In healthy individuals, "exercise training is not only safe but also is associated with a reduced risk of hospitalization and a decrease in mortality," (6). Despite the positive results of exercise among heart failure patients, Alvarez et al. state that only 10.4% of eligible patients in this study received a cardiac rehab referral after hospitalization. If the individuals to which this information pertains were aware of such data, this percentage may be higher.

Prescribing an exercise plan for heart failure patients involves a variety of factors, the first of which is identifying any contraindications to exercise therapy that the patient may have. It is important to perform a graded exercise test for the patient in order to determine what the patient can and cannot do and what their specific goals are for rehabilitation. Several additional factor such as age, gender, comorbidities, previous physical activity, and orthopedic/musculoskeletal factors must be considered when creating a personalized exercise plan for a patient. Moderate level exercise is most often prescribed, and this is defined as 40 to 60% of heart rate reserve (peak heart rate minus resting heart rate), 40 to 60% of VO_2 reserve (peak VO_2 minus resting VO_2), and a rating of perceived exertion of 12 to 13 (6). Once information is gathered from an exercise test and patient goals, an exercise professional can use this information to create a plan that is safe and efficient in recovery for heart failure patients. Part of the efficiency rests on whether or not the individual will perform the exercise, so it is also important that the plan is feasible and the patient is motivated. This means the exercises must be able to be performed with equipment that is available to the patient, and the time required each day should be discussed with the patient so that they are aware and willing to follow through with the exercise plan.

Type 1 Diabetes and Cardiovascular Disease

The link between type 1 diabetes and heart disease—though not widely discussed—is shocking when examined more closely. According the de Ferranti et al., the prevalence of CVD in type 1 diabetes variessubstantially based on duration of DM, age of cohort, and sex, and possibly race and ethnicity (4). "Patients with type 1 diabetes have a fourfold (in men) to eightfold (in women) excess risk of coronary heart disease compared with that for the general population," and "it has been shown that type 1 diabetic patients aged 20-39 years have a fivefold higher risk of dying from cardio- and cerebrovascular events compared with that for healthy individuals," (6). This excess mortality seen in individuals with type 1 diabetes "has been attributed to both acute diabetes complications as well as to chronic diabetic renal and cardiovascular disease (CVD)," with renal disease being the dominate cause of mortality in the first 20 years of type 1 diabetes, and CVD leading subsequently (8). Overall incidence of major coronary artery disease increases as type 1 diabetics age, with the incidence being 0.98% among young adults aged 28-38 and surpassing 3% per year after age 55 years. This makes CVD the leading cause of death among this population. When comparing this with the incidence of CVD in people without type 1 diabetes, it ranges from 0.1% in 35 to 44-year-olds to 7.4% in adults 85-94 years (4). From this it can be seen that people with type 1 diabetes become more at risk of CVD comparatively than nondiabetic individuals as they age.

Aside from the more major instances of cardiovascular disease, "abnormal vascular findings associated with atherosclerosis are also seen in patients with T1DM," (4). Carotid intima-media thickness and plaque are also increased in children, adolescents, and adults with type 1 diabetes (4). The de Ferranti et al. article states that endothelial function is already altered even in childhood, showing that this function is altered at a very early stage of type 1 diabetes. A study conducted in Pittsburgh showed that type 1 diabetic adults with endothelial dysfunction markers were more likely to develop cardiovascular disease. This suggests that "preclinical CVD can be seen more frequently and to a greater extent in patients with T1DM, even at an early age," (4).

When discussing children, it is important to note that cardiovascular events are not generally thought to occur in children, even when type 1 diabetes is present. However, "children and adolescents with T1DM have subclinical CVD abnormalities even within the first decade of

DM diagnosis . . . including flow-mediated arterial dilation, endothelial peripheral arterial tonometry, and arterial stiffness measured by pulse wave velocity," (4). While the risk of CVD is generally thought of as lower among children than adults, children with type 1 diabetes do more commonly have risk factors for cardiovascular disease. Rodriguez et al. discovered that "the prevalence of having at least two CVD risk factors was 21%," and the prevalence increased from 7% in children aged 3-9 years to 25% in those aged 10 to 19 years (9). The risk factors assessed in this study were high blood pressure, high triglyceride levels, low HDL cholesterol, and high waist circumference, and these were examined in groups of different ages, sexes, races/ethnicities, diabetes types, and duration of diabetes. Results showed that CVD risk factor prevalence increases with age in type 1 diabetic children as well as nondiabetic children (4). Duration of diabetes always had an effect, and children with a duration of one year had a greater prevalence of risk factors than children with a duration of less than one year (9).

Two major risk factors of CAD among both diabetic and non-diabetic individuals are blood pressure and lipid levels. While much is known about these risk factors—and appropriate levels—in non-diabetic individuals, a study from Orchard et al. sought to identify the point at which these risk factors significantly increase the risk of complications. According to this study, there is "general agreement that people with diabetes form a uniquely high-risk group in terms of cardiovascular disease," (10), although the guidelines are not particularly descriptive. The relative risk of CAD is higher at all levels of blood pressure and cholesterol, leading to recommendations that people with diabetes should be treated more vigorously in terms of risk factors and prevention, even going so far as to treat them at the same level as individuals with existing CAD. This study was conducted over a 10-year period with a group of 658 eligible individuals with childhood onset type 1 diabetes. The LDL cholesterol ranges—which were measured in milligrams per deciliter—were 100 to 129, 130 to 159, and ≥ 160. With each increase in LDL cholesterol, the risk of early all-cause mortality and CAD increased, and the study concluded that the appropriate level for LDL cholesterol is 100mg/dl, when speaking specifically in terms of mortality from CAD. The triglyceride ranges were also measured in milligrams per deciliter, and were 100 to 149, 150 to 159, and ≥ 200. Once again, these ranges each saw an increase in early mortality and CAD from the previous range, and triglycerides are recommended to be lower than 200 mg/dl. Systolic and diastolic blood pressure were also recorded, and measured in millimeters of mercury. The systolic blood pressure ranges followed the same trend in that early mortality and CAD both increased with each systolic blood pressure increase. CAD risk also increased with each increase in diastolic blood pressure; however, early mortality risk in relation to diastolic blood pressure did not follow this trend. Risk of early mortality decreased from the 80 to 84 range, but then increased from the 85 to 89 range to the $\geq$ 90 range. The recommendation given was 130/80 mmHg, rather than the typical 120/80, to indicate increased risk. While difference in age and sex were examined in the study, significant differences were not found, and it is not believed that sex- or age-specific goals are needed.

Since type 1 diabetes is often diagnosed in children, it is important to examine the effects of the condition—as well as exercise—in children and adults. Rodriguez et al. sought to discover the link between diabetes in children and cardiovascular risk factors. The risk factors examined were increased blood pressure (systolic or diastolic), increased triglycerides, decreased HDL cholesterol, and increased waist circumference. While this study included type 1 and type 2 diabetes, this paper is solely focused on the results pertaining to type 1 diabetes. Of the 2,096 children aged 3-19 years, 32% had at least two CVD risk factors, and specifically among children with type 1 diabetes this percentage was 14. Despite this the type 1 diabetic subjects still had a 22% occurrence of increased blood pressure, 14% occurrence of increased triglycerides, 9% occurrence of decreased HDL cholesterol, and 15% occurrence of increased waist circumference, proving that diabetes can affect these factors. These findings “suggest that the prevalence of multiple CVD risk factors is high among children and adolescents with diabetes, including children <10 years of age,” (9) and that they “may be at significant increased risk of premature CVD,” (9).

According to Lind et al., ketoacidosis—a condition caused insufficient insulin that results in excess blood acids known as ketones being produced—and hypoglycemia—low blood sugar—are the leading contributors of excess mortality among diabetic individuals younger than 30 years of age. However, “cardiovascular disease is the main cause of death later in life,” (11). Given this statement, it appears as though heart disease is not a worry among young patients with diabetes; however, the article also states that improving glycemic control leads to a reduced risk of cardiovascular disease for these individuals (11). This is to say that if individuals are able to properly manage their blood sugar levels as young people, they can decrease their risk of heart disease later in life. This study included diabetes patients registered in the Swedish National Diabetes Register after January 1, 1998, and a selected control group, and participants were followed until December 31, 2011. In this, deaths from various causes were reported and displayed according to glycated hemoglobin level in the diabetic individuals. This means to say that researchers were using a longer-term view of glucose control to examine the rate of deaths among these people.

The causes of death most pertinent to the topic at hand include all-cause mortality and mortality from cardiovascular disease. Both variables saw a steady increase in deaths when glycated hemoglobin level went from ≤ 6.9% to 8.7%, but then saw a decrease from 8.8 to 9.6%

before slightly increasing again at a glycated hemoglobin level of greater than 9.7% (11). From this study, researchers concluded that patients with type 1 diabetes who had on-target glycemic control had a risk of death from any cause and a risk of death from cardiovascular causes of more than twice the risk in the general population. In diabetic patients with poor glycemic control, this statistic increased to 8 and 10 times as high, respectively (11). When looking at the difference in men and women with type 1 diabetes, the study found that women had a significantly greater excess risk of death from cardiovascular disease than men, but this did not translate to a greater risk of death from any cause. Cancer-related deaths were also tracked, but a significant difference in the incidence of cancer-related deaths among type 1 diabetics and the general population was not found, further proving that "the excess risks of death among patients with type 1 diabetes were almost entirely accounted for by cardiovascular disease and diabetes," (Lind 1977). This shows that early effective control of blood sugar can greatly decrease the likelihood of cardiovascular disease later in life in type 1 diabetics. Both this and the Rodriguez et al. study showcase the importance of preventing and/or treating CVD risk factors in all people with type 1 diabetes, even young children.

Exercise and Diabetes

Exercise is typically split into aerobic exercise and strength training, and a good exercise routine should include a combination of both forms of exercise. Aerobic exercise "involves repeated and continuous movement of large muscle groups that rely primarily on aerobic energy-producing systems," while resistance training "is a type of exercise using free weights, weight machines, bodyweight, or elastic resistance bands that rely primarily on anaerobic energy-producing systems," (12). A more recent form of exercise—high intensity interval training—has gained popularity in recent years and is described as an "alternation between brief periods of vigorous exercise and recovery at low to moderate intensity," (12). Exercise is critical for all individuals, regardless of whether a person has type 1 diabetes and/or heart disease or not. Despite this, exercise can be particularly difficult to navigate for type 1 diabetic individuals, due to barriers including "hypoglycaemia, loss of glycaemic control, and inadequate knowledge around exercise management," (12).

The biggest obstacle present for type 1 diabetics wanting to exercise is the drop in blood glucose. In individuals without diabetes, blood glucose concentrations are normally within a rigid range of around 4-6 mmol/L or about 70-110 mg/dL (12), but this concentration cannot be as easily maintained in those with type 1 diabetes. This is because their bodies cannot rapidly decrease their insulin concentrations, resulting in an increased concentration of insulin in the blood flow. When this increased insulin circulates, it promotes increased glucose disposal relative to hepatic glucose production. Because of this, "hypoglycemia develops in most patients within 45 min[utes] of starting aerobic exercise," (12). If these individuals follow an increased carbohydrate intake diet or decrease their insulin dosage, they can exercise the same as non-type 1 diabetics.

Exercise has a variety of benefits for people with type 1 diabetes—adults and children, and according to Riddell et al., "the health benefits of being physically active outweigh the risks of being sedentary," (12). Furthermore, individuals with complications can derive many benefits from physical activity without increased risk of adverse side effects. As previously stated, hypoglycemia is of high concern when type 1 diabetic individuals engage in exercise, particularly aerobic exercise. This is shown in Figure 1 of the Riddell et al. study, which is displayed below.

	Endurance exercise performance in athletes with and without diabetes	Hypoglycaemia prevention under low insulin conditions	Hypoglycaemia prevention under high insulin conditions
Meal (low fat, low glycaemic index) consumed before exercise	A minimum of 1 g carbohydrate per kg bodyweight according to exercise intensity and type	A minimum of 1 g carbohydrate per kg bodyweight according to exercise intensity and type	A minimum of 1 g carbohydrate per kg bodyweight according to exercise intensity and type
Meal or snack consumed immediately before exercise (high glycaemic index)	No carbohydrate required for performance	If blood glucose concentration is less than 5 mmol/L (<90 mg/dL), ingest 10–20 g carbohydrate	If blood glucose concentration is less than 5 mmol/L (<90 mg/dL), ingest 20–30 g carbohydrate
Meal consumed after exercise	1·0–1·2 g carbohydrate per kg bodyweight	Follow sports nutrition guidelines to maximise recovery with appropriate insulin adjustment for glycaemic management	Follow sports nutrition guidelines to maximise recovery with appropriate insulin adjustment for glycaemic management
Exercise (up to 30 min duration)	No carbohydrate required for performance	If blood glucose concentration is less than 5 mmol/L (<90 mg/dL), ingest 10–20 g carbohydrate	Might require 15–30 g carbohydrate to prevent or treat hypoglycaemia
Exercise (30–60 min duration)	Small amounts of carbohydrate (10–15 g/h) could enhance performance	Low to moderate intensity exercise (aerobic): small amounts of carbohydrate (10–15 g/h) depending on exercise intensity and blood glucose concentration measured during the activity High intensity exercise (anaerobic): no carbohydrate required during exercise unless blood glucose concentration measured during the activity is less than 5 mmol/L (<90 mg/dL); if so, ingest 10–20 g carbohydrate; replace carbohydrate needs after exercise	Might require up to 15–30 g carbohydrate every 30 min to prevent hypoglycaemia
Exercise (60–150 min duration)	30–60 g carbohydrate per h	30–60 g carbohydrate per h to prevent hypoglycaemia and enhance performance	Up to 75 g carbohydrate per h to prevent hypoglycaemia and enhance performance*
Exercise (>150 min duration); mixture of carbohydrate sources	60–90 g carbohydrate per h spread across the activity (e.g. 20–30 g carbohydrate every 20 min) Use carbohydrate sources that use different gut transporters (eg, glucose and fructose)	Follow sports nutrition guidelines (60–90 g/h) with appropriate insulin adjustment for glycaemic management	Follow sports nutrition guidelines (60–90 g/h) with appropriate insulin adjustment for glycaemic management

These guidelines are based on published studies,[59–61] and on our own expert opinion. *Carbohydrate consumption at a high rate might cause gastric upset in some individuals and might contribute to hyperglycaemia during and after the activity. To increase the rate of carbohydrate absorption during exercise, and maintain hydration status, sports beverages containing glucose and fructose might be preferable.

***Table 1*: Carbohydrate requirements for endurance (aerobic) exercise performance and hypoglycaemia prevention**

Table 1 from the Riddell et al. study. It shows the safe exercise recommendations for people with type 1 diabetes.

There are several effects that have been seen from regular exercise among young people. These effects include improvements in body composition, cardiorespiratory fitness, endothelial function, and blood lipid profile, all of which can be seen with regular physical activity (12). Similar statements are echoed by Herbst et al., who noted that "increasing physical activity in children with type 1 diabetes is associated with a beneficial cardiovascular risk profile, such as lower lipoprotein levels and diastolic blood pressure, and with better glycemic control," (7). Riddell et al. lists the recommended exercise as 150 minutes per week of physical activity, with no more than two consecutive days without exercise. These 150 minutes may be acquired however is most convenient to the individual, but there should be some form of resistance exercise included two to three times a week. There are exercise recommendations for children with diabetes—type 1 and type 2—which can lead to these improvements listed above. Riddell et al. states that children and young people with diabetes should get at least 60 minutes of physical activity per day. Even though recommendations can differ, it is most important to note that exercise in any form and for any amount of time is critical for both children and adults with diabetes.

While only cardiorespiratory fitness is a direct link to heart disease among the improvements listed by Riddell et al., blood pressure affects the heart, and blood pressure is linked to exercise in the Herbst et al. study. When a person has high blood pressure, their heart must work harder to pump blood. This is dangerous because it can lead to left ventricle thickening, which in turn can lead to heart attack or heart failure. The Herbst et al. study showed that the "percentage of patients with elevated diastolic blood pressure was lower in the RPA1 and RPA2 groups than in the RPA0 group," (7) meaning that children that engaged in physical activity 1-2 or ≥ 3 times per week had lower diastolic blood pressure on average. These groups also had lower percentages of patients with elevated systolic blood pressure, although this factor was not discussed in as great of detail. A more direct correlation has also been found between exercise and heart disease prevention in adults. This lower blood pressure means that the heart does not have to pump as hard, thus lowering the risk of heart attack or failure. According to Riddell et al., "having a higher exercise capacity in adulthood is associated with a reduced risk of coronary artery disease, myocardial ischaemia, and stroke, regardless of whether a person has diabetes or not," (12). This includes people with type 1 and type 2 diabetes as well as healthy adults.

As exhibited by this information, much more research is needed to connect the individual factors involved type 1 diabetes, heart disease, and exercise. While there is much information available in relation to type 2 diabetes and exercise, the same attention is not paid to type 1 diabetes. There is ample support for the use of exercise in heart disease prevention, recovery, and management; however, it is not known exactly how type 1 diabetes fits into the equation. Diabetes puts individuals at a higher risk for heart disease, but this statement is not specific to type 1 or type 2. This is an important distinction to make because the causes and treatments of the two types are vastly different, and they have different effects on the body, which can be carried over into heart disease risk and effects of exercise.

In general, it was seen that individuals with early onset type 1 diabetes were at risk for heart disease—or CAD—with increases in the other identified risk factors, but this can also be found in individuals without type 1 diabetes. It can be said, though, that since diabetes itself is a risk factor for heart disease, that these people would have a far greater risk of heart disease. However, since exercise lowers risk of heart disease in both healthy and diabetic populations, it can be said that exercise decreases risk in type 1 diabetics, when diet and insulin recommendations are followed, and exercise is performed safely.

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