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REVIEW ARTICLE

The Impact of Cardiovascular Exercise on Diabetes Management

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ABSTRACT: Diabetes is one of the most prevalent chronic conditions in the United States, with both Type 1 and Type 2 diabetes (T1D and T2D) affecting millions of people. T1D is an autoimmune disorder, where the immune system targets the insulin-producing cells in the pancreas, resulting in little to no insulin production and uncontrolled blood glucose levels. T1D is typically diagnosed in children and young adults. In contrast, T2D is characterized by a progressive decline in insulin secretion from pancreatic beta cells and insulin resistance in muscle tissue, leading to elevated blood sugar levels. While T2D usually develops after 45, it can happen at any age. Chronic high blood sugar (hyperglycemia) is harmful because it can damage blood vessels and organs, increasing the risk of complications such as heart disease, kidney failure, nerve damage, and vision problems. T2D is serious but not always irreversible. With proper management, including medical treatment and lifestyle changes, particularly exercises, individuals with T2D can prevent or delay complications and maintain a good quality of life. Research studies have provided mounting evidence that regular cardiovascular exercise helps improve insulin sensitivity, allowing the body to use glucose more efficiently. These physical activities also help lower blood sugar levels and improve cardiovascular health. While T1D is considered irreversible and requires lifelong insulin therapy, exercise can still positively impact glucose management for individuals with T1D. In this review, we highlight the positive impact of different cardiovascular exercise regimens, such as running, cycling, and swimming, on diabetes management, with a focus on T2D. These physical activities are effective in reducing insulin resistance and controlling blood sugar levels, making them critical components in the diabetes management plan. When combined with medical interventions, exercise offers a powerful tool to mitigate the long-term complications of diabetes and improve overall quality of life.

KEYWORDS: Translational Medical Sciences, Disease Treatment and Therapies, Type 2 Diabetes, Insulin Sensitivity, Cardiovascular Exercise.

Introduction

Approximately 1 in 10 Americans are diagnosed with diabetes mellitus, a chronic disorder in which the body produces little to no insulin (T1D) or experiences a decline in insulin secretion along with insulin resistance in muscle tissue (T2D), causing abnormally high blood sugar levels. Figure 1 describes the main characteristics of T1D and T2D. In 2010, there were 18.8 million cases in the US,[1] which doubled to 38.1 million in 2021.[2] These cases are expected to skyrocket, and by 2050, nearly 1 out of 3 Americans will have diabetes. It is projected that 578 million individuals will contract diabetes worldwide by 2030.[3] In 2022, the estimated cost of diabetic management in the US was ~307 billion dollars, excluding indirect costs attributed to diabetes, which translated to an average annual cost of $12,000 for T2D patients.[4] Diabetic patients with pre-existing health conditions will experience complications, such as cardiovascular dysfunction, stroke, kidney failure, blindness, circulation issues that lead to lower-extremity infection and amputation. Numerous studies [5-8] have implied that physical exercise is critical in mitigating T2D and the associated complications by increasing insulin sensitivity, which allows our body's cells to sufficiently uptake blood glucose, thus reducing blood sugar levels.

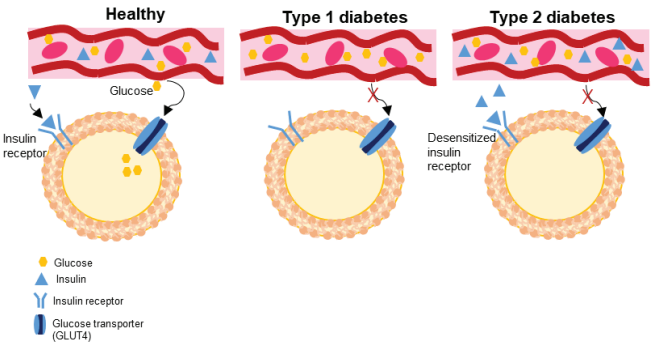

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Figure 1: Characteristics of type 1 and type 2 diabetes. Cellular glucose uptake in healthy individuals (left), impaired glucose uptake in type 1 diabetes due to insulin deficiency (middle), and reduced glucose uptake in type 2 diabetes due to insulin resistance (right), leading to uncontrolled blood sugar levels.

Insulin, secreted by the beta cells in the pancreas, is an essential hormone that helps regulate blood glucose by facilitating the body's cells to absorb glucose for energy or storage. Glucose comes from carbohydrate-rich foods, such as rice, bread, pasta, potatoes, and sugary fruits. Persistent consumption of these starchy foods causes the beta cells to secrete more insulin, which leads to diminished insulin secretion from the beta cells over time. T1D usually occurs early in life due to the

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autoimmune condition that damages the insulin-producing pancreatic beta cells, resulting in little to no insulin production. Meanwhile, the onset of T2D usually occurs later in life, and it happens when our body's cells become more resistant to insulin.[9] Without sufficient insulin, blood sugar levels will elevate. Early complications that patients experience include frequent thirst, urination, lightheadedness, and blurry vision. If these symptoms remain untreated, it will lead to more drastic long-term health issues. Serious complications of uncontrolled diabetes involve heart attack, stroke, kidney failure, blindness, and poor circulation, resulting in limb amputation. Over time, patients with uncontrolled diabetes will require multiple hospitalizations, and eventually, they will be unable to maintain their daily activities.

Treatments for T1D and T2D vary in their approach to managing the disease. T1D depends on insulin therapy due to the inability of beta cells to produce sufficient insulin,[10] whereas T2D can be managed through various methods, including lifestyle modification, diet approach, exercise, and medical intervention. Currently, many medical platforms in T2D treatment are comprised of insulin therapy[11] and various drugs with different mechanisms to help lower blood sugar levels.[12] In recent years, one of the drugs that are frequently mentioned in the medical field as well as in the media is Ozempic, a glucagon-like peptide 1 receptor (GLP-1) agonist, which not only helps diabetic patients control their blood sugar but also aids with weight loss as its side effect.[13] It has become increasingly popular to sidestep exercise while relying on this medication for managing diabetic symptoms and overall metabolic health. While Ozempic is effective in treating T2D, it may cause potential side effects, including nausea, abdominal discomfort, constipation, headache, fatigue, etc.[14]

Diet alone or medication alone is not enough to successfully control diabetes and prevent complications. Research studies have shown that a multifactorial approach that combines diet, exercise, and medication is essential to control this chronic condition.[15] According to a recent Yale study, the author stated, "Sticking to an exercise program for even eight weeks can lower blood sugar levels to points that are on par with diabetes medications."[16] The most common cardiovascular exercises people engage in to maintain a healthy lifestyle are running, cycling, and swimming. This paper aims to assess the effects of these three cardiovascular exercises on T1D and T2D patient populations by looking at their blood sugar levels, HbA1c levels, insulin sensitivity, insulin resistance, and glycemic control throughout their exercise regimen by analyzing previously published data. We selected these parameters to assess the effectiveness of exercise on T2D management because they are the common clinical markers of T2D. Furthermore, we will discuss the advantages and disadvantages of each exercise.

Discussion

Exercise and Its Health Benefits:

There are many risk factors for T2D, including age, inactivity, prediabetes, genetics, ethnicity, and an overweight BMI (25-29.9 kg/m^2).[17] About 40% of American adults are obese, and approximately 1 in 4 Americans are not getting enough exercise.[18,19] An unhealthy diet is another severe risk factor due to increased sugar intake, leading to insulin cell resistance. Research[15] has shown that a proper diet and exercise can improve insulin sensitivity, resulting in a greater glucose-lowering effect.

Exercise and diet are among the most critical components in diabetes management. Patients need to adapt to a healthy lifestyle, which includes eating a wholesome diet and frequent physical activities. Several studies[5-8] have demonstrated that exercises can help relieve T2D symptoms. An increase in the incidence rate of diabetes may be attributed to the lack of physical activity. Implementing exercise into daily routines helps reduce T2D occurrences. Neglecting exercise in these at-risk populations, T2D patients with advanced age, family history, or other medical conditions, can lead to susceptibility to major cardiovascular and neurological disorders. Most doctors have already implemented exercise into their patients' treatment regimens. Compiling several research papers focusing on the effects of running, cycling, and swimming in healthy adults, T1D, and T2D in humans, mice, or rats, Table 1 summarizes the impacts of these cardiovascular workouts on managing diabetes.

Despite diabetes being a severe disease and potentially life-threatening, only ~24% of those people are meeting the standard 150 minutes of exercise per week guideline.[20] As the disease progresses, increased BMI leads to lipid buildup and an increased likelihood of developing cardiovascular and other diseases.[21] Implementing exercise and physical activity into a daily routine helps increase blood circulation and insulin sensitivity, resulting in better control of blood sugar levels in T2D patients.[22] Exercise also helps reduce body fat levels and enhances overall metabolism.

Aerobic exercises like running, cycling, and swimming are some of the most common physical activities recommended for diabetic management due to their ability to improve insulin-induced glucose uptake, responding more efficiently to insulin.[23] A high-intensity aerobic exercise may decrease blood glucose levels even more, increasing insulin sensitivity.[24] For instance, a low-intensity exercise will lower the blood glucose levels by 20-30 mg/dL, whereas a moderately intense exercise will further bring it down by 40-50 mg/dL.

Table 1: Effects of different cardiovascular exercises on T1D and T2D. Summary of various studies investigating the impact of running, cycling, and swimming on T1D and T2D. The research involved different subject models, including humans, mice, and rats, and assessed key parameters such as glucose levels, HbA1c, and insulin sensitivity.

Study	Title	Exercise	Population	Effects on T2D	Area for further study
Running					
Wang *et al.* 2019	Leisure-Time Running Reduces the Risk of Incident Type 2 Diabetes.	Running	Healthy, non-Hispanic white adults	Adults who participated in running had a 28% reduced risk of getting T2D and reduced risk of cardiovascular disease.	Did not differentiate between T1D and T2D patients. A more diverse population, including different races and socioeconomic status, is more desirable.
Nakamoto *et al.* 2020	Effects of Voluntary Running Exercise on Skeletal Muscle Properties in Non-obese Rats with Type 2 Diabetes.	Running	Type 2 diabetic non-obese Goto-Kakizaki rats	Voluntary running lowered fasting glucose and HbA1c levels. Running also enhanced oxidative metabolism in cells & tissues.	More studies with larger populations are needed to confirm the results further.
Ruegsegger *et al.* 2017	Running from Disease: Molecular Mechanisms Associating Dopamine and Leptin Signaling in the Brain with Physical Inactivity, Obesity, and Type 2 Diabetes.	Running	Mice, rats	Obesity causes central dopaminergic dysfunction and central leptin resistance, reducing physical activity.	Further studies are needed to understand how dopamine dysfunction contributes to obesity and physical inactivity.
Cycling					
Usui *et al.* 1998	The Effect of Low-Intensity Bicycle Exercise on the Insulin-Induced Glucose Uptake in Obese Patients with Type 2 Diabetes.	Cycling	Type 2 diabetic obese males	Cycling improved insulin sensitivity and allowed cells to take in glucose more effectively.	More studies are needed to include both male & female participants. It is ideal to study the effect of a prolonged exercise duration.
Petersen *et al.* 2022	High-Intensity Interval Training Combining Rowing and Cycling Efficiently Improves Insulin Sensitivity, Body Composition, and VO_2 max in Men with Obesity and Type 2 Diabetes.	Cycling and rowing	Men with obesity and T2D	Increased insulin sensitivity by 30-40%	Could not distinguish the effect of cycling & rowing. More studies with larger sample sizes, including both men and women, are needed to validate the results further.
Rasmussen *et al.* 2016	Associations Between Recreational and Commuter Cycling, Changes in Cycling, and Type 2 Diabetes Risk: A Cohort Study of Danish Men and Women.	Cycling	Men and women 50-65 years free of T2D and other chronic diseases.	People who commuted by cycling had a 20% reduction risk of getting T2D	More studies are required to investigate the associations between cycling and T2D in other chronic disease groups.
Swimming					
Syahrastani *et al.* 2018	The Impact of 200 Meter Breaststroke Swimming Activity on Blood Glucose Level of The Student.	Swimming	Healthy students	After 30m swimming activity, blood sugars dropped by 14%.	Further research is needed to investigate the impact of 200m breaststroke swimming activity on T2D.
Sideraviciute *et al.* 2006	The Effect of Long-Term Swimming Program on Glycemia Control in 14-19 Aged Healthy Girls and Girls with Type 1 Diabetes Mellitus.	Swimming	Healthy teen girls and girls with type 1 diabetes.	HbA1c level decreased by ~12%, and blood glucose level decreased by 30% after the swimming program.	A small sampling of teen girls only. Additional studies with a wider population are necessary to confirm the results.
Yang *et al.* 2017	Swimming Training Alleviated Insulin Resistance Through Wnt3a/ß-catenin Signaling in Type 2 Diabetes Rats.	Swimming	Type 2 diabetes rats.	Fasting insulin levels and resistance decreased by ~30% after an 8-week swimming training.	More studies in humans are required to corroborate the result and to establish that the Wnt3a signaling pathway is connected with regulating insulin resistance.

Impact of Running on Diabetes Management:

Running is one of the most recommended exercise regimens for individuals with diabetes, particularly T2D. Its widespread popularity is attributed to its simplicity and minimal equipment requirement, making it an attractive option for high-intensity exercise. Evidence suggests that running can positively impact glucose levels and improve overall well-being. In Wang *et al.*'s paper,[25] the authors analyzed data from a longitudinal cohort study of 19,347 healthy adults (both men & women) who were free of cardiovascular disease, cancers, and diabetes. The participants were classified into two groups based on their running log: non-runners (n=13,640) and runners (n=5,707). The study aimed to examine the correlation between running and the incidence of T2D, which was defined as having a fasting glucose level of ≥126 mg/dL. During an average follow-up of 6.5 years, they found that running reduced the risk of developing T2D by 28%, with those running at least 175 minutes per week reducing their risk by an impressive 52%. Further analysis revealed that higher running frequency, distance, and intensity, such as running ≥6 miles per week, frequency ≥3 times per week, and at speeds ≥6.7 mph, remarkably reduced T2D incidence. This dose-dependent response suggests the direct correlation between running and the reduction in T2D risk.

Notably, the study by Wang *et al.* is comprehensive where the authors considered several running parameters, duration, distance, frequency, and intensity, demonstrating a robust association between running and reduced T2D incidence. However, this study has certain limitations. It did not differentiate between T1D and T2D cases, which may have affected the results, although the onset of diabetes in all participants was after 30, suggesting a higher likelihood of T2D. Another limitation of this investigation is the uniformity of the population, where all participants were non-Hispanic Caucasian adults with middle-to-upper socioeconomic status. Other factors associated with the high social status could potentially confound the results. The findings would be more generalized with a more diverse population, incorporating different racial, ethnic, and socio-economic groups.

The role of skeletal muscle in glucose homeostasis further emphasizes the benefits of exercise, particularly running, in diabetes management. In individuals with T2D, there is a well-documented decrease in oxidative capacity in skeletal muscles, along with a shift in fiber type distribution, from high-oxidative to low-oxidative fibers, an opposite shift compared to non-diabetic counterparts. Nakamoto *et al.*[26] investigated the relationship between voluntary running and skeletal muscle characteristics in rats. Their analysis involved non-obese T2D Goto Kakizaki non-exercise (GK, n=5), non-obese T2D Goto Kakizaki exercise (GK-Ex, n=10), and non-diabetic male Wistar rats (WS, n=5) served as the control. Goto Kakizaki rat is a model of T2D mellitus that is characterized as having insulin resistance and an insulin secretory defect.[27] The GK-exercise rats had voluntary running on a running wheel 24 hours/day for 6 weeks. The rats in this group were allowed to run voluntarily at their own pace on the running wheel in their cage. The number of revolutions on

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each running wheel was recorded daily. The authors monitored the food intake, body weight, glucose, and HbA1c levels, as well as the characterization of different types of muscles. Their study demonstrated that voluntary running improved fasting glucose, HbA1c levels, and muscle fiber composition in these rats. Notably, running resulted in a shift toward a more favorable oxidative fiber profile, similar to that observed in healthy non-diabetic rats. This change in fiber distribution was associated with enhanced muscle oxidative metabolism. Some limitations in the study include the small sample size and the lack of fiber improvement observed in certain muscles. Nonetheless, this research provides more evidence that running can mitigate the muscle dysfunction associated with T2D, hence can positively impact T2D management. Although the study was conducted in rats, the similarities between human and rat genomes and proteomes suggest that these findings could be relevant to T2D management in humans.

Despite the mounting evidence that cardiovascular exercise is effective in T2D management, physical inactivity remains a serious issue, resulting in a significant increase in T2D and obese populations in the US. Are there any underlying biological factors, and what is the molecular mechanism responsible for physical activity or physical inactivity? Which is the precursor, inactivity or obesity? Does inactivity lead to obesity or vice versa? In a review article in 2017, Ruegsegger *et al*.[28] summarized previously published data and suggested the hypothesis that obese-induced dysfunction in dopamine signaling resulted in physical inactivity. By reviewing previous studies that compared high-running mice or rats and obese animals, they discovered the role of leptin and dopamine signaling pathways that influenced physical activity. These studies offered sufficient evidence to support the connection between dopamine, leptin dysfunction, and physical inactivity. Regarding our question above, is inactivity the precursor of obesity, or vice versa? It appears that it is a feedback loop relationship. Lack of physical activity causes obesity, impairing the dopamine-signaling pathway, resulting in more inactivity, further increasing obesity. This finding is significant because it could provide scientists with a new strategy to target these pathways, reducing sedentary behavior and promoting physical activity. In turn, increased physical activity can help prevent several chronic diseases, including T2D and obesity. Additional studies in humans are necessary to confirm these findings and fully understand the molecular mechanisms underlying inactivity and obesity.

Given the substantial benefits of running in controlling T2D, patients must consider incorporating this exercise into their daily routine to manage sugar levels. This also applies to healthy individuals in preventing T2D occurrence. T2D patients must adhere to their healthcare team's guidelines to balance food intake and calories consumed. Those opting for a high-intensity running regimen need to follow an appropriate procedure. A proper high-intensity session should include a warm-up and a cool-down process. Warming up helps lose the joints and improves blood flow to the muscles, ultimately lowering the risk of injuries. The cool-down step is just as important, and the goal is to gradually transition the body back to a normal heart rate and blood pressure after a vigorous exercise. Additionally, T2D patients should discuss with their healthcare team a specific running regimen, such as running time, distance, speed, and frequency. Patients, especially those with complications, need to take extra caution to prevent extreme exhaustion, which can lead to glucose levels dropping to dangerously low levels with serious health consequences. Professional staff at the Mayo Clinic shared helpful guidelines for common exercise practices for T2D patients to lower blood sugar levels while maintaining the right energy state to avoid extreme exhaustion and fainting.[29]

Taken together, running presents a highly beneficial form of exercise for managing T2D and preventing its onset. The accumulating evidence supports the idea that regular running can improve glucose control, enhance muscle function, and reduce the risk of associated complications. With appropriate guidance, T2D patients can safely integrate running into their daily routines to manage their condition, while healthy individuals can use it as a preventative measure. Future research should aim to further clarify the mechanisms underlying the relationship between physical activity and diabetes, particularly through larger and more diverse human studies, and explore ways to overcome barriers to exercise in high-risk populations.

Impact of Cycling on Diabetes Management:

In addition to running, cycling is a highly recommended cardio regimen for diabetic patients. Cycling is a great alternative because it has less burden on the joints and bones, and patients can easily incorporate it into their daily routine.

Usui *et al*.[30] studied the effect of cycling on glucose uptake in both healthy men and obese men with T2D. Using the hyperinsulinemic-euglycemic clamp (HEC) technique, they evaluated the insulin sensitivity and glucose uptake in healthy men (n=7) and obese men with T2D (n =7) before, during, and after a 30-minute cycling session on a bicycle ergometer. Then, they calculated the glucose-infusion rate (GIR) 30 min before, during, and 120 min post-exercise. The study revealed that 30 minutes prior to exercise, obese individuals with T2D had ~60% lower GIR compared to the healthy group, suggesting insulin resistance in the T2D group. However, there was a significant increase in GIR during the cycling exercise, followed by a decrease in both T2D and healthy groups 30-60 min post-exercise. Moreover, GIR in the T2D group gradually increased to levels similar to the healthy group 80-120 minutes post-exercise. These findings suggest that a 30-minute cycling exercise could sufficiently increase the insulin-induced glucose uptake and improve insulin sensitivity, particularly in individuals with T2D. One critical factor not mentioned in the paper is whether the healthy and T2D groups were subjected to the same food intake. This variable could influence their result if the food intake differed. The study also did not explore the effects of extending the cycling duration beyond 30 minutes, which could potentially have a more prolonged impact on insulin sensitivity. It would be beneficial if this study also assessed fasting blood glucose and HbA1c levels, as these standardized parameters are highly relevant to T2D. Additionally, this study was conducted exclusively in male adults; there could be a pos-

sibility that the impact observed herein was associated with males only. To have a more generalized conclusion, more studies, including both male and female participants, are necessary. Moreover, to assess the long-term effects, additional research needs to be conducted over a longer period, ranging from several weeks to several months.

In another research, Petersen *et al*.[31] investigated the effect of high-intensity interval training (HIIT) combining cycling & rowing on insulin sensitivity. The study enrolled a group of obese men with T2D (n=15), glucose-tolerant obese men (n=15), and lean men (n=18). All three groups underwent an 8-week supervised cycling and rowing HIIT on ergometers, 3 sessions/week. They determined the effects of this training using dual-energy-X-ray absorptiometry (DEXA) and HEC methods. DEXA scan measures the strength and mineral composition of the bones. The results indicated a HIIT-induced clinically relevant reduction in HbA1c and fasting glucose levels in obese men with T2D. The study also revealed an overall increase in insulin-stimulated glucose disposal rates (GDR) across all three groups, with the greatest improvements seen in the obese T2D group. This HIIT-induced increase in GDR reflects a ~30-40% increase in insulin sensitivity. The higher the insulin sensitivity, the more cells can uptake glucose for energy and storage, significantly lowering blood sugar levels. Additionally, following the 8-week HIIT, the study demonstrated an increase in VO_2 max and an overall improvement in body composition across all three groups. VO_2 max is the maximum amount of oxygen our body can absorb and utilize during exercise. These studies were thoroughly conducted and well designed by meticulously tracking both clinical and biochemical markers to evaluate the effects of high-intensity interval training (HIIT) on body composition. The finding provides a comprehensive understanding of how HIIT impacts metabolic health and offers valuable insights into the benefits of exercise on body composition and overall metabolic function.

Moreover, the authors also evaluated the risk factors such as risk of bodily injury and exercise adherence. Having patients adhere to exercise is important to achieve the optimal effects on metabolic health and maintain these positive effects. The result of this study corroborated Usui *et al*.'s work mentioned above. However, one challenge in interpreting these results is the combination of cycling and rowing, which makes it difficult to isolate the specific contributions of cycling to the observed effects. Food intake is another critical parameter that was not discussed in this study. The results could be influenced if there was no proper food intake control. Coincidentally, this study also enrolled male-only participants, limiting the ability to generalize the findings across genders. Certainly, enrolling participants who can commit to an 8-week program can be challenging. Still, a larger population that includes both men and women is necessary to evaluate further the benefits of cycling in managing T2D.

Undoubtedly, cardiovascular exercise is rewarding and improves our physical state and health. To achieve and maintain physical function, one has to adhere to the exercise regimen. How can one improve exercise adherence? Setting a realistic, measurable goal or forming a habit is one way to improve adherence. Integrating readily accessible exercise into daily life is also an excellent way to stay physically fit. For instance, one can consider riding a bike instead of driving to work. In another study by Rasmussen *et al*.,[32] scientists surveyed healthy middle-aged Danish men and women from 50-65 years old to interrogate if cycling helped prevent T2D development. Participants were surveyed about their lifestyle and cycling habits, and the study followed up five years later. The findings indicated that there was an association between cycling, particularly commuter cycling, and a reduced risk of getting T2D, with the effect being dose-dependent. The more participants cycled, the lower their risk of developing T2D. This result supports the idea that regular cycling can offer a protective effect against T2D. One of this investigation's drawbacks was the population heterogeneity, which made statistical analysis challenging. Any underlying confounding factors (age, gender, food/alcohol intake, smoking status, etc.) not accounted for during statistical analysis could lead to misleading results. Moreover, this study is entirely based on the self-reported system, which might introduce bias or inaccuracies. In addition, there was no distinction in the diagnosis of diabetes. However, given the age of the participants being 50-65, it likely aligned with the onset of T2D. Although in this study, the authors established the relationship between cycling and the risk factor of T2D in healthy adults, T2D patients will likely also receive similar positive effects from cycling.

Overall, these studies provided promising data suggesting that cycling effectively improves insulin sensitivity and reduces glucose levels in T2D, hence reducing the risk of T2D development. Cycling requires no special equipment, and one can easily incorporate it into daily routines. Cycling is a fairly low-impact exercise, so there is less stress on the knees and joints as long as one has proper bike fitting and cycling techniques. Due to cycling being low-impact, it is a feasible long-term exercise option, particularly for individuals with diabetes or those at risk of developing the disease. In addition, cycling recruits different muscle groups, which is complementary to other forms of exercise, such as running, to further enhance its health benefits. While the existing studies have provided promising results, further research is necessary to address the limitations in these studies, including the need for more diverse participant samples, better control of dietary intake, and the investigation into the long-term effects of cycling on T2D management.

As it provides all the health benefits of cycling, healthy individuals and T2D patients should consider incorporating recreational, commuter cycling, or both to improve insulin sensitivity and reduce T2D incidence.

Impact of Swimming on Diabetes Management:

In addition to running and cycling, swimming is another popular cardiovascular activity. It is a low-impact, full-body workout that engages almost all body muscles. Swimming puts minimal stress & pressure on the joints, which is suitable for diabetic patients, particularly those with weak leg strength

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due to complications. Furthermore, swimming can be a viable option for long-term exercise due to its low impact on the body.

In 2018, Syahrastani *et al*.,[33] reported the positive impact of 200m breaststroke swimming on blood glucose levels. In this analysis, they enrolled 15 healthy male students who participated in 200m breaststroke swimming over 6 months. The impact of swimming was assessed by measuring fasting, non-fasting (2 hrs after eating), and post-exercise blood glucose levels. Their results showed a significant reduction in blood sugar, by ~16 mg/dL or ~14%, after a 200-meter breaststroke swimming activity. This data highlighted the benefit of swimming in reducing blood glucose levels, even in healthy individuals. One limitation of this research was the lack of information regarding the frequency of swimming sessions over the 6-month period, making it unclear how frequently the positive effect was observed over 6 months. We also recognize the limitation of this research: the small and male-only sampling size, limiting the generalizability of the findings.

Corroborating this result, Sideraviciute *et al*.,[34] also evaluated the effect of swimming on blood glucose levels. This study monitored the blood glucose levels in 19 T1D girls and 28 healthy girls (ages 14-19) before and after a 14-week swimming program (2 times/week, 45 min/session). The data showed a decrease in HbA1c levels in all participants, and the effect was more pronounced in diabetic individuals. Consistently throughout the program, there was a significant decrease in blood sugar levels in both healthy and T1D groups. Midway through the program, blood glucose levels decreased by approximately 30% in the T1D group, and overall, blood sugar levels dropped by 15% from the first to the final session. This study complements Syahrastani *et al*.'s work and provides additional evidence that swimming helps reduce blood glucose levels in healthy and T1D individuals. Although in these studies, the authors only investigated healthy and T1D cases, it is reasonable to extend the effect of swimming in reducing blood glucose levels in T2D patients. However, to have well-founded evidence, we need additional research specifically targeting T2D populations to confirm these benefits.

Thus far, these studies have supported the benefit of swimming in controlling blood sugar levels in diabetic individuals. However, there are limited studies assessing the potential benefits of swimming and insulin resistance, the hallmark of T2D, and the underlying molecular mechanisms are not well understood. Recent research has suggested that the Wnt/ß-catenin signaling pathway is a critical regulator in metabolic syndrome such as diabetes. Yang *et al*.,[35] experimented to prove if this pathway is responsible for alleviating insulin resistance due to swimming. In this study, 56 male Sprague Dawley rats aged 8-10 weeks were divided into 2 groups: normal & T2D. The latter was induced using a low dose of Streptozotocin (STZ). The rats were subjected to a swimming program, which was classified into different intensities (low, moderate, and high) over 8 weeks (5 times/week). Their finding revealed that swimming reduced fasting blood glucose levels in a dose-dependent manner. Swimming also reduced fasting insulin levels and insulin resistance by ~30% in T2D rats. Specifically, fasting insulin levels in the low, moderate, and high-intensity swimming groups were almost the same as in the healthy control group. Their histology analysis showed that swimming improved muscle fiber health and reduced glycogen deposit in the skeletal muscles of T2D rats. The result suggested swimming improved glucose uptake and utilization, hence helping alleviate insulin resistance. The authors linked these effects to changes in the Wnt/ ß-catenin signaling pathway, with swimming downregulating Wnt3A at both mRNA and protein levels (mRNA change was larger in magnitude than protein level change) and altering ß-catenin and GSK3ß phosphorylation. This research offers valuable insights into the molecular mechanisms that explain how swimming impacts insulin resistance. Research by Yadav *et al*.[36] corroborated the role of Wnt modulation in insulin pathways and glucose homeostasis. These studies pave the way for new anti-diabetic drugs targeting the Wnt signaling pathway. However, this is an emerging area of research that requires further investigations to gain a better understanding of these molecular pathways and how to target them therapeutically.

In addition to insulin resistance, mitochondrial dysfunction and endoplasmic reticulum stress (ERS) are also key characteristics of T2D. Mitochondrial-associated membranes (MAM) reversibly tether the ER to the mitochondria and play an important role in glucose homeostasis. Physical exercise is known to improve glucose uptake/utilization, insulin sensitivity, and muscular function. Does physical activity positively affect insulin resistance via MAM? To establish this relationship, Zhang *et al*.[37] investigated the effects of swimming on MAM quality in diabetic mice. The experimental design included four groups of mice: control, exercise, diabetic sedentary, and diabetic exercise, n=8 for each group. A diabetic model was induced using STZ, and the exercise mice were subjected to a swimming program over 6 weeks (1h/day, 5 days/week). The study found that swimming not only improved glucose tolerance but also mitigated ERS in diabetic mice. Quantitation of MAM levels by measuring Sigma-1R level by Western blot suggested that diabetes significantly reduced MAM quantity, but swimming effectively alleviated MAM loss. By assessing the prevalence of mitochondrial dysfunction, a parameter tied to diabetes pathogenesis, Zhang *et al*.[37] found that swimming helped increase MAM quantity and improve mitochondrial quality, which is vital for energy metabolism in skeletal muscles. This research suggests that swimming may improve mitochondrial function and muscle energy utilization, potentially shedding light on new anti-diabetic therapeutics through the regulation of MAM and ERS. While these findings are promising, this is a newly developing area of study, more investigation is required to further explore the mechanisms linking mitochondrial function, MAM quality, and exercise in various animal models, and eventually in humans.

Taken together, the existing literature provides strong evidence for the role of swimming in improving blood glucose levels and insulin sensitivity in both healthy and diabetic individuals. Swimming offers a low-impact, full-body exercise that can be easily incorporated into daily routines, making it a sustainable exercise option for long-term diabetes management, in particular T2D. In addition, the potential molecular mech-

anisms, such as the regulation of the Wnt/β-catenin pathway and the mitochondrial function, offer new avenues for understanding how swimming affects metabolic health. However, additional research is needed to confirm these mechanisms and to assess the impact of swimming on insulin resistance and glucose regulation in larger and more diverse populations.

Given its effectiveness, swimming should be considered an essential component of a diabetes management plan. Future studies exploring the long-term effects of swimming and its underlying molecular mechanisms will help solidify its role in preventing and managing diabetes.

Advantages & Disadvantages of Running, Cycling, and Swimming:

The above research studies consistently highlighted the positive impacts of running, cycling, and swimming on controlling blood glucose levels, improving insulin sensitivity, and alleviating insulin resistance in diabetes, especially T2D. However, the lack of standardized experimental designs, population sampling methods, and outcomes poses challenges to compare findings and draw broad conclusions across these studies. Nonetheless, the results underscore the importance of each cardiovascular exercise in T2D management.

Every exercise offers great benefits in managing diabetes, but each also has potential drawbacks, as shown in Figure 2. Running, cycling, and swimming offer several benefits for diabetic patients and healthy individuals, particularly in mitigating T2D symptoms and overall cardiovascular health. Running does not require specialized equipment and can easily be integrated into one's daily routine. A high-intensity running exercise offers more health benefits. However, it also requires higher food intake to compensate for the calories burnt, which may be challenging to maintain or lose weight, especially in diabetic patients with obesity. Running may stress the joints and bones, especially for patients with complications resulting in weak feet and legs. Cycling can be done on a regular bike or a stationary bike at the gym. Cycling does not exert much strain and pressure on the joints and knees. Therefore, one can exercise over a long period without injuries. However, cycling can expose individuals to the risk of road accidents, especially for those who do not have access to stationary bikes, particularly in cities without bike lanes or sidewalks. Swimming is an all-body exercise with the least strain and stress compared to running and cycling. This activity works on different body muscles: arms, legs, shoulders, and abdominal region. However, swimming is not readily accessible to everyone because not everyone has access to a pool.

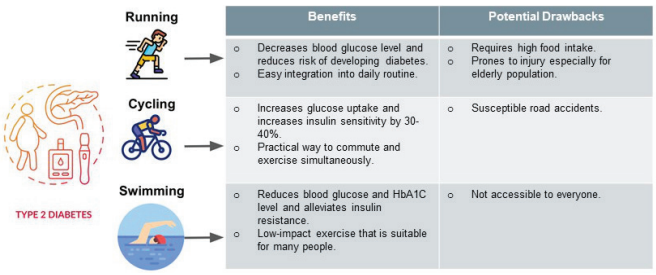

Figure 2: Advantages and disadvantages of cardiovascular exercises in diabetes management. Running, cycling, and swimming all offer significant benefits in controlling blood glucose levels. However, each activity has its drawbacks: running is prone to injury, cycling carries the risk of road accidents for those who do not have access to stationary bikes, and swimming may not be accessible to everyone.

Conclusion

This review highlights compelling evidence that running, cycling, and swimming help improve glucose uptake, reduce blood glucose levels, alleviate insulin resistance, and enhance insulin sensitivity, making them effective for both preventing and managing diabetes. While each exercise offers unique benefits, rotating between all three cardiovascular workouts can offer an effective approach to mitigate both T1D and T2D symptoms. This approach can be tailored to individual preferences and environmental conditions, such as indoor swimming in winter and running or cycling in spring and summer.

Although physical exercise is a cornerstone of diabetes management, not all individuals with diabetes will respond favorably or consistently. The response to exercise depends on several factors such as disease progression, complications from other disorders, fitness level, exercise adherence, and lifestyle choices. It is important for patients to discuss their exercise plan with their healthcare team to create a personalized regimen that suits their specific circumstances.

The individualized exercise plan should be tailored based on the type, intensity, and frequency of exercise to promote long-term sustainability, which is critical in diabetes management. In addition to frequent physical activities, patients should also focus on a healthy diet. A combination of cardiovascular exercises and a well-balanced diet is essential for managing blood glucose levels effectively and improving the overall quality of life.

Despite the promising findings, these studies have some limitations. One of the drawbacks is the lack of using standardized clinical outcomes relevant to diabetes, making it difficult to compare and draw broad conclusions from different studies. Additionally, many studies had small sample sizes and lacked diversity, limiting the generalizability of their findings. Furthermore, while animal studies have provided valuable insights into the positive impacts of exercise on diabetes management, translating the results to humans is more complex. It is necessary to conduct more research to confirm their relevance for human diabetes management. In this regard, the results of animal studies can provide a foundation for developing personalized exercise plans for diabetic patients.

Ongoing studies into the molecular mechanisms linking glucose and insulin regulation to various signaling pathways

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hold promise for novel T2D therapeutic strategies. However, they are beyond the scope of this review and warrant further investigation.

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