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What is the Effect of Physical Activity on the Reduction of Macrovascular Complications in Patients Diagnosed with Type 2 Diabetes Mellitus?

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What is the Effect of Physical Activity on the Reduction of Macrovascular Complications in Patients Diagnosed with Type 2 Diabetes Mellitus?

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Abstract

The increasing prevalence and healthcare burden of type 2 diabetes is a worldwide concern. It is the seventh leading cause of mortality and a significant cause of morbidity. While both the macrovascular and microvascular complications of diabetes can have a profound impact on overall health and quality of life, cardiovascular events are the leading cause of mortality in patients with type 2 diabetes. Adults with diabetes have a two to four-fold increased risk of cerebrovascular events and myocardial infarctions. Oral medications combat insulin resistance and aid in the control of hemoglobin A1c, blood pressure, and cholesterol, therefore, contributing to a decrease in potential complications of diabetes. However, these medications may be costly and unobtainable for those who are uninsured or face barriers in accessing healthcare. The foundation of diabetes management and prevention is rooted in lifestyle modifications, including physical activity. Physical activity has been shown to decrease the risk factors associated with macrovascular complications in adults with type 2 diabetes. Through the optimization and implementation of physical activity into diabetes management, patients with type 2 diabetes can reduce the risk of mortality associated with coronary heart disease, cerebrovascular disease, and peripheral artery disease.

Introduction

According to the Centers for Disease Control and Prevention, diabetes is the seventh leading cause of death in the US; with 1 in 10 Americans (approximately 34 million people) living with diabetes.[1] Of those 34 million people, roughly 29.8 million have type 2 diabetes.[1] Globally, according to the World Health Organization, 422 million people have diabetes, disproportionately affecting low and middle-income countries.[2] Unfortunately, these numbers

show no sign of dwindling and are projected to continue to rise due to a variety of factors including rising rates of genetic predisposition, poor nutritional habits, and sedentary lifestyles.[3]

This projected rise in global diabetes diagnoses is accompanied by a projected upsurge in poor health outcomes, secondary to macrovascular and microvascular complications of diabetes as a result of poor overall disease control. Macrovascular complications account for an increased risk of mortality due to coronary heart disease, cardiomyopathy, arrhythmias, cerebrovascular disease, and peripheral artery disease. Cardiovascular disease is the leading cause of mortality in patients with type 2 diabetes[4,5] and adults with diabetes have a two-to-four-fold increased risk of developing coronary heart disease, cerebrovascular disease, and peripheral artery disease.[4] The current approach to diabetes management largely focuses on oral medications and insulin, which have been shown to improve health outcomes in patients with diabetes. However, these medications may be costly and unobtainable for those who are uninsured or face barriers in accessing healthcare, leading to improper glycemic control and increased risk for adverse outcomes. The current increasing incidence, overall prevalence, and unfavorable health outcomes associated with diabetes may suggest that the current management strategies are not entirely sufficient for comprehensive diabetes management and decreasing unfavorable health outcomes.[3]

The foundation of diabetes management and prevention is lifestyle modifications, including a well-balanced diet and physical activity. The term "physical activity" refers to any bodily movement produced by skeletal muscles and can include a broad range of occupational, leisure, and daily activities. On the other hand, "exercise," refers to planned or structured physical activity, involving repetitive movements. By definition, all exercise is physical activity,

but not all physical activity is exercise. Thus, a balance of exercise and physical activity has long been recognized in the treatment regimen of type 2 diabetes.

The physiology behind the effect of physical activity on HbA1c, hypertension, and cardiorespiratory fitness will be reviewed in this paper. Furthermore, the type, quantity, and duration of an optimal physical activity plan will also be explored. Ultimately, this paper will analyze the possible outcomes of implementing physical activity as a means for the reduction of coronary heart disease, cerebrovascular disease, and peripheral artery disease among patients with type 2 diabetes.

Background: Literature Review

Despite advances in medication management for type 2 diabetes, the current research does not foresee any decrease in incidence, prevalence, or unfavorable health outcomes associated with type 2 diabetes.[3] In addition, there are numerous possible barriers to patients including unequal access, cost of treatment, and unpleasant adverse reactions of medications that can be prohibitive and ultimately lead to low levels of medication adherence and inadequate disease control. Lifestyle changes have been the cornerstone of type 2 diabetes prevention and management, but the efficacy of physical activity as a central component in the reduction of macrovascular complications and risk of overall mortality may be an underrated and valuable treatment option for patients with type 2 diabetes.

Physiology of Physical Activity

It is well known that physical activity can assist in the protection of the heart and blood vessels by optimizing insulin sensitivity, dyslipidemia, blood pressure, leptin sensitivity, and nitric oxide production.[6] While the improvement of these processes can improve overall health

and decrease the risk of potential macrovascular complications of type 2 diabetes, the distinct ability of physical activity to reduce overall blood glucose and increase insulin sensitivity is of particular relevance. During physical activity, the functioning skeletal muscle receives an increase in blood flow and uptakes more glucose from the blood to replenish depleted glycogen stores and match the increased demand for energy. Depending on the variation of physical activity, the effect can be substantial. For example, aerobic exercise can increase muscle glucose uptake up to fivefold. [16] This exercise-mediated glucose uptake is not insulin-mediated, allowing it to occur regardless of the level of insulin resistance existing within the body tissues.[7,8]

Glucose uptake into the contracting skeletal muscle is mediated by three key processes: delivery, transport, and metabolism.[7] Glucose delivery is mediated by the amount, frequency, and intensity of the contractions within the individual muscle cell. Glucose transport into the skeletal muscle is dependent on the translocation of the most abundant glucose transporter, GLUT4, to the skeletal muscle cell surface. This process is controlled by molecular signaling in response to skeletal muscle contractions (Figure 1).[7] Once glucose is in the skeletal muscle, metabolism begins with phosphorylation to glucose-6-phosphate (G6P). G6P can then proceed to be used for glycogen synthesis, glycolysis, the hexosamine pathway, or the pentose phosphate pathway.[9]

The positive effects of physical activity on blood glucose extend past this acute phase of active skeletal muscle contraction. Physical activity has also been shown to be beneficial in decreasing overall insulin resistance. Within skeletal muscles, "as the acute effect of exercise on glucose transport wears off, it is replaced by an increase in insulin sensitivity."[10] The duration of this increased insulin sensitivity is dependent on the type and duration of the physical activity. 20-minute bouts of vigorous aerobic activity can increase insulin sensitivity for up to 24 hours.[11]

Even low-intensity aerobic exercise performed for 60 minutes can produce similar effects for at least 24 hours.[11] This phenomenon, notably, is also not mediated by the insulin-signaling pathway; further suggesting that this process can be advantageous for glucose regulation even in the insulin-resistant skeletal muscle cell.[10] The combination of these mechanisms within the skeletal muscle makes physical activity a sustainable option to increase insulin sensitivity and consistently decrease blood glucose over time - the key in the management of type 2 diabetes.

HbA1c, Blood Pressure, Cardiorespiratory Fitness, and Physical Activity

Insufficient glycemic control has been identified as the key risk factor in the development of diabetes complications, particularly cardiovascular mortality.[12,13] Studies suggest that regular physical activity is beneficial in A1c control [14–16], and a lower A1c has been linked to lower rates of macrovascular complications in adults with type 2 diabetes.[12,13] Specifically, HbA1c levels greater than 8.0% have been associated with a higher risk of cardiovascular mortality in patients with type 2 diabetes.[13] In addition, every 1% increase in glycosylated hemoglobin has been associated with a 17% increase in cardiovascular disease and a 25% increase in mortality due to cardiovascular disease.[12] HbA1c has a clear relationship with coronary heart disease. There is a 15% increase in coronary heart disease and a 17% increase in mortality secondary to coronary heart disease per every 1% increase in HbA1c.[12] These findings suggest that even seemingly modest improvements in blood glucose control over time may be favorable in decreasing cardiovascular disease rates and mortality in patients with type 2 diabetes.

Exercise-mediated glucose uptake and increased insulin sensitivity are highly dependent on the timing, nature, duration, and intensity of the physical activity or exercise. The American Diabetes Association's current exercise recommendations for patients with type 2 diabetics align with the general recommendations and consist of a minimum of 150 minutes of aerobic exercise

at moderate-to-vigorous intensity spread over a minimum of 3 days per week, with no more than two consecutive days without activity.[11] Resistance exercise is recommended at least 2 days a week.[11] Realistically, only 23% of Americans aged 18-64 years old are achieving these recommended physical activity requirements.[17]

In patients with type 2 diabetes, more recent literature suggests that postprandial exercise significantly improves glycemic control as compared to exercise performed without regard to the timing of meals.[18,19] Furthermore, postprandial aerobic activity, such as moderate-intensity walking, has been shown to be more powerful in decreasing HbA1c than postprandial resistance exercise.[18–20] In a study conducted on older adults with diabetes, benefits in 24-hour blood glucose control were seen with just 15 minutes of postprandial walking.[19] Improvements in glucose values were strongly correlated with improvements in 3-hour post-dinner values, suggesting that walking after dinner may have the greatest benefit in overall blood glucose homeostasis.[19] These results were especially notable when the exercise occurred after consuming meals that contained a substantial amount of carbohydrates.[18]

There is conflicting evidence about whether resistance and aerobic training alone improves glycemic control in type 2 diabetes, but the combination of resistance and aerobic training was shown to be most effective for improving HbA1c levels.[14,15] In patients with type 2 diabetes, a 9-month combined resistance and aerobic program consisting of resistance exercise twice per week and aerobic exercise expending 10kcal/kg per week decreased HbA1c levels by an average of .34%.[14] In addition to hyperglycemia control, physical activity has been widely known to reduce hypertension[21] and improve cardiorespiratory fitness,[22] two powerful and modifiable risk factors for the development of cardiovascular disease. Specifically, in patients with type 2 diabetes possessing a low baseline cardiorespiratory fitness level, moderate to

vigorous aerobic exercise alone and in combination with resistance exercise was capable of increasing cardiorespiratory fitness.[22] Higher intensity aerobic activity had a larger effect on VO2 max.[23] An exercise intensity that reached 75% of VO2 max increased the baseline VO2 max by 40.9% as compared to the lower intensity exercise that only increased the VO2 max by 9.5%.[23]

Largely due to nitric oxide release in response to the physical stress on the blood vessels, both normotensive and hypertensive individuals experience transient reductions in blood pressure with exercise, as well as postexercise hypotension.[6] In particular, aerobic exercise was shown to reduce blood pressure in individuals with resistant hypertension.[21] An average decrease of 6 mmHg in systolic and a 3 mmHg in diastolic blood pressure was seen with an 8–12-week treadmill exercise program, consisting of an interval training pattern 3 times per week.[21] Although seemingly marginal, epidemiological studies indicate that even a decrease of 5 mmHg in the systolic blood pressure is likely to reduce the mortality associated with stroke by 14% and coronary heart disease by 9%.[24]

Coronary Heart Disease

As previously mentioned, cardiovascular disease is the leading cause of mortality among patients diagnosed with type 2 diabetes.[4,5] The implementation of physical activity as an adjunct to diabetes management may be a feasible option to decrease mortality secondary to coronary heart disease. Moreover, studies suggest that even small increases in volume or intensity of physical activity can be beneficial.[25] Increasing physical activity by 11.25 MET hours/week was associated with a statistically significant decrease in CVD incidence and mortality, as well as CHD incidence and mortality.[25] Additionally, physical activity was shown to be more protective against CVD mortality than CVD incidence.[25] The greatest cardiovascular protective benefits

may be seen with the transition from inactive to moderate physical activity, corresponding to an additional 6 MET hr/week.[25] These modest increases in weekly physical activity can lead to large decreases in cardiovascular risk and outcomes. Each additional MET hr/week corresponds to a risk reduction of 4.3% for CVD mortality and 1.7% for CVD incidence.[25]

In patients with type 2 diabetes, low physical activity levels have been correlated to an increased risk of CVD and mortality.[26] Middle-aged patients (median age of 60) with type 2 diabetes who reported low baseline levels of physical activity, defined as at least 30 minutes of exercising never, less than 1 time per week, and 1-2 times per week, were found to have an increased risk of cardiovascular disease and mortality of 25-70% over 5 years when compared to patients who had higher levels of physical activity at baseline, defined as exercising for 30 minutes 3–5 times per week or daily.[26] Importantly, the risk of cardiovascular disease can be altered with alterations in the frequency of physical activity. Modification of physical activity levels, increasing from low to high physical activity, over the course of five years was also shown to reduce CVD risk.[26]

In patients with stable CHD, no or reduced leisure-time physical activity (LTPA) has been associated with a two-fold increased risk of cardiovascular events compared to patients who engaged in LTPA more than three times a week.[27] Individuals that achieved the recommended physical activity guidelines of at least 150 minutes/week of moderate-intensity LTPA had a 14% lower CHD risk compared to those reporting no levels of LTPA.[28] Furthermore, those reaching the advanced guidelines of 300 minutes/week of moderate-intensity LTPA had a 20% lower risk of CHD.[28] These findings suggest a dose-response correlation between physical activity and CHD, showing that even modest amounts of LTPA are beneficial and may be more sustainable over time than an intensive exercise intervention program for CHD.

While the previously reported results support the idea that any amount of physical activity is better than no amount, high-intensity interval training (HIIT) has been shown to be more beneficial than moderate continuous training (MCT) in reducing CHD risk and mortality.[29] Both MCT and HIIT can improve VO2 max, a marker that has been closely linked with survival in patients with cardiovascular disease.[29] An 8-week program of HIIT consisting of 20-second bouts at 50% maximum effort, followed by 40 seconds of rest, for a total of 40 minutes of aerobic activity has been shown to increase VO2 max by 24% in patients with stable CHD compared to a 12% increase secondary to an MCT program.[29]

Cerebrovascular Disease

The positive impact of physical activity on cerebrovascular disease is evident in both the prevention of strokes and the reduction of post-stroke complications.[30–32] Specifically, pre-stroke physical activity has been shown to reduce stroke severity and improve functional outcomes after a stroke.[30,31] Patients with less than 3,000 MET minutes/week of physical activity, regardless of the combination of walking, moderate, or vigorous activity, were more likely to have higher NIH Stroke Scale scores corresponding to more severe strokes,[32] potentially leading to poorer outcomes and more complications. Nonetheless, similar to the themes of the previous research discussed, any physical activity is better than no physical activity. Participating in at least 1,000 MET min/week, an amount achieved by 1 hour of walking per day for 5 days walking or by doing 1 hour of vigorous aerobic activity twice a week, was independently associated with better functional outcomes at 3 months post-stroke.[32]

LTPA may be a significant predictor of stroke and mortality in Japanese patients with type 2 diabetes.[34] LTPA was quantified using metabolic equivalents (MET) and took into account the frequency and duration of the reported physical activity. There was a significant

reduction in stroke risk and mortality risk in patients who performed more than 15.4 MET h/week.[34] The opposite was true for patients who performed less than 3.7 MET h/week, showing an increased risk of stroke and mortality risk.[34]

Physical activity's impact on post-stroke functional outcomes can somewhat be explained by an increase in vascular endothelial growth factor (VEGF). VEGF is an independent predictor of good functional outcome at 3 months and was associated with smaller infarcts.[33] In a study of 83 patients, with a median NIHSS score of 17 upon admission, patients who reported to be more physically active before their stroke had a significantly higher level of serum VEGF on post-stroke day seven compared to less active patients.[33]

Peripheral Artery Disease

While the manifestation of peripheral artery disease (PAD) is not necessarily as deadly as coronary heart disease or cerebrovascular disease, it can significantly contribute to a decreased quality and comfort of life. Physical activity is beneficial in both the prevention and severity reduction of PAD.[35,36] There is a clear association between both physical activity itself and the frequency of physical activity with the risk for peripheral artery disease development. Of more than 3 million self-referred participants, in a study from 2015, subjects who reported any aerobic physical activity had a 36% lower risk of PAD compared to those who reported none.[36] Furthermore, it is encouraging that even minimal frequency is protective against PAD. Individuals reporting any physical activity just 1x/week have 26% lower odds of PAD compared to no physical activity.[36] These odds increase with frequency of physical activity, with a report of >3x/week having 45% lower odds of PAD.[36] The type and intensity of aerobic physical activity varied from walking to running, with running having the most impact on odds of PAD.[36]

Higher levels of arterial stiffness have been linked to PAD.[37] Exercise has previously been well known to decrease arterial stiffness and increase endothelial function through nitric oxide release, but the intensity of the exercise remains controversial. Over the course of a 1-year intervention of implementing a physical activity program into the care of patients with PAD and type 2 diabetes, a graded program of high-intensity interval training (HIIT) was shown to have a positive impact on peripheral arterial stiffness markers.[35] The exercise program consisted of approximately 34-minute sessions of 17 1-minute bouts at 90% of the VO2 max. [35] Stiffness was measured by pulse wave values from the carotid to radial artery and from the carotid to the distal posterior tibial artery, with the carotid to distal posterior tibial artery having a significant reduction of 1.1m/s.[35] These findings suggest that HIIT may be a reliable exercise intervention to reduce the occurrence and severity of PAD in patients with type 2 diabetes.

Methods

The Augsburg Lindell Library search engine, Mendeley, PubMed, Google Scholar, World Health Organization (WHO), Centers for Disease Control and Prevention (CDC), UpToDate, and the American Diabetes Association database were utilized to complete the literature review related to physical activity and the reduction of macrovascular complications in patients with type 2 diabetes. Peer-reviewed articles were used in the search for primary literature sources. Only articles available in English were utilized in this literature review. This review included randomized controlled trials, clinical trials, case reports, systematic reviews, and meta-analyses. Search terms included: type 2 diabetes, diabetes and physical activity, cardiorespiratory fitness and physical activity, blood pressure and physical activity, cardiovascular outcomes in diabetes, hemoglobin A1c and cardiovascular mortality,

macrovascular complications, peripheral artery disease and physical activity, cerebrovascular disease and physical activity, coronary heart disease and physical activity.

Discussion

The prevention and management of type 2 diabetes are grounded within lifestyle interventions, with an emphasis on achieving the recommended physical activity requirements. Realistically, however, the benefits of simplistic lifestyle interventions can be all too often overlooked, by both the patient and the provider, in favor of treatment that is largely is centered around oral medications. Even with this increasing popularity and prevalence of medication management, the worldwide prevalence of type 2 diabetes shows no indication of decreasing, and macrovascular complications continue to be a major contributor to morbidity and mortality. The risk factors for cardiovascular events and mortality in patients with type 2 diabetes are known to be positively altered by physical activity.

While there is conflicting evidence for the best type of physical activity to prevent and reduce macrovascular complications in patients with type 2 diabetes, the current research supports the overall message that "some movement is better than none" and "the more movement the better". Current data and research suggest that aerobic activity, preferably moderate to vigorous, alone or in combination with resistance training, is the most optimal form of physical activity for patients with type 2 diabetes. Moderate to vigorous aerobic activity has been shown to produce the greatest benefits in patients with type 2 diabetes, but it is encouraging that even modest amounts of LTPA can be protective against macrovascular complications through the modification of various cardiovascular risk factors including HbA1c, blood pressure, and cardiorespiratory fitness. Notably, the timing of exercise in patients with type 2 diabetes may

play a compelling role in the regulation of blood glucose and insulin sensitivity, with benefits in glucose control being seen from a modest 15 minutes of postprandial moderate aerobic activity.

While the many health benefits of physical activity are widely known, only about 23% of Americans between 18 and 64 years old are achieving the recommended physical activity requirements.[17] Since physical activity is a socially desirable act, self-reporting of levels tends to contain some bias. This may suggest that the reality of this number is potentially even lower. For a large majority, the recommended 150 minutes/week of moderate to vigorous aerobic activity is simply unobtainable due to a variety of factors, ultimately leading to discouragement and further sedentary behaviors. Perhaps rather than contributing to the possible pressure of the daunting 150 minutes/week, providers should shift focus onto praising and supporting even seemingly marginal levels of physical activity in their patients with type 2 diabetes, regardless of the total minutes per week. This slight shift in the tone of patient-provider interactions may help to positively alter the patients' ideas about physical activity, setting them up for the creation of more realistic goals and increased benefits.

Conclusion

Physical activity can better nearly all modifiable risk factors that contribute to the development of macrovascular complications associated with type 2 diabetes, ultimately reducing morbidity and mortality. In addition to the current guidelines, patients with type 2 diabetes should be recommended to participate in postprandial moderate aerobic activity to optimize blood glucose control. The majority of current research focuses on patients whose disease state is overall stable and well-controlled; unfortunately, this does not fully capture an accurate portrayal of a large portion of patients living with type 2 diabetes. With the understanding that comorbidities and varying levels of disease control can act as a barrier to safe

exercise, more explicit research surrounding these potential obstacles to physical activity should be done to reflect the population of patients living with type 2 diabetes. Additionally, it is known that type 2 diabetes and its associated complications disproportionately affect racial and ethnic minority communities. Yet, this population is not adequately reflected within the research literature surrounding type 2 diabetes and physical activity. Moving forward, studies that specifically address this higher burden of diabetes and the ability of physical activity to potentially aid in the reduction of that burden would be both constructive and valuable in the effort to amend this discrepancy.

To work to prevent unfavorable health outcomes, increased risk of morbidity, and ultimately mortality due to the macrovascular complications of type 2 diabetes, the importance of physical activity and especially the consequences of sedentary behavior, needs to be more heavily considered and discussed in the treatment and management plans in addition to traditional medication management. Not doing so, is a disservice to patients with type 2 diabetes. Although these concepts are rooted within the foundation of diabetes management, the increasing prevalence and pandemic of type 2 diabetes would suggest that this foundation is not strong enough. Empowering a patient with the knowledge and ability to potentially alter their disease progression and outcome through their own actions is one of the most valuable tools a healthcare provider can utilize.

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Appendices

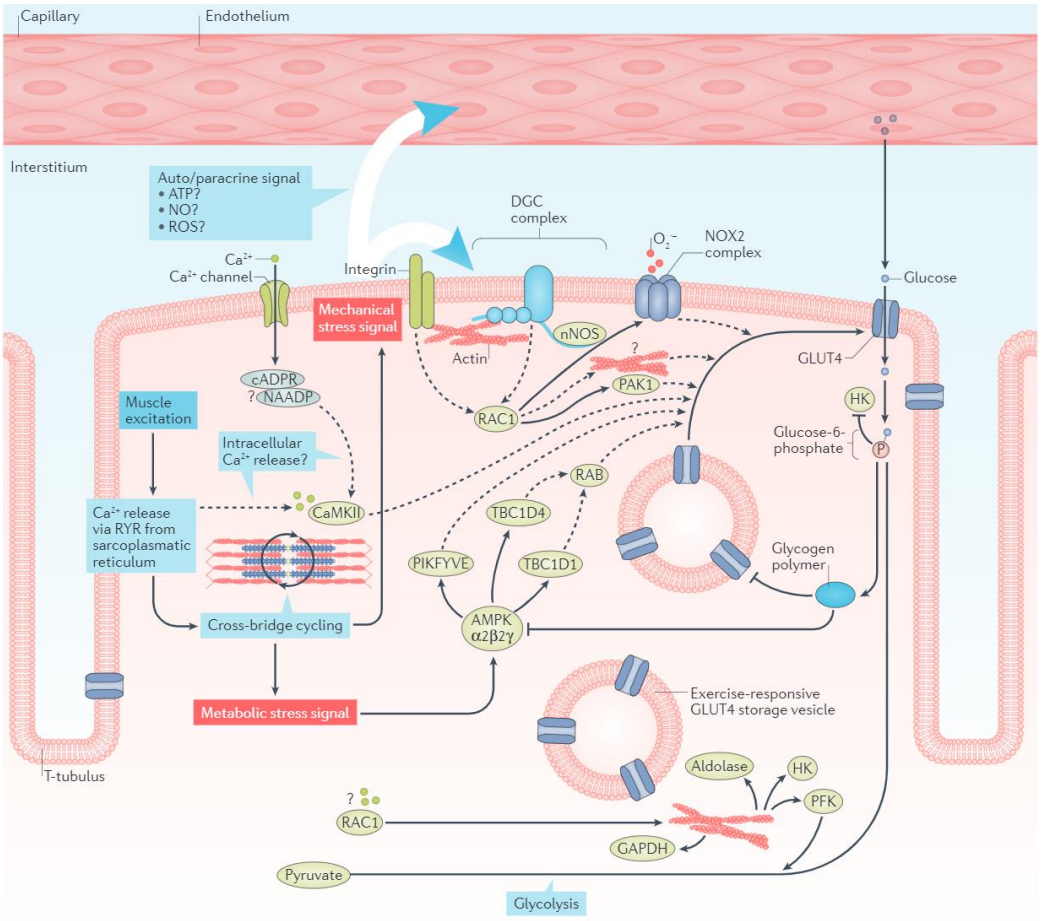

Figure 1: Molecular mechanisms of exercise-regulated glucose uptake by skeletal muscle.

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Work (s) to be deposited

Title: What is the Effect of Physical Activity on the Reduction of Macrovascular Complications in Patients Diagnosed with Type 2 Diabetes Mellitus?

Author(s) of Work(s): Rachael Marie Gordon

Depositor's Name (Please Print): Rachael Marie Gordon

Author's Signature: Rachael M Gordon Date: 08/12/2021

If the Deposit Agreement is executed by the Author's Representative, the Representative shall separately execute the Following representation.

I represent that I am authorized by the Author to execute this Deposit Agreement on the behalf of the Author.

Author's Representative Signature: _____ Date: _____