THE ROLE OF EXERCISE IN DIABETES

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ABSTRACT

Exercise is a key component to lifestyle therapy for prevention and treatment of type 2 diabetes (T2D). These recommendations are based on positive associations between physical activity and T2D prevention, treatment, and disease-associated morbidity and mortality. For type 1 diabetes (T1D), we have evidence to support that exercise can reduce diabetes associated complications. However, there are physiological and behavioral barriers to exercise that people with both T2D and T1D must overcome to achieve these benefits. Physiological barriers include diabetes-mediated impairment in functional exercise capacity, increased rates of perceived exertion with lower workloads, and decision making regarding glycemic management. There are additional social and psychological stressors including depression and reduced self-efficacy. Interestingly, there is variability in the response to exercise by sex, genetics, and environment, further complicating the expectations for individual benefit from physical activity. Defining optimal dose, duration, timing, and type of exercise is still uncertain for individual health benefits of physical activity. In this review, we will discuss the preventative value of exercise for T2D development, the therapeutic impact of exercise on diabetes metabolic and cardiovascular outcomes, the barriers to exercise including hypoglycemia, and the impact of sex and gender on cardiorespiratory fitness and adaptive training response in people with and without diabetes. There are still many unknowns regarding the diabetes-mediated impairment in cardiorespiratory fitness, the variability and individual response to exercise training, and the impact of sex and gender. However, there is no debate that exercise provides a health benefit for people with and at risk for diabetes.

INTRODUCTION

Exercise, together with medical nutrition therapy, forms the cornerstone of diabetes therapy. In their 2022 Standards of Medical Care in Diabetes, The American Diabetes Association (ADA) recommends that adults with diabetes participate in both aerobic activity and resistance training. They specify that this

should entail at least 150 minutes of moderate-to-vigorous aerobic activity per week, spread over at least three days per week to minimize consecutive days without activity, and two to three sessions of resistance exercise per week on nonconsecutive days (1). Regular exercise is associated with prevention and minimization of weight gain, reduction in blood pressure, improvement in insulin sensitivity and glucose control, and optimization of lipoprotein profile, all of which are independent risk factors for the development of T2D (2,3). Meeting physical activity guidelines has been associated with a 40% decrease in cardiovascular mortality with an even greater impact on all-cause mortality (3,4). This association is especially significant given that people with T1D and T2D have a two to six-fold increase in morbidity and premature mortality from clinical cardiovascular disease (CVD) (5).

Despite these positive links, 34.3% of Americans diagnosed with diabetes are categorized as physically inactive (<10 minutes per week of moderate or vigorous physical activity) and 23.8% are meeting the 150-minute segment of physical activity guidelines (6). A worldwide pooled analysis of data from 358 surveys across 168 countries showed that the global age standardized prevalence of insufficient physical activity was 27.5% in 2016. The highest levels of insufficient activity were in women in Latin America and the Caribbean (43.7%), South Asia (43.0%) and high-income Western countries (42.3%) and the lowest levels were in men in Oceania (12.3%) (7). It is important for health care providers to understand that diabetes can lead to significant physiological barriers to exercise. These barriers include impaired maximal and submaximal exercise capacity (8,9), social and psychological barriers to exercise in T2D (10,11), the direct stress on the cardiovascular system caused by exercise, and the risk of hypoglycemia (12). Additionally, exercise studies have shown individual variation in response to physical activity, suggesting that there may be some individuals who are “non-responders” to exercise, in that they do not reap the specific anticipated benefits of exercise therapy such as improved glucose, blood pressure, or lipid profiles. This variation in “response” may be due to the modality employed (aerobic vs resistance exercise), the adaptive response to timing of intervention, and the endpoint examined (13). For example, someone with diabetes may respond with increased fitness but experience no change in glucose. There are also sex differences in cardiorespiratory fitness (CRF), discussed in more detail below (14). These findings speak to the complexity of the pathophysiology involved in exercise and the impact that diabetes has on these processes (Figure 1).

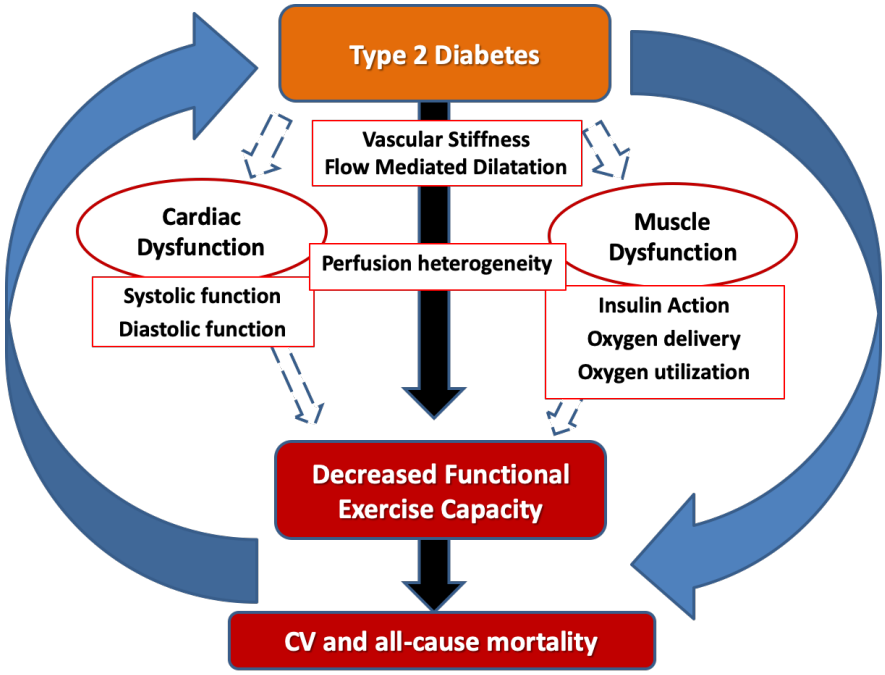

Figure 1. Cardiorespiratory fitness and Premature Mortality. CRF is a systems biology measure of the physiological response to a workload. Exercise requires cardiac, vascular, and skeletal muscle integration. Impairment is this integration is a risk for cardiovascular and all-cause mortality. Evidence supports a model wherein multiple modest functional derangements contribute to impaired CRF in uncomplicated type 2 diabetes.

In this chapter, we will discuss the relationship between exercise physiology and diabetes pathophysiology via an overview of the literature demonstrating the associations between exercise and preventative effects for diabetes, therapeutic value for established diabetes, and prognostic value for development of diabetic complications. We will discuss physiological and behavioral barriers that contribute to lack of achievement of physical activity guidelines including hypoglycemia and the impaired exercise capacity that diabetes itself can cause. We will conclude with a discussion on sex differences in exercise in diabetes.

THE VALUE OF EXERCISE IN DIABETES PREVENTION

Exercise is an established strategy for T2D prevention (3). The incidence of T2D is inversely proportional to participation in physical activity. In a systematic review by Warburton et al that analyzed 20 cohort studies, all were noted to show this inverse relationship with T2D incidence; additionally, when comparing the most active participants to the least active participants, they calculated the average risk reduction of the exercise intervention to be 42%. Within these studies, 84% showed a dose-response relationship to suggest that even small changes in physical activity level led to great reductions in T2D incidence (15). Manson et al demonstrated that women who reported at least weekly vigorous exercise had a 16% reduced risk of developing T2D, when controlled for age and body mass index (16). In Hu et al's analysis of the nurses' Health Study, there was a 34% reduction in diabetes incidence for each hour per day of brisk walking (17). Furthermore, among high-risk women with a history of gestational diabetes, physical activity has been shown to be inversely associated with the incidence of type 2 diabetes in a dose-dependent manner (18).

Physical activity is also a modifiable risk factor that influences CRF; there is a strong association between CRF and incidence of T2D. In the Henry Ford Exercise Testing Project, people who achieved >= 12 metabolic equivalents (METs) had a 54% lower risk of incident diabetes compared to people achieving <6 METs (controlled for age, sex, race, obesity, hypertension, and hyperlipidemia) (19). In a study of middle-aged men by Lynch et al, men with CRF levels greater than 31.0 mL of oxygen per kilogram per minute who exercised at moderate intensity (>5.5 METs) for >40 minutes per week had a decreased incidence of diabetes. This effect was seen even within a subgroup of men at high risk for diabetes (overweight or hypertensive with positive parental history); engagement in this level of moderate intensity exercise in this group reduced their risk of diabetes by 64% compared to men who did not engage in physical activity (20). For reference, 1 MET is equivalent to the amount of oxygen consumed while sitting at rest, which is 3.5 ml/O2/kg/min (21) and expending 2 METs means that an individual is exerting 2 times the energy than they would be while sitting still. Examples of common activities and their associated energy costs in METs are shown in Table 1 (21, 22).

Table 1. Metabolic Equivalents (METs) Expended for Common Activities

Activity	METs
Slow Walking (3 kilometers/hour)	3
Walking up stairs	4.7
Brisk Walking (6 kilometers/hour)	5.4
Bicycling (20 kilometers/hour)	7.1
Running (8 kilometers/hour)	8.2
Hockey	12.9
Boxing	13.4

CRF can be measured in a few different ways. The gold standard includes gas analysis and is reported as maximal oxygen uptake (VO2max) or peak oxygen uptake (VO2peak) (23). This can be impractical in a clinical setting, so several walk tests have been developed to estimate CRF that either measures how much distance a person can cover within the designated time frame or how long it takes them to cover a designated distance. The 6-minute walk test is used in at-risk populations (23) and the 400-meter walk test is often used in older adults (24).

At a practical level, it is useful to ask individuals a few questions about their ability to climb stairs, any changes in their ability to walk a given distance, and if they've experienced any changes in perceived exertion or shortness of breath with activity.

Weight loss is important for prevention of T2D (25). Analysis of people in the intensive lifestyle intervention arm of the Diabetes Prevention Program (DPP) Intensive Lifestyle indicated that there was a 16% reduction in diabetes risk per kilogram of weight loss (26). Theoretically, an increase in physical activity can lead to negative energy balance, which may result in weight loss if diet is unchanged. A study by Ross et al analyzed the effect of exercise-induced weight loss via a 500-700 kcal/day deficit during a 12-week intervention and showed an average weight loss of 7.6kg (8% initial body weight). Their findings also showed that exercise-induced weight loss decreases total fat percentage with increases in cardiovascular fitness to a greater degree than similar diet-induced weight loss (27). This degree of

weight loss is uncommon in exercise interventional studies without simultaneous calorie restriction, so diet and exercise interventions should be administered simultaneously for maximal benefit (25). At the same time, there is a dynamic relationship between exercise dose, weight status, and diabetes incidence, wherein each of these components affects the other (3). To assess the complex association between obesity and physical inactivity for interaction, Quin et al conducted a systematic review that showed positive biological interaction on an additive scale (28). This interaction was further shown in a meta-analysis of 9 prospective cohort studies by Cloostermans et al, where there was a 7.4-fold increased risk of T2D in those who were obese and with a low physical activity level when compared to normal weight, highly active individuals (29).

Exercise aids with diabetes prevention even if weight loss is not achieved. There is a strong association between increased physical activity and prevention of weight gain (3). In DPP, those who achieved 150 minutes of moderate intensity activity per week had a 46% reduction in diabetes incidence, despite not always meeting weight loss goals (21). This effect was similarly seen in other international studies (Sweden (30), Finland (31), China (32), Japan (33), India (34)) when intensive lifestyle intervention was used for prevention of diabetes. The effect of exercise alone was specifically evaluated in the Chinese study where there was a reduction in incidence of diabetes by 33% in the diet-only group, 47% in the exercise-only group, and 38% in the diet-plus-exercise group; this effect was seen even when adjusting for interaction of BMI (31%, 46%, and 42% for diet, exercise, and diet-plus-exercise groups, respectively) (32). Additionally, Dai et al looked further into the efficacy of the type of exercise on prevention of diabetes. They randomized patients with prediabetes into 3 intervention groups of aerobic training (AT), resistance training (RT), and combined training (AT + RT). After 2 years of intervention, the T2D incidence was reduced by 74% in the AT + RT group, 65% in the RT alone group, and 72% in the AT alone group compared to controls. There was no significant difference in 2-hour glucose tolerance tests between intervention groups, providing support for both AT and RT, alone or in combination, benefiting T2D prevention (35).

Physical activity can also lead to improvement in cardiovascular risk factors. With regards to hypertension, there is an inverse relationship between blood pressure and physical activity level, with greater responses noted in those with hypertension/pre-hypertension compared to individuals with normal blood pressure (3). In the DPP, participants who received intensive lifestyle intervention had improved cardiovascular disease risk factor profiles (decreased blood pressure, LDL cholesterol, and triglyceride levels) compared to the metformin treated and placebo groups after 5 years; this improvement was achieved with a decreased need for lipid and blood pressure medication initiation (36). Additionally, while the LOOK AHEAD trial in overweight or obese adults with T2D was negative for its primary cardiovascular outcome (37), further analysis showed that increasing fitness had a beneficial effect on fasting blood glucose, HbA1c, and other cardiovascular risk factors (HDL, triglycerides, and diastolic blood pressure), and cognition beyond the effect of weight change (38).

There is significant variability in changes to CRF with exercise therapy; not all individuals respond positively to exercise intervention. CRF is not always related to physical activity and is determined by genetics and other factors. In the HERITAGE Family Study, maximal oxygen uptake (VO_2max, a measurement of CRF) response to exercise therapy varied significantly with some participants showing no improvement with exercise training and others exhibiting maximal improvement (>1L/min). Interestingly, there was 2.5 times more variance between families than within families, suggestive of a possible genetic component to exercise response (39). These individuals with little to no improvement

with exercise are termed “non-responders.” In cross-over interventional studies that assessed poor responsiveness to aerobic exercise and resistance training, it was found that those who did not benefit from aerobic training, improved their CRF with resistance training. Alternatively, not all individuals who improved CRF with aerobic training had improvements with resistance training. This finding suggests that “non-responsiveness” may be related to exercise modality and that incidence of non-responsiveness to exercise for the endpoint of CRF may be resolved by changing the mode of training (40,41). All in all, to achieve the desired benefits of exercise (improvement in weight, glucose control, endurance, etc.), an individualized approach is key. One gap in practice is a lack of a commonly employed clinical measure of response to an exercise intervention. There is a need for exercise physiology expertise or provider comfort with exercise as a therapeutic tool to tailor and adjust sustained exercise interventions and employ exercise as medicine.

THERAPEUTIC VALUE OF EXERCISE IN DIABETES MANAGEMENT

Diet and exercise (lifestyle modification) are considered by all diabetes clinical guidelines to be the foundation for diabetes management. Exercise can augment glucose disposal and improve insulin action, and thus can be a tool to aid in glucose regulation. Muscle contraction and contraction-mediated skeletal muscle blood flow leads to glucose uptake via insulin-dependent and independent mechanisms. Exercise-mediated glucose disposal can decrease circulating blood glucose but may be affected by other determinants of systemic glucose metabolism. The components of glucose disposal need to be considered to better understand the impact of exercise on glucose clearance. Glucose transporter 4 (GLUT4) translocation is acutely stimulated by muscle contraction, increasing facilitated transport of glucose into the muscle. In addition, contraction augments skeletal muscle blood flow and thereby increases the rate of glucose dispersion into the muscle interstitial space (42). Insulin also recruits GLUT4 to the muscle surface. Muscle glycogen stores and exogenous glucose are consumed during exercise leading to a glucose/glucose-6-phosphate gradient that favors additional glucose entry into the skeletal muscle. Based on these factors and other molecular changes in skeletal muscle signaling, exercise can impact glucose homeostasis for up to 48 hours (43).

Exercise training increases skeletal muscle GLUT4 expression and augments insulin receptor signaling and oxidative capacity which optimizes insulin action and glucose oxidation and storage (44). Therefore, routine moderate exercise usually improves sensitivity to insulin in individuals with T2D (45). This exercise effect is impacted by exercise type (aerobic versus resistance), dose, duration, and intensity of activity. For example, the energy expended per week, is a product of frequency, intensity, and duration of exercise and correlates with changes in insulin sensitivity (46,47). There is also an impact of each bout of exercise. Newsom et al found that low intensity activity (50% VO_{2peak}) improved insulin sensitivity for ~19 hours after exercise in obese adults (48). These findings support the recommendation that people with T2D should engage in daily exercise, with no more than 2 days elapsing between episodes of physical activity; consistency is key and even small amounts of exercise are beneficial (49).

The modality of exercise to induce maximal intended benefit in individuals with T2D is not as clear. Physical activity guidelines for Americans suggest a mixture of resistance and aerobic activity based on limited prospective studies in this population (50,51). Studies vary by intervention structure and duration and in most cases specific exercise interventions have not been compared head-to-head. In one randomized control trial of sedentary individuals with T2D, a combination of aerobic and resistance training for 9 months significantly lowered HbA_{1c} levels

compared to a non-exercise control group (50). Similarly, high intensity interval training (HIIT) session (10 minutes of intense exercise) reduces postprandial hyperglycemia in patients with T2D, suggesting that it can be a time efficient way to achieve benefits of exercise training (52). At the same time, any type of exercise is beneficial. Individuals with T2D who engage in exercise have a decrease in HbA_{1c} by 0.67%, regardless of type of exercise (structured aerobic, resistance, or combined exercise training) (53). Therefore, the best therapy is one that an individual can and will maintain.

In patients with T1D, available evidence is mixed for whether exercise improves overall glycemic control, but it has been shown to have multiple benefits (54). Supervised exercise programs increase fitness in patients with T1D and in one study, VO_{2max} increased by 27% after 4 months of participation in a bicycle exercise training program (55,56). Insulin requirements have also been shown to be reduced with exercise training in patients with T1D, with anywhere from a 6% to 18% daily insulin dose reduction across multiple studies (56–58). In the Pittsburgh Insulin-dependent Diabetes Mellitus Morbidity and Mortality Study, activity level was inversely related to mortality risk and men who were sedentary were 3 times more likely to die than active males. A similar but nonsignificant trend was seen in women (59).

Regular exercise provides a physiological stress to the body and can generate adaptations such as induction of antioxidant defense mechanisms. Low exposure to a toxic or stress environment leads to positive biological responses, hormesis, whereas high exposure leads to negative responses (U-shaped dose response effect). Exercise induces low amounts of reactive oxygen species (ROS) acutely, which positively stimulates oxidative damage-repairing enzyme activity and results in improved biological fitness (60). For example, in the context of exercise, ROS formation can stimulate nuclear factor erythroid 2-related factor 2 (Nrf2), a transcription factor that is dormant in the cytoplasm. Low levels of oxidative stress stimulate Nrf2 translocation to the nucleus to stimulate expression of antioxidant enzymes; when Nrf2 activity is diminished, as in endothelial dysfunction, insulin resistance and abnormal angiogenesis is seen, such as in individuals with T2D (61). This is one example of the molecular response to exercise. Many such examples exist and demonstrate similarly positive profiles: reduction in inflammatory markers (c-reactive protein, interleukin-6, and tumor necrosis factor-α) and upregulation of anti-inflammatory substances (interleukin-4 and interleukin 10) (62). Ristow et al showed that exercise mediated ROS are integral to the process by which exercise improves insulin sensitivity (as measured by glucose infusion rates during a hyperinsulinemic, euglycemic clamp and plasma adiponectin) (63). In their study, exercised muscles of previously untrained individuals showed a two-fold increase in oxidative stress (as measured by thiobarbituric acid-reactive substances [TBARS]). However, daily intake of antioxidant dietary supplementation (vitamin C and E) blunted this affect by blocking this initial step of transient increase of oxidative stress. Exercise mediated ROS induced expression of molecular regulators (*PPARγ* and its coactivators *PGC1α* and *PGC1β,*) that coordinate insulin-sensitizing gene expression. Those treated with vitamin C and E had decreased expression of these molecular regulators. Consequently, non-supplemented individuals without diabetes had significant improvement in insulin sensitivity while those on antioxidant supplements had no change in insulin sensitivity. The NIH Molecular Transducers of Exercise (MoTrPAC) program will examine the molecular response to exercise in healthy people and rodent models to set the stage for more detailed assessments of these endpoints in disease states such as diabetes (64).

While lifestyle intervention through diet and exercise are the initial step in T2D treatment, pharmacologic therapy may also be needed to achieve glycemic targets for a person with T2D. Regardless, at each

step of intensification of medical therapy for glucose or blood pressure lowering, exercise should be reinforced as an important part of treatment. Combination therapy with metformin monotherapy plus post-meal exercise, led to a 21% reduction in postprandial hyperglycemia, a comparable effect to that of sulfonylureas (-14%), thiazolidinediones (-20%), and dipeptidyl peptidase-4inhibitors (-23%) (65). At the same time, there is some evidence to suggest that metformin may attenuate the positive effects of exercise on insulin sensitivity and inflammation (66,67). Of note, these studies were performed in people with insulin resistance or increased risk of T2D and not in people with diabetes. Incorporation of exercise and diet into all diabetes management strategies is crucial for cardiometabolic health.

IMPACT OF EXERCISE ON DIABETES OUTCOMES

Beyond the therapeutic and preventative benefits of exercise discussed in previous sections, exercise also holds great prognostic value for people with diabetes. Observational studies have shown an inverse linear dose-response relationship between physical activity amount and mortality (68). Exercise capacity has been shown to be predictive of mortality in people with diabetes (69), echoing findings in the general population (70). Furthermore, decreased exercise capacity in people with T2D is associated with development of future cardiovascular events (71).

Additionally, associations between higher levels of physical activity and reduced complications in diabetes have been noted. Gulsin et al were able to show that exercise improved diastolic function in adults with T2D whereas weight loss via a low-energy diet alone did not improve diastolic function despite the diet leading to weight loss, improved glycemic control, and improved aortic stiffness and concentric LV remodeling (72). A meta-analysis on 18 studies of patients T1D and T2D showed that physical activity also increased glomerular filtration rate and decreased the urinary albumin creatinine ratio (73). In the Finish Diabetic Nephropathy (FinnDiane) Study, low levels of self-reported leisure-time physical activity in people with T1D was associated with a greater degree of renal dysfunction, proteinuria, CVD, and retinopathy (74) and Kriska et al found that men with insulin-dependent diabetes who reported higher levels of physical activity in their past had lower prevalence of nephropathy and neuropathy (75). Bohn et al also found an inverse relationship between physical activity level and both retinopathy and microalbuminuria in people with T1D in the Diabetes-Patienten-Verlaufsdokumentation (DPV) database (76). Interestingly, a large cohort study of adults with T1D and T2D in Australia found that physical activity was protective against developing advanced diabetic retinopathy requiring retinal photocoagulation (however this finding was only significant for men) (77).

EXERCISE INTOLERANCE AS A BARRIER TO EXERCISE ADHERENCE IN DIABETES

Exercise holds great promise as a preventative and therapeutic intervention for people with diabetes. Yet, diabetes presents significant physiological, psychological, and socioeconomic barriers to physical activity. Despite these barriers, exercise remains a cornerstone of treatment for diabetes, and as such, it is useful to understand the barriers to exercise in diabetes and consider strategies for overcoming them (Table 2).

Table 2. Barriers to Exercise in Diabetes	
Physical	Overall discomfort

		↓ fitness ↑ weight
Pathophysiological		↓ cardiorespiratory fitness ↑ pulmonary capillary wedge pressure Mismatch between skeletal muscle oxygen extraction and oxidative flux Vascular endothelium degradation Impaired in vivo mitochondrial capacity Hypoglycemia
Diabetes Complication-Related	**Cardiovascular**	↑ stress→ CV event
	Nephropathy	Anemia→ ↓ oxygen perfusion
	Neuropathy	Pain Loss of Balance
	Retinopathy	Loss of vision
	Foot Disease	Need for special footwear ↑ frequency of self-foot exam
Social/Psychological		Depression Diabetes Distress ↓ socioeconomic status Community culture

People with T2D are disproportionately sedentary and overweight (78) and report more physical discomfort during exercise (10). Excess weight itself can be a physical barrier to increased activity; in a study of obese subjects with diabetes, those who reported physical discomfort as a barrier to exercise had a significantly higher body mass index compared to those individuals who did not report it (36 vs 34, respectively, p=0.021) (79). A decreased level of fitness also contributes to this barrier of discomfort with physical activity. Functional exercise capacity (FEC), measured by VO_{2max}, is impaired in both youth and adults with uncomplicated T1D and T2D (8,69). Insulin sensitivity has a direct association with VO_{2peak} (80,81). Studies by Reusch, Regensteiner, and colleagues have demonstrated that adolescents and adults with uncomplicated T2D have reduced CRF compared to those without T2D. These findings persist in the absence of clinical cardiovascular disease and when matched by baseline exercise status and weight (82-84).

CRF is an outcome determined by various measures of cardiac and skeletal muscle function. Reductions in CRF are associated with reduced cardiac performance (85,86). Women recently diagnosed with T2D have been shown to have significantly increased pulmonary capillary wedge pressure and abnormal diastolic parameters during exercise compared to healthy control subjects, a finding concerning for subclinical diastolic dysfunction (14,87). Additionally, adolescents with T2D have been shown to have abnormal cardiac circumferential strain (CS), increased indexed LV mass, and decreased CRF compared to obese and lean healthy controls. In this study of youth with T2D, fat mass and low adiponectin correlated with CS and CRF. These associations suggest a role for obesity in cardiac impairment and CRF in T2D (88). In skeletal muscle, Reusch, Regensteiner and colleagues have reported a mismatch between skeletal muscle oxygen extraction, oxidative flux, and VO_{2peak} in individuals with T2D (89,90). Additionally, studies have shown evidence of degradation of the vascular endothelial glycocalyx in individuals with T2D (91). These changes at the muscular level are thought to cause impaired microvascular perfusion, which likely ultimately contributes to decreased CRF in these individuals (92,93). Consistent with a relationship between microvascular dysfunction and fitness, people with diabetes who have developed microvascular complications (retinopathy, neuropathy, nephropathy with microalbuminuria) have decreased CRF compared to those without these complications (94). Fortunately, certain types of exercise can resolve the T2D associated impairment of skeletal muscle *in vivo* mitochondrial oxidative flux. Scalzo et al showed that single-leg exercise training for 2 weeks increased *in vivo* oxidative flux in participants with T2D but not in matched controls without T2D (95).

In addition to these cardiovascular contributions to impaired exercise function in diabetes, mitochondrial capacity is impaired (96), and mitochondrial content is reduced (97). Observations of an association between insulin sensitivity and exercise capacity (81) may also reflect additional metabolic determinants of exercise impairment beyond impaired muscle perfusion and reduced mitochondrial function. As a proof of concept, the PPARγ insulin sensitizer rosiglitazone has been shown to improve exercise capacity and insulin sensitivity in T2D in a three-month intervention (despite weight gain) (98,99). Improved CRF correlated with an improvement in endothelial function and blood flow (98). In contrast, in men with established coronary artery disease and T2D, a year-long-treatment with rosiglitazone lead to a decrease in CRF related to increased weight and subcutaneous fat mass expansion. Our current interpretation is that insulin action is a modifiable target for augmenting CRF but that currently available insulin sensitizers are not a durable intervention (100).

Exercise can be a cardiovascular stressor, and while chronic exercise is associated with a reduction in cardiovascular risk (101), acute exercise may precipitate events in susceptible individuals (102). Thus, in people at high risk for acute cardiovascular events, some caution is warranted in initiating a new exercise regimen. Low intensity exercise with high consistency may be a safer and more effective strategy than more sporadic, high intensity exercise. A cardiac rehabilitation approach is a great consideration, but not often covered by insurance. Discussion with a provider for people with diabetes prior to initiating an exercise program is recommended by the American College of Sports Medicine, especially if they are currently sedentary or have chronic complications from their diabetes (103). This recommendation is echoed but less formal in the ADA guidelines. In the opinion of these authors, people with diabetes should be encouraged to exercise and to build up to an exercise program. Providers should discuss anginal equivalents, and significant changes in exercise tolerance (for example, change in the distance a person can walk, or fewer flights of stairs) or shortness of breath with exercise as an indication for concern. Since exercise

should be a vital sign, these discussions should happen with each clinical encounter.

Additionally, presence of diabetes complications can be a barrier to exercise (74). There is a high association between diabetes complications and depression (104), which can reduce the desire to perform any activity. Decreased kidney function, such as that seen in diabetic nephropathy, is associated with a higher prevalence of anemia (105) which can make it difficult to exercise due to decreased oxygen delivery. Additionally, diabetic retinopathy with decreased vision, diabetic neuropathy with loss of balance, and diabetic foot ulcers can all pose physical limitations to exercise (106). Weight bearing exercise can increase foot trauma. Therefore, it is important for people with T2D to conduct frequent foot examinations when participating in physical activity. Contact footwear use can reduce rate of foot-related injury (107,108). However, these special considerations can lead to decreased incentive and increased distress when engaging in physical activity.

As may be expected, motivating people with diabetes to exercise regularly is often a considerable challenge in both T1D and T2D. Engaging people with diabetes to exercise generally requires changing ingrained lifestyle habits. Habitual and social barriers to exercise also add to the motivational difficulties of lifestyle-based interventions. Finally, barriers to exercise in T2D may be confounded by socioeconomic class. People with T2D tend to have lower socioeconomic status (109), which is itself associated with less physical activity (110). There is also increased concern for safety in low socioeconomic neighborhoods. Overcoming this array of physiological, psychological, and socioeconomic barriers to regular exercise in people with diabetes requires a nuanced, patient-specific approach. Strategies for motivating patients to engage in regular physical exercise include motivational interviewing (111), community-based interventions (112), group exercise, and surveillance using activity-tracking devices such as pedometers (113). Each of these strategies has been shown to achieve at least modest success, but the increasing prevalence and costs of T2D (114,115) indicate that more work is needed.

EXERCISE INDUCED HYPOGLYCEMIA

Exercise can be acutely dangerous for people with diabetes who are on certain glucose lowering medications, such as insulin and sulfonylureas medications, as exercise can increase the risk of hypoglycemia in these patients. Hypoglycemia and fear of hypoglycemia with exercise represent real and major considerations for people with diabetes. These considerations are especially relevant to people with T1D, as episodes of severe (and particularly nocturnal) hypoglycemia are associated with large increases in mortality (116), and exercise can precipitate nocturnal hypoglycemia and impaired counterregulatory responses in people with T1D (117,118). This is also a risk, albeit to a lesser extent, for people with T2D on insulin or sulfonylureas (119). Exercise increases both the translocation and expression of GLUT4 (120), thus potentiating the effects of insulin, and greatly increases the metabolic demand for glucose (121). These factors predispose towards hypoglycemia. Exercise can impact glucose homeostasis for up to 48 hours (43). Fear of hypoglycemia is the primary barrier to exercise in people with T1D (12).

Different exercise modalities can cause varied effects on blood glucose in the acute setting. We will discuss simplified differences during a bout of moderate vs vigorous physical activity in the setting of a healthy individual (Figure 2) to contextualize the discussion that follows. The uptake of blood glucose by skeletal muscle increases with increasing intensity and duration of physical activity. With moderate activity, the fall in plasma glucose from muscle glucose uptake is coordinated with a fall in plasma insulin and increase in counterregulatory hormones, particularly glucagon, that help mobilize glucose (122). With vigorous activity, the distinction is that there is an

exercise stimulated surge of counterregulatory hormones, independent of plasma glucose level, and this can stimulate an acute increase in plasma glucose (123). People with diabetes who are treated with insulin lose the ability to physiologically decrease circulating insulin with exercise and can have an impaired ability to augment secretion of glucagon, cortisol, growth hormone and catecholamines with exercise; factors that particularly predispose them to hypoglycemia. Post bout, muscle glycogen depletion from physical activity will lead to increased skeletal muscle glucose uptake for glycogen repletion and this increased insulin-independent glucose clearance contributes to a decrease in plasma glucose (124) (Figure 3).

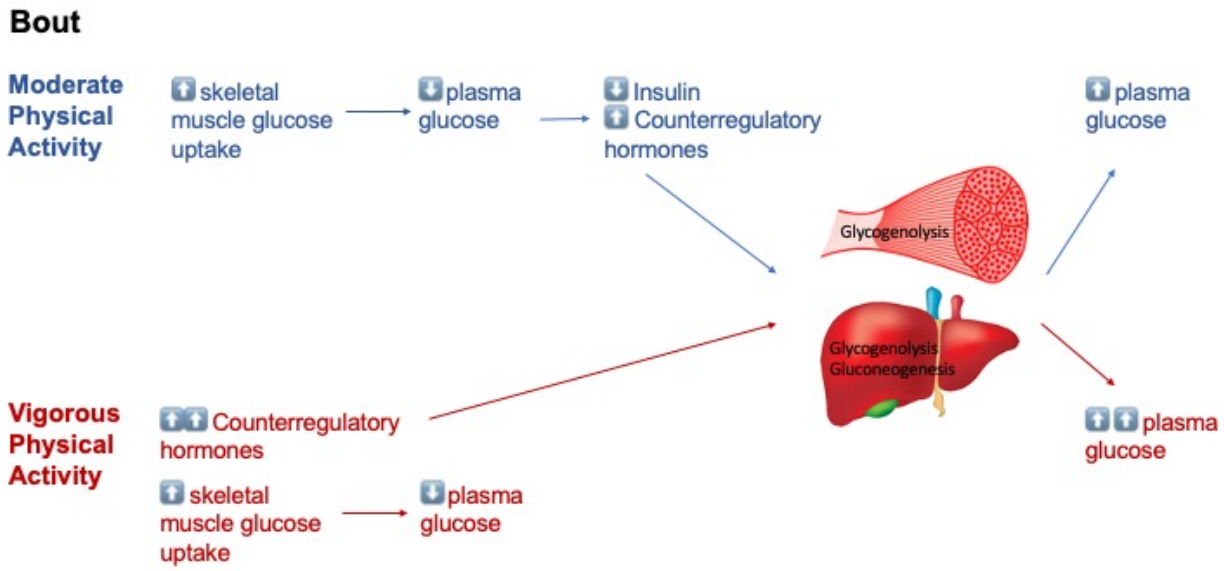

Figure 2. Glucose homeostasis during a bout of moderate vs. vigorous physical activity.

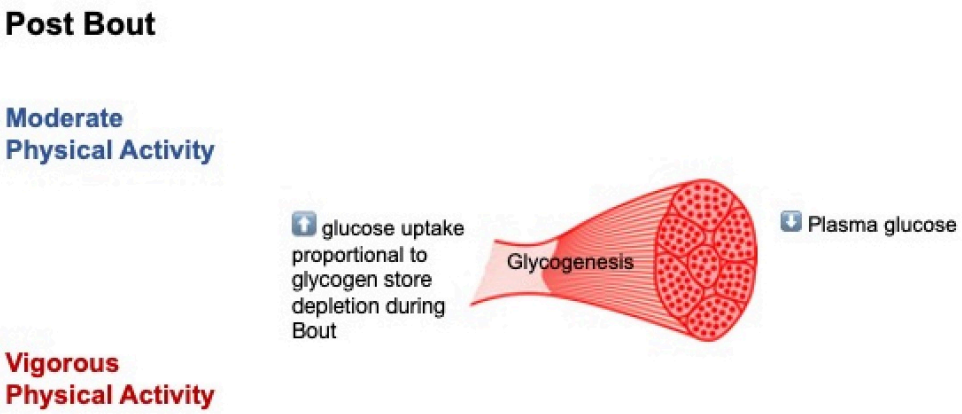

Figure 3. Glucose homeostasis following a bout of physical activity.

In the literature, aerobic and resistance exercise are often compared as activities that have differing effects on hypoglycemia. The aerobic exercise regimens specified in the studies presented here are of moderate intensity and can be conceptualized as a moderate bout of physical activity and the resistance exercise regimens can be conceptualized as a vigorous bout. Yardley et al showed that resistance exercise tends to cause an acute increase in blood glucose superimposed with a subsequent increase in insulin sensitivity, whereas aerobic exercise causes a larger initial decrease in blood glucose but somewhat less sustained hypoglycemic effect. However, resistance exercise was associated with overall less blood glucose variability post-exercise (125). Additionally, a HIIT session is less likely to cause hypoglycemia compared to moderate-intensity aerobic exercise (126). There is also evidence that performing resistance exercise prior to aerobic exercise can also lead to decreased glucose variability during exercise and attenuate post-exercise hypoglycemia (127). The optimal duration, intensity, and order of specific types of physical activities to prevent hypoglycemia in patients with T1D is the subject of continued research. Steineck et al found that the time patients with T1D spent in hypoglycemia over a 5-day period was similar if they exercised 5 consecutive days, consisting of 4 minutes of resistance training followed by 30 minutes of aerobic training per session, or if they exercised 2 days in this 5-day period and performed 10 minutes of resistance training followed by 75 minutes of aerobic exercise each session (128). Much like all aspects of diabetes management, the way an individual responds to exercise can be anticipated based on the literature, however, each individual will need to measure their blood glucose pre- and post-exercise for 4-24 hours post bout to understand their needs. Other factors such as sleep, stress, general physical fitness, and prior exercise training can all impact the glucose response to an exercise bout.

Beyond the features of a session of exercise, the cornerstone of mitigating the risk of exercise induced hypoglycemia in patients who are on multiple daily injections of insulin or insulin pumps *without hybrid closed loop features*, includes insulin dose reduction and consumption of carbohydrates. Consensus recommendations consist of complex and personalized algorithms, but some generalizations are to reduce pre-exercise meal bolus within 90 minutes before aerobic exercise by 30-50% and to consume 30-60gm of high glycemic index carbohydrates per hour of sport. Post-exercise recommendations are especially important for afternoon and evening exercise as nocturnal hypoglycemia occurs commonly in individuals with T1D and this risk is increased with exercise that is done later in the day. Some recommendations are to decrease the bolus for the meal after exercise by 50% and reduce basal rate by 20% for 6 hours at bedtime if exercise occurred in the afternoon (129).

Hybrid closed loop (HCL) systems are becoming more widely available and used in practice. They require clinicians to modify recommendations for exercise to account for the principles that affect a specific system's automated insulin delivery algorithms. One clear advantage of HCL systems in this context is that they have a predictive low glucose suspend feature that suspends insulin delivery when a low glucose is predicted in the next 30 minutes (130). An adage that does need to be re-examined for HCL is one described in the previous paragraph wherein patients may eat uncovered carbohydrate snacks or partially covered meals prior to exercise. In

HCL systems, the rise in glucose from eating uncovered carbohydrates prior to exercise can lead to an increase in automated insulin delivery (130) and in our clinical experience, extra insulin on board can then sometimes precipitate hypoglycemia with exercise. More research is needed in this arena. One main strategy that is agreed upon to use for hypoglycemia prevention with HCL is to increase the target glucose for a session of exercise. Some systems call this a “temporary target” while in others, an increased target is embedded into their “exercise mode”. Based upon personalized factors, the increased target should be set anywhere from 30 minutes to 2 hours prior to initiating physical activity and it should remain on for the duration of the activity and in some situations, up to a few hours afterwards (130). In a study of patients with T1D placed on HCL, their target was increased from 2 hours prior to exercise initiation to 15 minutes after. They engaged in either HIIT or moderate intensity exercise in a cross-over study design and only 1 of 12 participants experienced hypoglycemia and it was during their session of moderate intensity exercise. Time spent in hypoglycemia for 24 hours afterwards measured by continuous glucose monitors was minimal in both groups (0 and 0.4% respectively for HIIT and moderate intensity) (131). Tagougui et al studied adults with T1D using a HCL system during 60 minutes of 60% VO2 peak exercise who were randomized to either 1) increase target glucose level and reduce their meal bolus by 33% 90 minutes before exercise 2) increase target glucose but take a full meal bolus 90 minutes before exercise or 3) not change target glucose and take a full meal bolus. The increased target was maintained until 1 hour after exercise. During exercise and the 1-hour recovery period, time spent in hypoglycemia was significantly reduced in both groups 1 and 2 compared to 3 and there was a trend towards less time in hypoglycemia in group 1 vs group 2 ($p=0.06$) but at the expense of 24.6% more time in hyperglycemia (132).

SEX DIFFERENCES WITHIN DIABETES AND EXERCISE

According to the IDF Diabetes Atlas, the prevalence of diabetes in adult women in 2021 was 10.2%, compared to 10.8% of men worldwide (133). When adjusted for associated risk factors, women with diabetes have a higher incidence of CVD death and congestive heart failure compared to men (134). Excess CVD in women with T2D correlates with increased adiposity and CVD risk factor burden present in T2D women (135,136).

Additionally, based on National Health and Nutrition Examination Surveys between 2007 and 2016, girls and women with T2D have lower physical activity levels than men across all age groups and settings (137). This observation may be due to barriers to exercise, as mentioned above. Of importance, there are sex differences in barriers to exercise as well (138). Women are more likely than men to consider activities of daily living as exercise when referring to physical activity behavior. They are also more likely to report decreased knowledge or skills associated with physical activity (139). Additional barriers for exercise specific to women include decreased perceived neighborhood safety and decreased perceived easy access to locations for physical activity (140). Women also had less self-efficacy, i.e. successful execution of a physical activity behavioral change, than men for participating in physical activity when other common barriers emerged (e.g. time constraints, bad weather) (139). In a meta-analysis of T2D across the lifespan it was shown that across all ages, males participated in more moderate and vigorous activity than females and in adulthood and late adulthood, men were more likely to achieve physical activity recommendations than women (141).

Furthermore, women with T2D have a more pronounced exercise impairment in cardiorespiratory fitness then men with T2D (84,87). Interestingly, while obese women with T2D have reduced VO_2

kinetics when compared with controls, there is no difference in impairments based on menopausal status (142). The mechanism behind these differences and how it relates to insulin-mediated cardiac and skeletal muscle perfusion impairments is currently being studied.

CONCLUSIONS AND FUTURE DIRECTIONS

Exercise is an important therapy in prevention and treatment of diabetes. At the same time, this is easier said than done, especially given the barriers to exercise that individuals with diabetes must overcome. These barriers are further complicated by sex differences, with sex also affecting prognosis with a diabetes diagnosis. The etiology of diabetes-related decreases in cardiorespiratory fitness is not yet fully understood; further research is being undertaken in this area to address potential therapeutic targets. Given the discussed correlation between CRF and morbidity and mortality, such an approach could aid in reduction of disability and mortality associated with diabetes. Additionally, a better strategy is needed to measure response to exercise therapy to aid in modification of a regimen to ensure continuous benefit. Given the high heterogeneity in response to exercise, other genetic and environmental components may be responsible. Further research on genetic contributions to exercise response is needed. Ultimately, future therapy will need to be more personalized such that every individual with diabetes receives a specific prescription for exercise based on factors such as sex, diabetes type and duration, comorbidities, genetic background and exercise phenotype, and environment.

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