**THE ROLE OF EXERCISE IN DIABETES**

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**ABSTRACT**

Exercise is a key component of lifestyle therapy for prevention and treatment of diabetes. These recommendations are based on positive associations between physical activity and diabetes prevention, treatment, and disease-associated morbidity and mortality. However, there are physiological and behavioral barriers to exercise that people with diabetes must overcome to achieve these benefits. Physiological barriers include decision-making regarding glycemic management, diabetes-mediated impairment in functional exercise capacity, and increased rates of perceived exertion with lower workloads. There are additional social and psychological stressors, including depression and poor self-efficacy. Interestingly, there is variability in the adaptive response to exercise by sex, genetics, and environment, further complicating the expectations for individual benefit from physical activity. Defining optimal dose, duration, and timing is still uncertain for individual health benefits of physical activity. In this review, we will discuss the preventative value of exercise for diabetes, the therapeutic impact of exercise on diabetes metabolic outcomes and cardiovascular outcomes, the barriers to exercise, 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.

**INTRODUCTION**

Exercise, together with medical nutrition therapy, forms the cornerstone of diabetes therapy. In their 2019 Standards of Medical Care in Diabetes, the American Diabetes Association (ADA) recommends that adults with diabetes should participate in at least 150 minutes of moderate-to-vigorous aerobic activity per week and two to three sessions of resistance training per week (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 development of type 2 diabetes (T2D) (2,3). Meeting physical activity guidelines is also 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 diabetes have a two to six-fold increase in morbidity and premature mortality from clinical cardiovascular disease (CVD) (5).

Despite these positive links, 40.8% of people with T2D are categorized as physically inactive (<10 minutes per week of moderate or vigorous activity within work, transportation, or leisure time) (6). It is important for the health care provider to understand that diabetes can lead to significant physiological barriers to exercise. These barriers include impaired maximal and submaximal exercise capacity (7,8), social and psychological barriers to exercise in T2D (9,10), the direct stress on the cardiovascular system caused by exercise, and the risk of hypoglycemia (11). 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 (12). There is also intersex variability within diabetes in cardiorespiratory fitness (CRF), discussed in more detail below (13). These findings speak to the complexity of the pathophysiology involved in exercise and the impact that diabetes has on these processes (Figure 1).



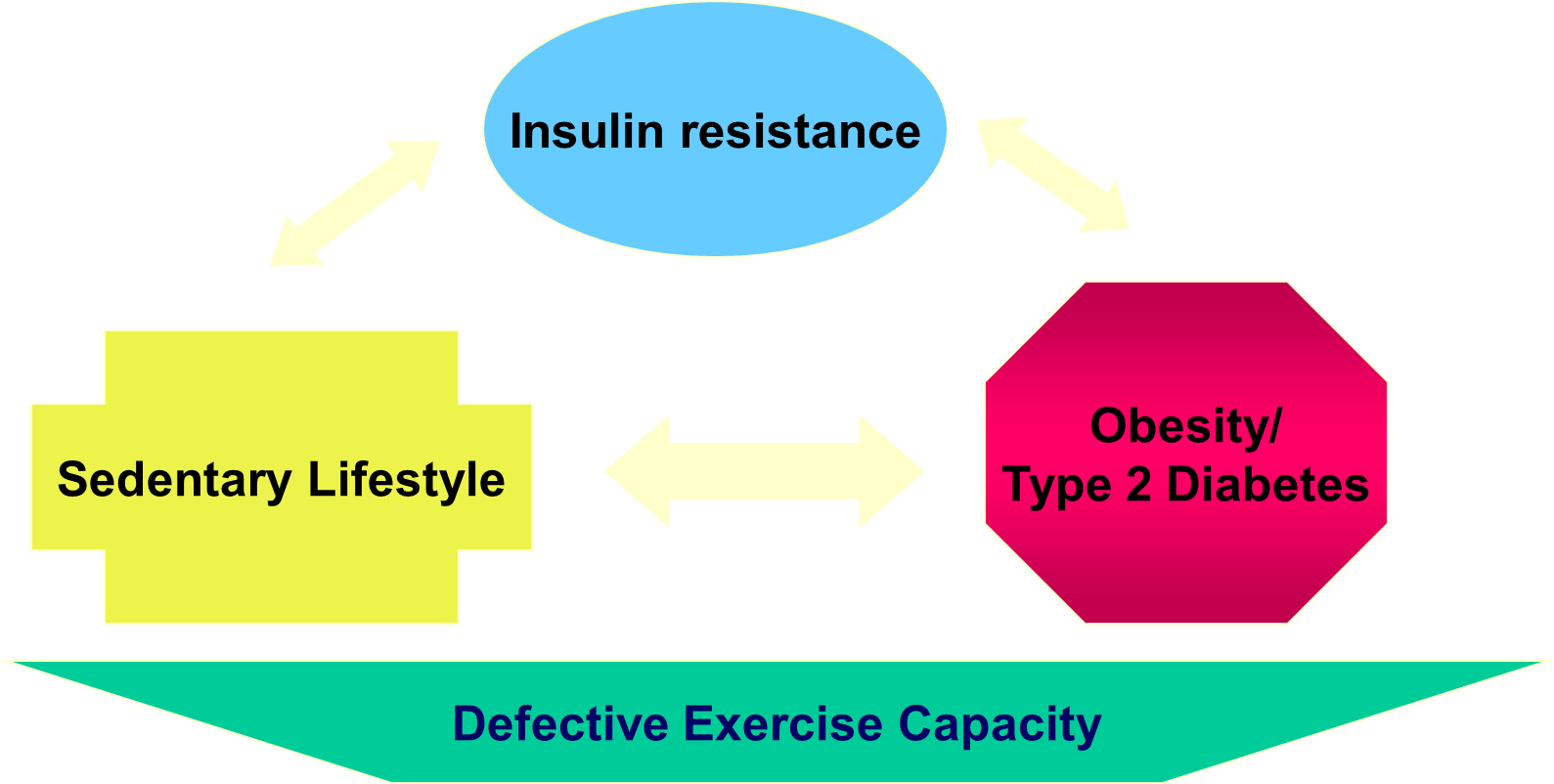
**Figure 1. Functional Exercise Capacity and Premature Mortality.** **FEC is a systems biology measure of the physiological response to a workload. Exercise requires a cardiac, vascular and skeletal muscle integration. Impairment is this integration is a risk for cardiovascular and all-cause mortality.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

In this chapter, we will discuss the relationships 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. For the remainder of this article, we will use functional exercise capacity (FEC) and CRF interchangeably as FEC is more aligned with the clinician/patient interface. We will discuss physiological and behavioral barriers that contribute to lack of achievement of physical activity guidelines; one significant barrier is that diabetes per se leads to impaired exercise capacity. We will conclude with a discussion on sex differences in exercise in diabetes.

**Preventative Value of Exercise in Diabetes Treatment**

Exercise is an established strategy for diabetes 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 an average risk reduction of exercise intervention to be 42%. Within these studies, 84% showed a dose-response relationship to suggest that even small changes in physical activity level leads to great reductions in T2D incidence (14). In a study by Manson et al, women who reported at least weekly vigorous exercise had a 16% reduced risk of developing T2D, when controlled for age and body mass index (15). 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 (16).

Physical activity is also a modifiable risk factor that influences FEC; there is a strong association between FEC 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) (17). 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 (18) (Figure 2).



**Figure 2: Vicious Cycle.** **Interaction between insulin resistance, sedentary lifestyle, and obesity/type 2 diabetes leading to decreased FEC.**

Weight loss is important for prevention of T2D (19). 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 (20). 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 7.6 kg (8% of 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 (21). 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 (19). 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 (22). 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 (23).

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 met the physical activity goal (150 min of moderate intensity activity per week) had a 46% reduction in diabetes incidence, despite not always meeting weight loss goals (20). This effect was similarly seen in other international studies (Sweden (24), Finland (25), China (26), Japan (27), India (28)) when intensive lifestyle intervention was used for prevention of diabetes. The effect of exercise alone was specifically evaluated in the Chinese study (Da Qing IGT and Diabetes 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) (26).

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, patients 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 (29). Additionally, while the LOOK AHEAD trial in overweight or obese adults with T2D was negative for its primary cardiovascular outcome (30), further analysis showed that increasing fitness had a beneficial effect on fasting blood glucose, HgbA1c, and other cardiovascular risk factors (HDL, triglycerides and diastolic blood pressure), beyond the effect of weight change (31).

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 (VO2max, 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 (32). 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 may be decreased by changing the mode of training (33,34). 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 lack of a commonly employed clinical measure of response to an exercise intervention and the need for exercise physiology expertise in tailoring and adjusting sustained exercise interventions.

**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 (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 (35). 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 (36).

Exercise training increases skeletal muscle GLUT4 expression and augments insulin receptor signaling and oxidative capacity which optimizes insulin action and glucose oxidation and storage (37). Therefore, routine moderate exercise usually improves sensitivity to insulin in individuals with T2D (38). 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 (39,40). There is also an impact of each bout of exercise. Newsom et al found that low intensity activity (50% VO2peak) improved insulin sensitivity for ~19 hours after exercise in obese adults (41). 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 (42).

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 (43,44). 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 HgbA1c levels compared to a non-exercise control group (43). 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 (45). At the same time, any type of exercise is beneficial. Individuals with T2D who engage in exercise have a decrease in HgbA1c by 0.67%, regardless of type of exercise (structured aerobic, resistance, or combined exercise training) (46). Therefore, the best therapy is one that an individual can maintain.

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 (47). 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 stimulates 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 (48). 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) (49). 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). 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 (50).

While lifestyle intervention though diet and exercise is the initial step in T2D treatment, pharmacologic therapy may be ultimately needed to achieve glycemic targets for a person with T2D. However, at each step of intensification of medical therapy, 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%) (51). At the same time, there is some evidence to suggest that metformin may attenuate the positive effects of exercise on insulin sensitivity and inflammation (52,53); however, these studies were performed in people with insulin resistance or increased risk of T2D and not in people with diabetes. As stated above, exercise and diet need to be incorporated into all diabetes management strategies for glycemia and overall cardiovascular 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 (54). Exercise capacity has been shown to be predictive of mortality in people with diabetes (55), echoing findings in the general population (56). Furthermore, decreased exercise capacity in people with T2D is associated with development of future cardiovascular events (57).

Additionally, associations between higher levels of physical activity and reduced complications in diabetes have been noted. Men with insulin-dependent diabetes who reported higher levels of physical activity in their past had lower prevalence of nephropathy and neuropathy (58). In the Finish Diabetic Nephropathy (FinnDiane) Study, low intensity of self-reported leisure-time physical activity in people with type 1 diabetes (T1D) was associated with a greater degree of renal dysfunction, proteinuria, CVD, and retinopathy (59). 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 (60).

**Exercise intolerance as a barrier to exercise adherence in DIABETES**

Exercise holds great promise as a preventative and therapeutic intervention for people with diabetes. However, 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 1).

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| **Table 1. Barriers to Exercise in Diabetes** | | |
| **Physical** | | * Overall discomfort * 🡫 fitness * 🡡 weight |
| **Pathophysiological** | | * 🡫 CRF/FEC * 🡡 pulmonary capillary wedge pressure * Mismatch between skeletal muscle oxygen extraction and oxidative flux * Vascular endothelium degradation * Impaired maximal mitochondrial capacity🡪 🡫 mitochondrial function * 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 (61) and report more physical discomfort during exercise (9). 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) (62). A decreased level of fitness also contributes to this barrier of discomfort with physical activity. Functional exercise capacity (FEC), as measured by VO2max, is impaired in both youth and adults with uncomplicated T1D and T2D (8,63). Insulin sensitivity has a direct association with VO2peak (63,64). Studies by Reusch, Regensteiner, and colleagues at the University of Colorado Anschutz Medical Campus have demonstrated that adolescents and adults with uncomplicated T2D have reduced CRF and FEC compared to those without T2D. These findings persist in the absence of clinical cardiovascular disease and when matched by baseline exercise status and weight (65-67).

FEC is an outcome determined by various measures of cardiac and skeletal muscle function. These reductions in CRF/FEC have been shown to be associated with reduced cardiac performance (68,69). 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 (13,70). Additionally, adolescents with T2D have been shown to have abnormal cardiac circumferential strain (CS), increased indexed LV mass, and decreased FEC compared to obese and lean healthy controls. In this study, fat mass and low adiponectin correlated with CS and FEC. These associations suggest a role for obesity in cardiac impairment and FEC in T2D (71). In skeletal muscle, Reusch, Regensteiner and colleagues have reported a mismatch between skeletal muscle oxygen extraction, oxidative flux, and VO2 peak in individuals with T2D (72,73). Additionally, studies have shown evidence of degradation of the vascular endothelial glycocalyx in individuals with T2D (74). These changes at the muscular level are thought to cause impaired microvascular perfusion, which likely ultimately contributes to decreased FEC in these individuals (75,76). This contribution is also evidenced by the finding that people with diabetes complicated by microvascular defects (retinopathy, neuropathy, nephropathy with microalbuminuria) have decreased FEC compared to those without these complications (77). In addition to these cardiovascular contributions to impaired exercise function in diabetes, maximal mitochondrial capacity is impaired (78), and mitochondrial content is reduced (79). Observations of an association between insulin sensitivity and exercise capacity (64) may also reflect additional metabolic determinants of exercise impairment beyond impaired muscle perfusion and reduced mitochondrial function. As a proof of concept, the PPAR insulin sensitizer rosiglitazone has been shown to improve exercise capacity and insulin sensitivity in T2D in a three month intervention, despite weight gain (80,81). This improved FEC correlated with an improvement in endothelial function and blood flow (80). In contrast, in men with established coronary artery disease and T2D, a year-long-treatment with rosiglitazone lead to a decrease in FEC related to increased weight and subcutaneous fat mass expansion. Our current interpretation is that insulin action is a modifiable target for augmenting FEC but that currently available insulin sensitizers are not a durable intervention (82) .

Exercise can be acutely dangerous for people with diabetes. Hypoglycemia can also be an imminent possibility and danger when exercising with diabetes. Hypoglycemia and fear of hypoglycemia represent major barriers to exercise in people with diabetes. This consideration is especially relevant to people with T1D, as episodes of severe (and particularly nocturnal) hypoglycemia are associated with large increases in mortality (83), and exercise can cause nocturnal hypoglycemia and impaired counterregulatory responses in people with T1D (84,85). This is also a documented risk, albeit to a lesser extent, for people with T2D (86). Exercise increases both the translocation and expression of GLUT4 (87), thus potentiating the effects of insulin, and also greatly increases the metabolic demand for glucose (88). These factors predispose towards hypoglycemia, and fear of hypoglycemia is the primary barrier to exercise in people with T1D (11).

Strategies for limiting the risk of hypoglycemia include insulin dose reduction and consumption of carbohydrates; however, exercise modality may also have effect on risk of hypoglycemia (89). 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 is associated with overall less blood glucose variability post-exercise (90). Additionally, a HIIT session is less likely to cause hypoglycemia compared to moderate-intensity aerobic exercise (91). 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 (92). Thus, different forms of exercise necessitate different approaches to maintenance of euglycemia. Consensus recommendations for blood glucose during and after exercise with T1D follow complex algorithms (89), and some personalization is usually required.

Exercise can be a cardiovascular stressor, and while chronic exercise is associated with a reduction in cardiovascular risk (93), acute exercise may precipitate events in susceptible individuals (94). 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.

Additionally, presence of diabetes complications can be a barrier to exercise (59). There is a high association between diabetes complications and depression (95), 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 (96), 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 (97). 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 (98,99). However, these special considerations lead to decreased incentive and increased distress when engaging in physical activity.

As may be expected under these conditions, motivating people with diabetes to exercise regularly is often a considerable challenge in both T1D and T2D. The upshot of these associations is that motivating 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 (100), which is itself associated with less physical activity (101). 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 (102), community-based interventions (103), and surveillance using activity-tracking devices such as pedometers (104). Each of these strategies has been shown to achieve at least modest success, but the increasing prevalence and costs of T2D (105,106) indicate that more work is needed.

**Sex Differences WITHIN Diabetes and Exercise**

According to the IDF Diabetes Atlas, the prevalence of diabetes in adult women in 2017 was 8.4%, compared to 8.9% of men worldwide. Despite the incidence of diabetes being equal between the sexes (6), when adjusted for associated risk factors, women with diabetes have a higher incidence of CVD death and congestive heart failure compared to men (107). Excess CVD in women with T2D correlates with increased adiposity and CVD risk factor burden present in T2D women (108,109).

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 (110). This observation may be due to barriers to exercise, as mentioned above. Of importance, there are sex differences in barriers to exercise as well (111). 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 (112). Additional barriers for exercise specific to women include decreased perceived neighborhood safety and decreased perceived easy access to locations for physical activity (113). 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) (112).

Furthermore, women with T2D have a more pronounced exercise impairment then men with T2D (67,70). Interestingly, while obese women with T2D have reduced VO2 kinetics when compared with controls, there is no difference in impairments based on menopausal status (114). 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 various 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 functional exercise capacity is not yet fully understood; further research is being undertaken in this area to address potential therapeutic targets. Given the discussed correlation between FEC/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 high heterogeneity in response to exercise, other genetic and environmental components may be responsible. Further research in 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, genetic background and exercise phenotype, and environment.

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