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The Effects of Chronic Aerobic Exercise on Cardiovascular Risk Factors in Persons with Diabetes Mellitus

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Abstract
Purpose of Review Aerobic exercise training is a component of diabetes mellitus (DM) care guidelines due to its favorable effects on glycemic control and cardiovascular disease (CVD) risk factors. The purpose of this review is to outline the recent evidence regarding the clinical effects of chronic aerobic exercise on CVD risk factors in persons with DM and to compare the effects of varying intensities and types of exercise.
Recent Findings Among individuals with DM, all types of aerobic exercise training can impact positively on some traditional and non-traditional risk factors for CVD. Training programs with a higher volume or intensity induce greater improvements in vascular function, cardiorespiratory fitness (CRF), and lipid profiles.
Summary The beneficial outcomes of aerobic training include improvements in glycemic control, endothelial function, oxidative stress, dyslipidemia, myocardial function, adiposity, and CRF. Findings regarding markers of inflammation are discrepant and further research should focus on the role of exercise to impact upon the chronic inflammation associated with DM.

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Introduction

The number of people living with diabetes mellitus (DM) globally was estimated to be 415 million in 2015 [1]. Diabetes has been labeled a "global emergency" with the number of cases predicted to reach 642 million by 2040 [1]. The USA had the highest diabetes-related health-care expenditure of any country in 2015, at 320 billion dollars [1]. Though the primary pathologic feature of DM involves altered glucose homeostasis, the leading cause of morbidity and mortality in these patients is cardiovascular disease (CVD). The risk of CVD is dramatically increased in those with DM, with a two to fourfold higher risk compared to healthy individuals [2]. In fact, the risk of CVD events in individuals with DM has been found to be comparable to that of individuals with a prior myocardial infarction [3]. Cardiovascular complications co-occurring with DM pose severe impairments to quality of life and increase treatment costs substantially. Aerobic exercise is known to be an efficacious component of DM care and as such is included in treatment guidelines for DM by the American Diabetes Association [4]. Chronic aerobic exercise, defined as aerobic exercise training for at least 12 weeks in the context of this paper, has been found to be effective in improving multiple modifiable CVD risk factors in individuals with DM [5]. These risk factors, which are commonly associated with DM include hyperglycemia, dyslipidemia, hypertension, systemic inflammation, endothelial dysfunction, increased adiposity, reduced cardiorespiratory capacity, and atherosclerotic progression; all of which can be positively influenced by aerobic exercise training.

It is estimated that type 2 diabetes (T2DM) constitutes about 90% of all DM diagnoses, while type 1 diabetes (T1DM) is less prevalent [1]. This review will cover both T2DM and T1DM, with a greater focus on T2DM given the larger body of recent evidence in that patient population. Current exercise guidelines for individuals with DM from the American College of Sports Medicine [6] and the American Diabetes Association [4] recommend accumulating at least 150 min of moderate-vigorous (64–95% maximal heart rate) aerobic exercise per week, over the course of 3–7 days [4, 6]. The incorporation of high-intensity interval training (HIIT; alternating intervals of vigorous-intensity exercise with active recovery intervals at a low-moderate intensity) has recently been added to exercise recommendations for individuals with DM [6]. This is due to evidence of its superior effects over traditional moderate (40–60% VO_{2peak}) continuous endurance training for some aspects of managing health risk with DM [7•], which will be covered in this review. Resistance exercise, flexibility exercise, and breaking up sedentary time are also included in exercise guidelines for DM. Of note, some studies have found a superior effect of combined aerobic and resistance training on glycemic control [8, 9]; however, the focus of this review will be only on chronic aerobic exercise training of at least 12 weeks in duration. The effects of exercise training in DM may be due to the cumulative effects of repeated acute responses to exercise as well as the gradual adaptations observed with exercise over a prolonged period of time. The purpose of this review is to summarize the recent evidence regarding the clinical effects of chronic aerobic exercise on CVD risk factors in persons with DM and the proposed mechanisms thought to be responsible for mediating these effects.

In recent investigations, there has been a great deal of focus on the effects of varying intensities and types of aerobic exercise training programs in DM. Studies included in this review investigated the effects of various types and intensities of aerobic exercise on the following factors associated with CVD risk: glycemic control, endothelial dysfunction, oxidative stress, inflammation, dyslipidemia, myocardial function, and cardiorespiratory fitness (CRF). Hypertension and increased adiposity will also be addressed. Appendix Table 1 includes a summary of the methodology and results of the investigations of primary focus in the current review.

Glycemic Control and Endothelial Function

Glycemic control is the hallmark of CVD prevention with DM, with a glycosylated hemoglobin (HbA1c) value of < 7% recommended as a goal [4]. Hyperglycemia is intimately connected to CVD risk in DM, through hyperglycemic toxicity which contributes to macro- and microvascular damage through complex pathways [10] outside the scope of this review. The accompanying endothelial dysfunction in DM, as detected by non-invasive measures of endothelium-dependent vasodilatation, is suggested to develop secondary to the limited availability of nitric oxide (NO) as well as increased oxidative stress [11, 12]. There is strong evidence regarding the role of aerobic exercise in reducing glucose excursions and improving glycemic control in DM [13–16]. The improvements in glycemic control with aerobic exercise have been attributed to prolonged increased insulin sensitivity, improved metabolic regulation of hormones which regulate glucose homeostasis, and the accumulation of acute increases in glucose transport and utilization via insulin-independent GLUT4 transporters [17, 18]. Figure 1 depicts the various effects of aerobic exercise training in DM in regard to CVD risk.

In an investigation comparing HIIT to moderate-intensity continuous training (MICT), Mitranun et al. [7•] assessed the effects of the forms of aerobic exercise on endothelial function and glycemic control, among other cardiovascular risk factors. In both HIIT and MICT, decreases were observed in body mass, body fat percentage, waist-to-hip ratio (WHR), resting heart rate (RHR), fasting glucose concentration, HOMA insulin resistance (HOMA-IR), and low-density lipoprotein cholesterol (LDL-C). Peak volume of oxygen consumption (VO_{2peak}) increased in both groups with a greater increase observed in the HIIT group consistent with findings of another recent trial [19]. Improvements were observed in the HIIT group but not the MICT group in systolic blood pressure (SBP), HbA1c, high-density lipoprotein cholesterol (HDL-C), malondialdehyde (MDA) levels (an indicator of oxidative stress), glutathione peroxidase (GPX), NO, and von Willeband factor (vWF). Overall, HIIT resulted in superior improvements in vascular function. There were increases in flow-mediated dilation (FMD), a measure of endothelium-dependent vasodilation, in both exercise groups, with a greater increase observed in the HIIT group. These results provide support for the positive effects of aerobic exercise on endothelial function and suggest that HIIT induces superior improvements in vascular function in the presence of DM than MICT, which has previously been the recommended exercise prescription.

The benefits of aerobic training in preventing CVD in T1DM are believed to arise largely from the improvements in vascular function and related tissue perfusion [20], which are often dysfunctional in DM [21]. These improvements may be associated with improvements in HDL sub particle size and increases in endothelial progenitor cells [22]. DeMoraes et al. [23•] investigated the effects of 12 weeks of low-intensity walking and running on microvascular reactivity in previously sedentary T1DM patients. The results of the study indicated that low-intensity non-supervised aerobic exercise training resulted in increases in cutaneous microvascular density, measured in the fingers. Basal capillary density and capillary recruitment were also improved during reactive hyperemia, indicating possible beneficial effects on perfusion. Uric acid, which is associated with endothelial dysfunction in DM, was

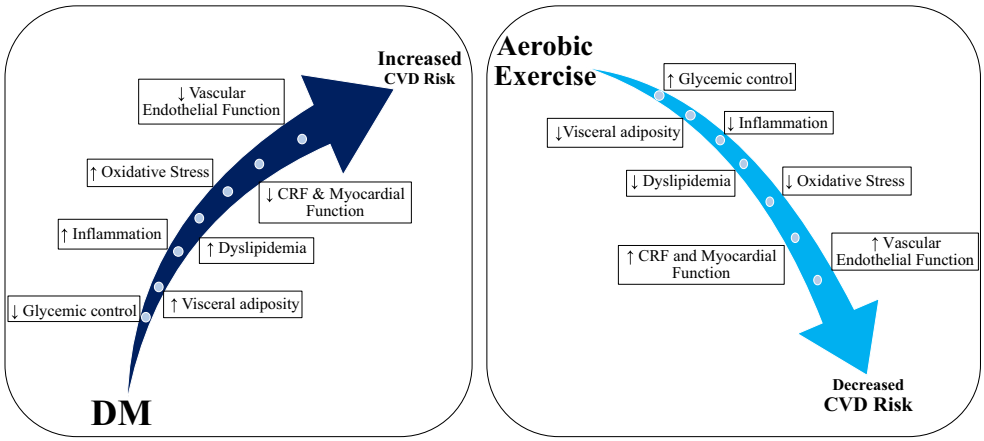

Fig. 1 Increased CVD risk and DM and associated beneficial effects of aerobic exercise

decreased and suggested to be associated with the observed increase in capillary density. Low-intensity aerobic exercise effectively enhanced markers of angiogenesis; however, microvascular reactivity following training was not changed. The authors of the study suggested that the low-intensity exercise may not have induced a great enough increase in blood flow to result in a shear stress that would elicit release of vasoactive substances such as NO. In the previously mentioned study conducted by Mitranun et al. [7•] utilizing HIIT, increases in FMD and NO were induced, supporting the need for higher intensities of exercise to induce microvascular reactivity. The levels of interleukin-6 (IL-6), an inflammatory marker, were also reduced compared to baseline following the 12-week low-intensity exercise training involved in the study by deMoraes et al. [23•].

Researchers examined the effects of supervised aerobic exercise on insulin sensitivity, fasting plasma glucose (FPG), and plasma ceramide concentrations in obese T2DM adults in a high-volume 12-week aerobic exercise training study [24]. Plasma ceramides have been identified as mediators of insulin resistance and have been found to be elevated in T2DM and obesity [25]. Following the exercise training, FPG and total plasma ceramides were decreased. Body weight, fat mass, subcutaneous and visceral adiposity, leptin, triglycerides (TGs), and total cholesterol (TC) were also decreased. Insulin sensitivity and VO_{2peak} were both increased following training. Of note, the exercise-induced reduction in ceramide levels was related to the improvement in peripheral insulin sensitivity and the decreases in whole body and abdominal adiposity.

In a study involving low-volume, high-intensity aerobic exercise training over 12 weeks, Revdal et al. [26] revealed that while volumes of exercise well below the recommended doses were not effective in improving glycemic control in T2DM, the time-efficient training did result in improvements in cardiovascular function. The investigators compared 27 min of HIIT to 10 min of sprint interval training (SIT) three times per week and found that neither resulted in changes in HbA1c, fasting glucose, or HOMA-IR. HIIT induced improvements in adiposity and HR recovery, a marker of cardiac autonomic function that is associated with CVD mortality when compromised [27]. SIT resulted in decreases in DBP, with no other changes in blood pressure observed.

Inflammation and Oxidative Stress

DM is associated with a state of chronic systemic inflammation, which is a major driver of CVD risk. Inflammation in DM is a self-seeding phenomenon in that its contribution to beta-cell death contributes to the hyperglycemic state [28, 29]. Inflammation has been implicated in the development of hyperglycemia by mediating β-cell death [28], while inflammation is also perpetuated by the characteristic hyperglycemic state of DM [29]. Pro-inflammatory cytokines resulting from the insulin-resistant state induce increases in reactive oxygen species (ROS) and free radicals, leading to greater oxidative stress in DM often resulting in atherosclerotic disease [30]. Inflammation is manifested through the presence of cytokines, including tumor necrosis factor (TNF)-α and interleukin (IL)-1β, IL-6, and IL-1 receptor antagonist (IL-1ra) [31]. Exercise has been found to stimulate the release of anti-inflammatory cytokines released from muscle, or myokines, such as muscle-derived IL-6, IL-10, and IL-15 [10]. The direct anti-inflammatory effects of these myokines include the suppression of TNF-α and IL-1β, contributing to an overall reduced state of inflammation [31]. Additionally, decreases in high-sensitivity C-reactive protein (hs-CRP), a systemic marker of inflammation, have been found in response to aerobic exercise training [31–33]. As noted previously, in the study by Mitranun et al. [7•], increases in NO and GPX were found along with decreases in MDA only following the HIIT program, suggesting reduced oxidative stress with high-intensity training but not traditional moderate intensity continuous exercise training.

There have been inconsistent findings regarding the effects of aerobic exercise training on markers of inflammation and

oxidative stress. Mallard et al. [34] compared the effects of 12 weeks of HIIT and MICT on inflammatory markers and oxidative stress in T2DM. They also compared effects after a 12-month home program follow-up. The researchers found that neither 12-week training program resulted in improvements in oxidative stress or inflammation. These findings are in contrast to some previous findings which have indicated improvements in markers of both inflammation and oxidative stress in response to aerobic exercise training [19, 32], though others [35] have found similar findings to Mallard's group. Specifically, Mallard et al. [34] found no changes in IL-6, IL-10, protein carbonyls, glutathione peroxidase activity, F2-isoprostanes, or total antioxidant capacity. In concert with the findings of Mallard et al. [34] in a systematic review of randomized controlled trials, Melo et al. [36] concluded that there was not adequate evidence to show that moderate-vigorous aerobic exercise training improves plasma levels of inflammatory markers in T2DM. Following instruction to continue the exercise training program at home, at the 12-month follow-up, Mallard et al. [34] found that those assigned to the HIIT intervention were able to maintain total antioxidant capacity while those in the MICT group were not, suggesting a somewhat superior benefit of HIIT when performed over a longer time period.

Indirect anti-inflammatory effects of chronic exercise result from the reduction of adipose tissue mass. Obesity is present in over 50% of individuals with T2DM [37]. Obesity, specifically in the form of visceral adiposity, is directly linked to both inflammation and oxidative stress. Visceral adipose tissue has been found to secrete inflammatory cytokines such as TNF-α, IL-6, and visfatin and is associated with lower levels of the anti-inflammatory cytokine adiponectin, as well as increased levels of circulating free fatty acids [38]. The pro-inflammatory state induced by visceral adiposity contributes to endothelial dysfunction as well as the progression of insulin resistance leading to further hyperglycemia and increased risk for CVD [37]. While some investigations have indicated no change in body fat percentage with aerobic exercise training only [19, 35, 39], there are consistent findings of decreased visceral or abdominal adiposity with chronic aerobic exercise training [7•, 24, 40, 41].

Dyslipidemia

A recent study was conducted to assess the effects of a 25-week aerobic exercise training program on the lipid profiles of individuals with T2DM [42]. The investigators compared those participating in the supervised aerobic exercise training program (SSAET) to a group receiving routine medical management (RMM), with individuals in both groups continuing routine medications. The aerobic exercise consisted of three sessions per week with progressively increasing duration and intensity up to 150 min per week at a treadmill grade of 12% and unspecified speed. They found a superior effect of aerobic exercise, with a greater decrease in LDL-C and a greater increase in HDL-C in the SSAET group compared to the RMM group. It has been noted previously that a large volume of exercise is needed to impact upon the lipid profiles of DM patients [43–45]. The longer duration of this study compared to many exercise trials may have impacted the changes observed, pointing to long-term maintenance of aerobic exercise participation as an important aspect of CV risk reduction with DM.

Another recent study investigated the effects of aerobic rebound exercise using a mini-trampoline modality on insulin resistance and lipid profiles in T2DM [46]. The 12-week exercise training program consisted of jumping on the mini-trampoline at a moderate intensity for 30 min, three times a week. Compared to a control group, the exercise group experienced decreases in insulin resistance, LDL-C, and triglycerides (TGs), along with an increase in HDL-C. There is very little research involving the use of aerobic rebound exercise in DM. These findings highlight the use of a unique modality to achieve similar improvements in lipid profile and insulin sensitivity that are seen in training programs with standard treadmill or cycle modalities.

Myocardial Function

In a study comparing 12 weeks of HIIT to MICT, Hollekim-Strand et al. [19] examined the effects on myocardial function and other risk factors for CVD in T2DM. They found an improvement in diastolic function in both exercise groups. Both groups had an increased CRF in terms of VO_{2peak}, with a greater improvement found following HIIT compared to MICT. A decrease in waist circumference with no change in body fat percentage was found in both groups following training. Improvements in systolic function, FMD, HbA_{1C}, and hs-CRP were observed only in the HIIT group. Cardiac function was improved to a greater extent with the higher-intensity exercise. Utilizing HIIT may be more beneficial than MICT in preventing or reversing the detrimental cardiac modifications that occur with DM.

Cassidy et al. [40] studied the effect of a HIIT aerobic exercise program on various markers of cardiovascular health in T2DM. They found that the 12-week HIIT program resulted in positive structural cardiac changes and improvements in both systolic and diastolic function. The HIIT program also resulted in decreased visceral and liver adiposity as well as improved glycemic control, reflected in HbA_{1C} and 2-h glucose values. No changes in body weight or whole body fat mass were induced.

Reduced CRF

Individuals with DM have been shown to have decreased CRF compared with age- and training level-matched healthy

counterparts [47, 48]. Reduced CRF is itself a risk factor for cardiovascular disease, as every 3.5 mL/min/kg increase in aerobic exercise capacity has been found to yield a 12% improvement in survival [49]. Therefore, the improvements in CRF observed with endurance training reduce an individual's CVD risk. This effect is observed in the general population as well, indicating that reduction of CVD risk extends beyond mechanisms related to glycemic control. In a cross-sectional study, Schreuder et al. [50] compared the cardiovascular risk profiles of age-, sex-, and weight-matched life-long physically active individuals with T2DM and controls. They found that life-long physically active T2DM patients had a 50% higher VO_{2peak} than controls, as well as greater insulin sensitivity, endothelial function, and a lower 30-year risk of cardiovascular mortality. Several studies have revealed a greater increase in CRF with HIIT compared to MICT, including studies in DM [7•, 19]. In regard to increasing CRF, it appears that HIIT is more effective, though both forms of aerobic exercise training have been found to induce improvements in CRF [51].

Additional Considerations

Though this review highlights many beneficial effects of aerobic endurance exercise in managing CVD risk with diabetes, recent evidence has also shown that it is not merely a lack of exercise training but also time spent being sedentary that augments CV risk in T2DM. Cooper et al. [52] found that greater amounts of sedentary time were associated with higher CV risk independent of time spent in moderate-to-vigorous exercise. In addition, they found that total physical activity energy expenditure was associated with lower CVD risk, suggesting that endurance exercise training is not the only critical form of activity in mediating CV risk in T2DM. However, encouraging physical activity in most persons with DM is not sufficient. As noted previously, the effects of supervised exercise programs often vary from unsupervised programs. In a meta-analysis comparing supervised training studies to training advice alone in T2DM subjects, Umpierre et al. [53] concluded that supervised training resulted in improved glycemic control while training advice alone did not. This finding highlights the importance of clinical exercise professionals and supervised training programs in order to have an impact on the toll of CVD in the increasing number of DM patients.

Conclusion

Aerobic exercise training is an effective, albeit underutilized tool in the prevention of CVD complications in persons with DM. It is recognized that the risk factors for CVD with DM stem largely from a dynamic state of hyperglycemia and inflammation, the mechanisms of which act in concert to perpetuate the micro- and macro-vascular damage observed in DM. There is clear evidence of the positive impact of aerobic exercise on glycemic control via insulin-independent and insulin-dependent pathways. Though findings are controversial regarding the effects of aerobic exercise on inflammation in DM, it is important to consider that only a few markers of inflammation have been used as the basis for these conclusions. Inflammation is a complex pathway involving glycemic control, endothelial dysfunction, oxidative stress, dyslipidemia, and visceral adiposity, all of which are positively impacted by aerobic exercise training in DM. The intensity and type of exercise training does impact the improvements observed in certain risk factors with DM, with HIIT inducing greater improvements than MICT in CRF and vascular function, most notably.

Exercise prescriptions for persons with DM should be developed on an individual basis to maximize the benefits of the training program. There are risks that accompany exercise in patients with DM, most notably in those on insulin therapy and at risk of hypoglycemia as well as those with disease-related complications. Care should be taken to follow recommendations set forth by the ACSM [6] and ADA [4] in regard to special considerations for the safety of DM patients participating in exercise training.

Compliance with Ethical Standards

Conflict of Interest Emily M. Miele and Samuel A. E. Headley declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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