

Sex Differences in Cardiovascular Disease Risk and Exercise in Type 2 Diabetes

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Abstract: Diabetes currently affects approximately 14% of the US population, and cardiovascular disease (CVD) is a leading cause of morbidity and mortality in those with diabetes. Although in the general population women are at lower risk than men for CVD, women have a disproportionately greater increase in risk for CVD than do men in the context of diabetes. Physical activity is considered a cornerstone in the prevention and treatment of CVD and its risk factors, but greater barriers to physical activity may exist for women with diabetes compared to their male counterparts. In this article, we review sex differences in CVD incidence and risk among diabetics, sex differences in physical activity behaviors, cardiovascular abnormalities and impaired exercise capacity in women living with diabetes, and the effects of exercise on prevention and treatment of CVD in diabetic women. Finally, we discuss future research needed to clarify potential sex differences in the cardiovascular effects of diabetes and to establish ways to reduce the barriers to exercise in women with diabetes.

Key Words: diabetes, women, sex differences, cardiovascular disease, exercise

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The prevalence of diabetes is increasing at an alarming rate. In the United States, the percentage of the population with diabetes is predicted to increase from 14% in 2010 to 21% in 2050.¹ Currently, approximately one in 13 people living in the United States has diabetes, and 90% to 95% of these individuals have type 2 diabetes mellitus (T2DM).² Overall, the prevalence of T2DM is similar in men and women. In the United States alone, approximately 12.6 million women (10.8%) and 13 million men (11.8%), aged 20 years or older, are currently estimated to have T2DM.² However, the prevalence of T2DM is comparatively higher among women than men older than 60 years.³

Among individuals with T2DM, cardiovascular disease (CVD) is the leading cause of morbidity and mortality and accounts for greater than 75% of hospitalizations and greater than 50% of all deaths.⁴ Although nondiabetic women have fewer cardiovascular events than nondiabetic men, in the context of T2DM this advantage seems to be lost.⁵ The reasons for this are not entirely clear but are likely multifactorial with contributions from inherent physiological differences, differences in cardiovascular risk factors, and differences in behavior between the sexes with respect to physical activity and exercise training.

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More than two thirds of both men and women with T2DM do not meet the established guidelines for physical activity necessary to reduce cardiovascular risk.^{6,7} Because of the greater increase in risk of CVD in women compared to men with T2DM, meeting the recommended guidelines for physical activity is particularly important.

This article will briefly discuss sex differences in risk and incidence of CVD observed in T2DM. It will then discuss impaired exercise capacity and cardiac function in women with T2DM compared to men with T2DM. Finally, the importance of physical activity in preventing and treating T2DM and its associated morbidities among women will be discussed.

SEX DIFFERENCES IN RISK FACTORS FOR CVD IN DIABETES

Among both men and women with T2DM, as with nondiabetic individuals, overall risk factors for developing CVD include a high body mass index, high cholesterol, high blood pressure (BP), high hemoglobin A1c, family history of diabetes, poor cardiorespiratory fitness, and lack of physical activity.^{8,9} Management of risk factors for CVD is of key importance in all people with T2DM. However, multiple studies have observed that among men and women with both CVD and T2DM, women are less likely to meet BP and low-density lipoprotein cholesterol (LDL-C) goals.^{10–14}

One reason that women with diabetes have a worse cardiovascular risk profile may be that treatment of CVD is less emphasized in women than in men. Several studies have noted that cardiovascular risk factors are treated more aggressively in diabetic men in comparison to their female counterparts.^{10,11,13,14} For example, in a large Scandinavian study, only 35% of women with CVD or diabetes were prescribed a statin compared to 45% of men with similar medical histories.¹³ Another study observed that women with T2DM and CVD were significantly less likely to receive a lipid-lowering agent and significantly more likely to have elevated LDL-C compared to men with the same baseline risk factors.¹¹ Additionally, in a study of 3849 diabetic patients affiliated with a large US academic primary care system, women were significantly less likely than men to receive treatment addressing BP, LDL-C, and hemoglobin A1c goals. Interestingly, even when treatment was initiated, women were still less likely to achieve recommended goals.¹⁴ The investigators in this study suggested that lipids were less often aggressively treated in women because of a misconception among prescribing doctors relating to the protective effects of the female sex. Kautzky-Willer et al.¹² also found that in patients who had T2DM for fewer than 10 years, women were less likely than men to be treated with oral diabetes medications. Women in this study also were less likely to have hemoglobin A1c values less than 7%. Taken together, these studies suggest that more consistent treatment of CVD risk factors in diabetic women may be an important way to improve sex disparity in CVD morbidity and mortality.

As discussed previously, women may have a disproportionately greater increase in some CVD risk factors in association with diabetes than do men. In addition, women may also have a greater

TABLE 1. Characteristics of Meta-Analyses of Coronary Heart Disease (CHD) or Cardiovascular Disease (CVD) Mortality Risk in Men and Women With Type 2 Diabetes

First Author	Number of Studies	Design	Age (Years)	Sample Size (No. of Diabetics)	Conclusions CHD/CVD Mortality Risk
Orchard ²⁸ (1995)	8	Prospective, population based	0 to >80	50,499	Standardized mortality ratio for CHD/CVD mortality risk in men with diabetes was 1.97 (95% CI, 1.58–2.92) and 2.62 (95% CI, 1.98–4.00) in women with diabetes.
Lee ²⁹ (2000)	10	Prospective, cohort studies	35–80	>75,000	Relative risk of coronary death from diabetes was significantly greater in women (2.58; 95% CI, 2.05–3.26) than men (1.85; 95% CI, 1.47–2.33).
Kanaya ³⁰ (2002)	10	Prospective, population based	35–89	6521	Odds ratio for CHD mortality due to diabetes was 2.33 (95% CI, 1.9–2.8) for men and 2.92 (95% CI, 2.2–3.8) for women.
Huxley ³¹ (2006)	37	Prospective, cohort studies	>15	128,719	Relative risk for fatal coronary heart disease in patients with diabetes compared with no diabetes was significantly greater among women (3.50; 95% CI, 2.70–4.53) than it was among men (2.06; 95% CI, 1.81–2.34).

risk of CVD morbidity and mortality as a result of risk factors than do men.^{15,16} Juutilainen et al.¹⁶ found that elevated BP and dyslipidemia contributed more to coronary heart disease risk in women versus men with diabetes. Similarly, Hue et al.¹⁵ found that a large European cohort of women with newly diagnosed T2DM had a significantly higher hazard ratio for CVD mortality than did men with newly diagnosed diabetes when compared to normoglycemic women and men (3.29 vs 1.40). These women tended to have hypertension or hypercholesterolemia or were overweight. In men and women without these CVD risk factors, there was no difference in the relative risk of CVD death among men or women with insulin resistance or newly diagnosed diabetes compared to normoglycemic individuals.

Although it has been established that increased physical activity is of key importance to decreasing cardiovascular risk, many barriers to achieving the recommended level of physical activity remain, especially among women with T2DM.^{17–25} Defining these barriers and finding methods of overcoming or eliminating them is of high importance in the reduction of CVD in women with diabetes.

SEX DIFFERENCES IN INCIDENCE OF CVD MORBIDITY AND MORTALITY IN T2DM

As stated earlier, both men and women with diabetes are at increased risk for developing CVD. In some but not all studies, women with diabetes seem to have an even greater risk than men for CVD-associated morbidity and mortality. Large-scale population-based health surveys from the National Health and Nutrition Examination Survey (NHANES) examined 3 consecutive nationally representative cohorts from 1971–1986, 1976–1992, and 1988–2000. Data from these surveys published in 2007 revealed that whereas both all-cause and CVD-associated mortality decreased among men with diabetes in these cohorts, neither all-cause nor CVD mortality declined among women with diabetes over the same time period.²⁶ In fact, the same study actually noted that the difference in all-cause mortality rates between women with and without diabetes more than doubled in the same time period, with the increase in mortality among women with diabetes being great enough to essentially eliminate the sex difference in mortality observed in the earlier

2 cohorts. In contrast, an analogous study, which used data from the Framingham Heart Study restructured to match the NHANES analysis, reported a decline in all-cause and CVD mortality in both sexes.²⁷

Over the past decade and a half, 4 meta-analyses have examined the relative risk of fatal coronary heart disease among men and women with diabetes (Table 1).^{28–31} Three of these studies found that women with diabetes have an increased risk for death from CVD, which is significantly greater by approximately 1½ times than men with T2DM. The fourth study by Kanaya et al.³⁰ observed that although women with diabetes tend to have increased CVD risk compared to men, the result did not reach significance in their meta-analysis. Although not perfectly in agreement, these data overall strongly suggest that the female sex may be a significant factor in greater predisposition to CVD-associated mortality in those with T2DM.

SEX DIFFERENCES IN PHYSICAL ACTIVITY LEVELS IN T2DM

Overall, both men and women with T2DM tend to be sedentary. However, women with T2DM typically have lower levels of recreational physical activity than men with T2DM.^{6,32–35} Data from the NHANES survey demonstrated that 69% of both men and women with T2DM reported performing less physical activity than recommended but that significantly more women with T2DM were inactive or insufficiently active than men with T2DM (74% vs 62%).⁶ Zhao et al.³⁵ found similar results in the Behavioral Risk Factor Surveillance Survey of adults aged 65 and older: Among those surveyed, only 21% of women versus 30% of men with T2DM met the American Diabetes Association Guidelines for Physical Activity.³⁵ Barrett et al.³² also found that women with T2DM participate significantly less often in structured physical activity than do men with T2DM. The Health and Retirement Study evaluated 733 men and women with T2DM between the ages of 50 and 62 over a 4-year period and showed that significantly more women than men stopped exercising over the 4 years they were followed (60.7% vs 30.9%).³⁴

Men and women with T2DM also differed in how intensely and where they wanted to exercise.^{32,33,36} Forbes et al.³³ found that men preferred moderate or vigorous exercise more often

than did women. Not only did women prefer low-intensity exercise to higher-intensity exercise, but they also favored a scheduled session with supervision (eg, exercise classes) more than men. Additionally, Garcia et al.³⁶ found that more women than men perceived their neighborhood as being unsafe for exercise, which contributed to their lack of physical activity.

The causes of the disparities in physical activity levels in men and women with T2DM are likely multiple and are not clearly understood. Compared to men, women in one survey were more likely to consider activities of daily life as exercise (eg, walking, gardening, taking stairs, occupational activity) and were also more likely to report that they lacked skills and knowledge regarding exercise.³² A study of perceived exertion during exercise by Huebschmann et al.³⁷ found that women with T2DM perceive significantly harder effort during exercise compared to nondiabetic women; however, no comparable studies exist in men.

IMPAIRED EXERCISE CAPACITY IN WOMEN WITH T2DM

Previous studies have consistently shown that persons with T2DM have reduced exercise capacity compared to nondiabetic persons in both maximal and submaximal exercise.^{38–42} Peak oxygen consumption (VO_2 peak) has been shown to be reduced by between 10% and 30% in people with T2DM.^{43–46} These findings are reported in both adults and adolescents with T2DM. In a study of adolescent women comparing subjects with diabetes to lean and overweight controls, those with T2DM had the lowest peak exercise capacity of any group and achieved a mean of only 7.1 metabolic equivalents, significantly less than that achieved by lean and overweight controls.⁴⁵

There is evidence that the exercise impairment in those with T2DM, compared to nondiabetic controls, is greater in women than in men. Regensteiner et al.⁴³ found that the difference in VO_2 peak between subjects with and without diabetes was greater in women (31%) than in men (20%). Fang et al.⁴⁴ also found that being female was an independent predictor of lower exercise capacity and that factors associated with lower exercise capacity may differ between women and men (eg, heart rate recovery and duration of diabetes).

In addition to greater impairment in peak exercise capacity, women with T2DM may also have greater impairment compared to matched controls than men with T2DM in oxygen uptake kinetics, a measure obtained during constant load submaximal exercise. A study comparing women with and without T2DM found that oxygen uptake kinetics was abnormal in women with T2DM compared to both lean and obese female controls.⁴⁷ Alternatively, Wilkerson et al.⁴⁸ observed no differences in VO_2 kinetics in men with T2DM compared to controls, albeit with an older population. The reasons for the possibly greater impairment in women have not been completely explained.

CARDIAC ABNORMALITIES RELATED TO EXERCISE IMPAIRMENT IN WOMEN WITH DIABETES

Cardiac abnormalities are likely a key contributor to the reduced exercise capacity observed in patients with T2DM. Scholte et al.⁴⁹ found that 40% of asymptomatic male and female subjects with T2DM had an abnormal stress test. There is also evidence that at least in women, even subclinical cardiac dysfunction may be associated with reduced exercise capacity.⁴¹ Regensteiner et al.⁴¹ studied cardiac function of moderately obese women with and without recently diagnosed uncomplicated T2DM at rest and during exercise using a pulmonary ar-

tery catheter. Although there were no differences between the groups at rest, women with T2DM had significantly increased pulmonary capillary wedge pressure during exercise compared to nondiabetic controls and, when normalized, myocardial perfusion index was lower in the participants with diabetes. The strong correlation of these 2 findings suggests the possibility that underperfusion of the heart may be associated with the possibility of early diastolic dysfunction. Importantly, the cardiac abnormalities observed only during exercise are potentially early signs of subclinical cardiac dysfunction associated with T2DM. These abnormalities may precede the presence of impaired cardiac function at rest and with exercise observed in T2DM of longer duration. Although this study was only in women, other studies suggest that women with T2DM may have greater cardiac dysfunction than men during exercise.^{44,51} Ha et al.⁵¹ compared left ventricular (LV) diastolic elastance, a measure of LV stiffness, at rest and during exercise in men and women with and without T2DM. During exercise, LV elastance was worse in the women with diabetes than in any other group. They hypothesized that increased LV stiffness may be seen in women with diabetes because women's smaller ventricle size makes LV stiffening associated with diabetes more pronounced. These studies suggest that the earliest cardiac defects associated with T2DM may emerge only during exercise and may be more pronounced in women.

EFFECTS OF PHYSICAL ACTIVITY ON PREVENTION OF T2DM IN WOMEN

Clear evidence exists in both men and women regarding the use of exercise as a tool in prevention of diabetes. Several large US observational studies of women found that greater physical activity was associated with a lower incidence of diabetes.^{52,53} However, in one study, this relationship was present only in non-Hispanic white women and not in women of African American, Hispanic, or Asian descent.⁵⁴ Using data from the Nurses' Health Study, a prospective cohort of 87,252 US women aged 34 to 59 years, Manson et al.⁵³ found that women who engaged in vigorous exercise at least once per week had an age-adjusted relative risk of 0.67 for developing T2DM compared to women who did not exercise. Even after adjustment for body mass index, the benefit of such exercise remained significant. Using the same cohort, Hu et al.⁵⁵ found that walking as well as more intense forms of activity significantly reduced the risk of developing T2DM, with greater levels of protection conferred by more intense exercise. Folsom et al.⁵⁶ assessed the physical activity level of a cohort of 34,257 women aged 55 to 69 years and found that after the adjustment for other risk factors, women who reported regular physical activity of at least a few times per month had a relative risk of diabetes of 0.69 compared to sedentary women.

Most of the research findings on exercise training show that a combination of diet and exercise has more of an effect on diabetes prevention than exercise training alone.^{24,57,58} However, frequency of exercise remains one of the most powerful determinants of successful weight maintenance.^{59,60} The largest randomized controlled trial evaluating the effects of exercise on prevention of diabetes, the Diabetes Prevention Program (DPP), demonstrated that lifestyle intervention comprised of diet and increased physical activity reduced incidence of diabetes by a third similarly in both sexes.^{61,62} In this study, both diet and physical activity had an independent effect on preventing T2DM, although the effect of diet was greater. Importantly, even in those who did not lose weight, greater prevention of T2DM was seen in those who achieved physical activity goals. A similar outcome was found in the Finnish Diabetes Prevention Study.⁶³

EFFECTS OF EXERCISE ON PREVENTION AND TREATMENT OF CVD AMONG WOMEN WITH THE METABOLIC SYNDROME AND T2DM

Sedentary behavior is strongly associated with the development of the metabolic syndrome, T2DM, and CVD. Regular physical activity is critical to prevent the development of these conditions and to manage risk of developing morbid outcomes. No studies comparing the sexes have been performed to measure the effect of exercise on the prevention of the metabolic syndrome. However, men-only,¹⁷⁻¹⁹ women-only,²⁰⁻²² and studies including both sexes²³⁻²⁵ all showed similarly that physical activity and high levels of fitness may prevent development of the metabolic syndrome and improve cardiovascular risk in people with the metabolic syndrome: At least 120 to 180 minutes per week of moderate-intensity physical activity is consistently associated with a lower prevalence of metabolic syndrome⁵⁰ in both sexes and may reverse the metabolic syndrome once it has developed.⁶⁴

Regarding the role of exercise in reducing risk of CVD among women with T2DM, inconsistent findings have been reported. Hu et al.⁶⁴ observed that moderate to vigorous exercise was inversely associated with the risk of cardiovascular events in women with diabetes. Subjects who participated in 7 or more hours of physical activity per week reduced their relative risk of CVD by nearly 50% compared to sedentary subjects, suggesting that increased effort and/or hours of physical activity could further lower CVD risk.⁶⁵ Alternatively, Lyerly et al.⁶⁶ reported that increasingly higher levels of physical activity did not correlate to increasingly lower the risk of all-cause mortality in women with previously undiagnosed T2DM or impaired fasting glucose, suggesting that those with T2DM may benefit more from exercise than those lower on the spectrum of impaired glucose regulation. Subjects with moderate and high cardiorespiratory fitness had similar lower risk of all-cause mortality rates compared to women with low cardiorespiratory fitness. Nonetheless, the Physical Activity Guidelines for Americans states that at least 150 minutes per week of moderate-intensity physical activity results in significant reduction in cardiovascular risk, with even greater risk reduction seen with 300 minutes of moderate physical activity. The guidelines do not differ for men and women (except during and soon after pregnancy).⁵⁰ Although there is still a question as to what level of physical activity has an increased effect on lowering risk of CVD and all-cause mortality, the consensus seems to be that any activity level is beneficial to women with T2DM in improved control of blood glucose and reduction of cardiovascular risk.

Overall, it is apparent that physical activity is a critical component to reduce the risk of developing the metabolic syndrome, T2DM, and cardiovascular morbidity and mortality in women. However, it is not entirely obvious that the same degree of activity produces comparable results in both sexes, as there is a relative scarcity of data directly comparing men and women. Future studies should further evaluate sex differences in the effects of physical activity on the metabolic syndrome, T2DM, and CVD.

EFFECTS OF EXERCISE TRAINING IN WOMEN WITH DIABETES

Exercise training has been shown to improve, although not normalize, the exercise impairment observed in women with T2DM. Brandenburg et al.⁶⁷ compared premenopausal women with T2DM to lean and overweight controls before and after a 3-month exercise program and found that women with T2DM improved their VO₂ peak significantly more than the control

groups (28% vs 5% and 8%, respectively) and improved oxygen uptake kinetics. McGavock et al.⁶⁸ studied women with T2DM and found that those who participated in a supervised exercise program significantly increased their VO₂ peak and large artery compliance compared to women who did not participate in the exercise training. Both of these studies involved 3 days per week of supervised exercise sessions, suggesting that exercise training can improve the cardiorespiratory fitness profile of women with T2DM. Not all studies have reported improvements, however, particularly those with less than 3 supervised training sessions per week. Vanninen et al.⁶⁹ did not observe improvements in exercise capacity in men and women with T2DM after a 1-year intense albeit unsupervised diet and exercise education regimen. Segerström et al.⁷⁰ also observed no improvement in exercise capacity after an exercise program involving 2 supervised and one unsupervised session per week in women with T2DM. Exercise training does seem to improve exercise capacity in women with T2DM, but the amount of supervised versus unsupervised exercise necessary to achieve this change remains unclear.

Along with the improvement in exercise capacity observed, exercise training has also been shown to improve insulin sensitivity in women with T2DM or a family history of diabetes from anywhere between 5% and 17% in most but not all studies.^{68,70-72} Segerström et al.⁷⁰ observed that improvement in insulin sensitivity correlated with training intensity. Women with T2DM who increased their exercise intensity by 30% showed significant improvement in insulin sensitivity after 6 months in contrast to those who did not.⁷⁰ It also seems that sex difference may exist in the extent of improved insulin sensitivity. A study by Boule et al.⁷¹ reported a 3-fold greater improvement in insulin sensitivity in men with T2DM compared to women undergoing the same training program. They suggest that such issues as dose of exercise should be carefully considered and that more studies should compare men and women in exercise training results.

Some studies additionally evaluated the effects of exercise training on cardiovascular risk factors in people with T2DM. Most research findings suggest greater improvement in risk factors for those with diabetes compared to nondiabetic persons.^{47,70,73} Men and women with T2DM who participated in exercise training also improved their fasting glucose and hemoglobin A1c.⁷⁰ Walker et al.⁷³ observed a greater reduction in fat mass and more improved lipid profiles in women with T2DM compared with women without T2DM after participating in an exercise training program. Soleimani et al.⁴⁷ observed a greater improvement in resting heart rate and heart rate reserve in women younger than 50 years with diabetes and coronary disease compared to nondiabetic counterparts after participating in cardiac rehabilitation.

CONCLUSION AND FUTURE RESEARCH DIRECTIONS

Diabetes is an epidemic in the United States, and the number of people affected is projected to increase dramatically over the next 40 years. Type 2 diabetes mellitus as a risk factor for CVD is of particular importance in women, as diabetes may reduce the protective effect of being female observed in nondiabetic women. Women with T2DM may have worse cardiovascular risk profiles and may be less aggressively treated for cardiovascular risk factors. Exercise has been repeatedly shown to be integral in both preventing diabetes and in treating cardiovascular risk factors in the presence of diabetes. Although this is well established, women with diabetes seem to engage less often in structured physical activity than do men with diabetes. Possible reasons for

this difference include less accessibility to preferred methods of exercising as well as potential physiological differences.

Research is needed to determine whether the degree to which exercise capacity is impaired in T2DM differs between men and women and, if it does, to identify the underlying physiological differences, which create such a disparity. Studies have indicated that cardiac dysfunction may be more severe in women with diabetes, but this has not been well-established. However, given that CVD risk is increased in women compared to men with diabetes, there is a need to further examine this potential difference and what can be done to more effectively manage it.

Further research is also needed to clarify barriers to exercise and examine potential ways to eliminate them. Potential studies could examine whether creating safe and accessible places for women with diabetes to perform physical activity would increase their adherence to exercise recommendations. The problem remains of translating the research showing the clear benefits of exercise training into increased participation for women in physical activity in the community, especially addressing the issue of more readily available supervised exercise programs.

Overall, CVD is a common source of morbidity and mortality among both men and women living with diabetes. Yet, greater awareness among physicians and researchers of the significant sex differences in diabetes can help improve outcomes and optimize management of patients' cardiovascular risk.

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