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Part G. Section 3: Metabolic Health

Introduction

Metabolic syndrome and diabetes are highly significant public health problems in the United States. Ford and colleagues (1) estimate, based on government surveys, that 47 million people in the United States have metabolic syndrome. It is also estimated that 20.8 million Americans (about 7% of the US population) have type 1 diabetes (T1D) or type 2 diabetes (T2D), of whom only two thirds have been diagnosed and the remaining one third are unaware of their condition (2;3). The great majority (estimated to be 90% or more) of these individuals have T2D. The prevalence of diabetes is higher among persons of Hispanic, African American, and Native American background than among persons of non-Hispanic white origins. The majority of deaths in persons with diabetes are caused by cardiovascular disease (CVD), including myocardial infarction and stroke. People with diabetes not only have a high prevalence of manifestations of atherosclerosis but also have increased prevalence of cardiovascular (CV) risk factors, including hypertension and the dyslipidemias. Alarmingly, type 2 diabetes, once called adult-onset diabetes because it chiefly presented in middle-aged persons, is now appearing in ever younger people, and its prevalence in adolescents and children is increasing rapidly. The potential ramifications of T2D in adolescents and children has yet to be determined.

Exercise and physical activity play a clear role in preventing and treating metabolic syndrome and T2D as well as the macrovascular complications of T2D. The importance of the role of exercise and physical activity is highly important and is of increasing interest both in the United States and in other countries as well, as the magnitude of the public health problems of metabolic syndrome and diabetes continues to increase and as solutions are being sought. The role of physical activity and exercise in treating T1D is less well established than for T2D, although evidence suggests that benefits are likely, perhaps most of all in the area of reducing mortality, CVD risk factors, and microvascular complications. For both T1D and T2D, physical activity may prevent the development of diabetic neuropathy and diabetic nephropathy. Finally, it appears likely that physical activity and exercise may help prevent and treat gestational diabetes although more research is needed to further establish these findings.

Review of the Science

Overview of Questions Asked

This chapter considers 6 major questions dealing with the potential role of physical activity and exercise in preventing and treating metabolic syndrome, T1D and T2D, common complications of diabetes, and gestational diabetes:

1. Does physical activity have a role in preventing or treating metabolic syndrome?
2. Does physical activity have a role in preventing and treating type 2 diabetes?
3. Does physical activity have a role in reducing macrovascular risks in type 2 diabetes?
4. Does physical activity have benefits for type 1 diabetes?
5. Does physical activity have a role in preventing and treating diabetic microvascular complications?
6. Does physical activity and exercise have a role in preventing and treating gestational diabetes?

Data Sources and Process Used To Answer Questions

The Metabolic Health subcommittee used the *Physical Activity Guidelines for Americans* Scientific Database as its primary source of references for the topics covered in this section of the report (see ***Part F: Scientific Literature Search Methodology,*** for a full description of the Database). The Database contains studies published in 1995 and later. In its search, the subcommittee used broad study selection criteria, which included: all age groups; all study designs; all physical activity types as well as cardiorespiratory fitness; disease conditions including T2D, T1D, diabetic nephropathy/neuropathy/retinopathy, metabolic syndrome, gestational diabetes, hypoglycemia, glucose, and insulin.

Studies were also identified through computerized searches of several databases, including PubMed, CINAHL, Health Plan, Cochrane Collaboration, and Best Evidence. Standard MESH terms often were only partially successful in identifying relevant articles. Articles also were found through a combination of searching published reference lists as well as references from meta-analyses and systematic reviews.

Question 1. Does Physical Activity Have a Role in Preventing or Treating Metabolic Syndrome?

Conclusions

Regular physical activity is associated with reduced risk of metabolic syndrome (Tables G3.A1, G3.A2, G3.A3, and G3.A4, which summarize these studies, can be accessed at http://www.health.gov/paguidelines/report/.). The available data demonstrate an inverse dose-response association between level of activity and risk of metabolic syndrome, with the minimal amount of activity to prevent metabolic syndrome ranging from 120 to 180 minutes per week of moderate-intensity physical activity, and many studies supporting a goal of 150 minutes per week. The findings derived from studies using self-report measures of physical activity are similar to those studies in which cardiorespiratory fitness was measured. The dose-response association between physical activity and prevention of metabolic syndrome is similar in men and women. Although limited data support the use of exercise for the treatment of metabolic syndrome, this is an area in great need of more work, as is the role of physical activity in preventing and treating metabolic syndrome in youth (Table G3.A5, which summarizes these studies, can be accessed at http://www.health.gov/paguidelines/report/.) and across ethnicities.

Introduction

A number of clinical criteria, such as those of the National Cholesterol Education Program and World Health Organization (4), have been developed to define the metabolic syndrome. These criteria are very similar and share the following cluster of characteristics: abnormal levels of lipids (low high-density lipoprotein and high triglycerides), elevated glucose, hypertension, and excess abdominal obesity (5-8). This review is not limited to any specific clinical definition of metabolic syndrome but rather includes any report in which the definition of metabolic syndrome was consistent with the above characteristics.

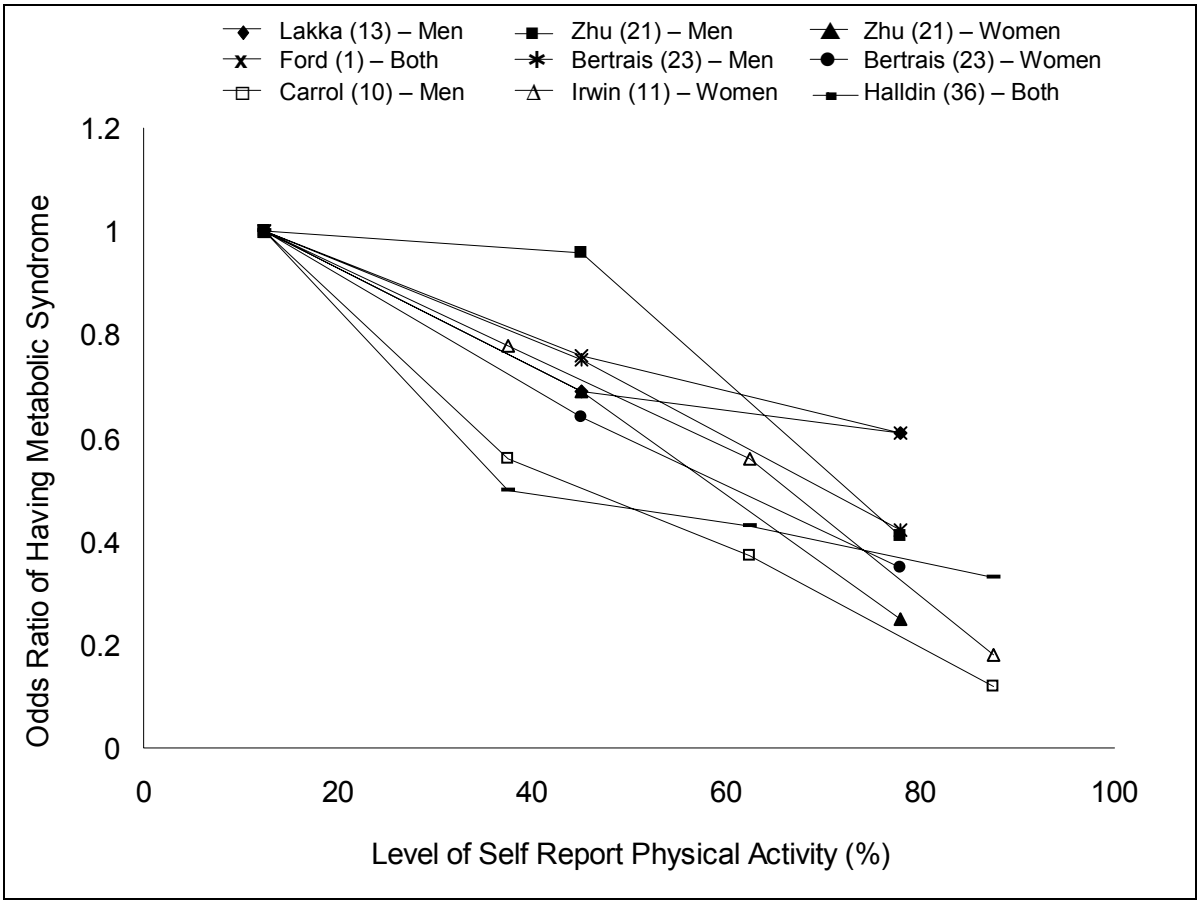
Rationale

In general both cross-sectional and longitudinal cohort studies consistently show a lower incidence and prevalence, respectively, of metabolic syndrome among physically active individuals as compared with their inactive peers (9-45).

Dose-Response Relation

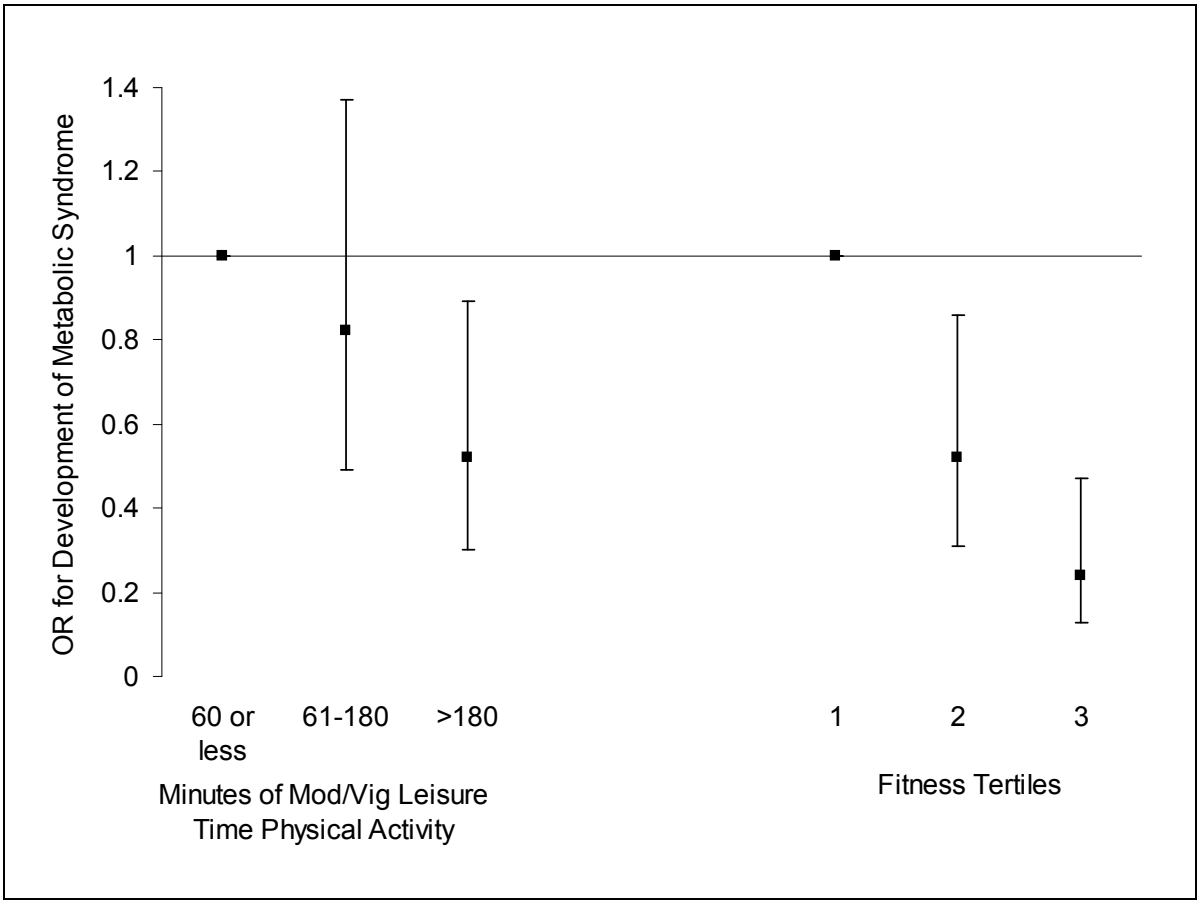
In the cross-sectional studies, which examined the prevalence of metabolic syndrome across levels of physical activity and primarily used questionnaires to obtain self-report data (Figure G3.1), (Table G3.A.3, which summarizes these studies, can be accessed at http://www.health.gov/paguidelines/report/.), all found an inverse gradient between amount of physical activity and metabolic syndrome (10;11;13;21;23;26;36).

Figure G3.1. Summary of Cross-Sectional Physical Activity and Metabolic Syndrome Studies Using Categories of Physical Activity That Could Be Used To Examine Dose-Response



From the cross-sectional studies in which minutes per week of moderate-intensity physical activity for each category were provided or could be estimated, 120, 150, and 180 minutes or more per week of moderate intensity activity have all been reported as minimum amounts associated with reduced prevalence of metabolic syndrome (13;23;26;36). It should be noted that these studies used different methods of activity assessment, the activity categories have large ranges, and the cut-points for the activity categories were not similar or generated using the same statistical methods. None of the studies was designed or powered to analyze the minimal dose of activity to prevent metabolic syndrome. However, the cross-sectional data supports that obtaining at least 120 to 180 minutes per week of moderate-intensity physical activity is consistently associated with a lower prevalence of metabolic syndrome. Only the 2002 report from Laaksonen and colleagues (Figure G3.2) provides data that could be used to examine the dose-response between physical activity and the development of metabolic syndrome (41).

Figure G3.2. Data Prospectively Demonstrating That Both Higher Levels of Physical Activity and Fitness Protect Against the Future Development of Metabolic Syndrome



Source: Laaksonen et al. (41)

Figure G3.2. Data Points

Development of Metabolic Syndrome	Time Physical Activity Low	Time Physical Activity Middle	Time Physical Activity High	Fitness Tertiles Low	Fitness Tertiles Middle	Fitness Tertiles High
Odds Ratio	1	0.66	0.55	1	0.59	0.36

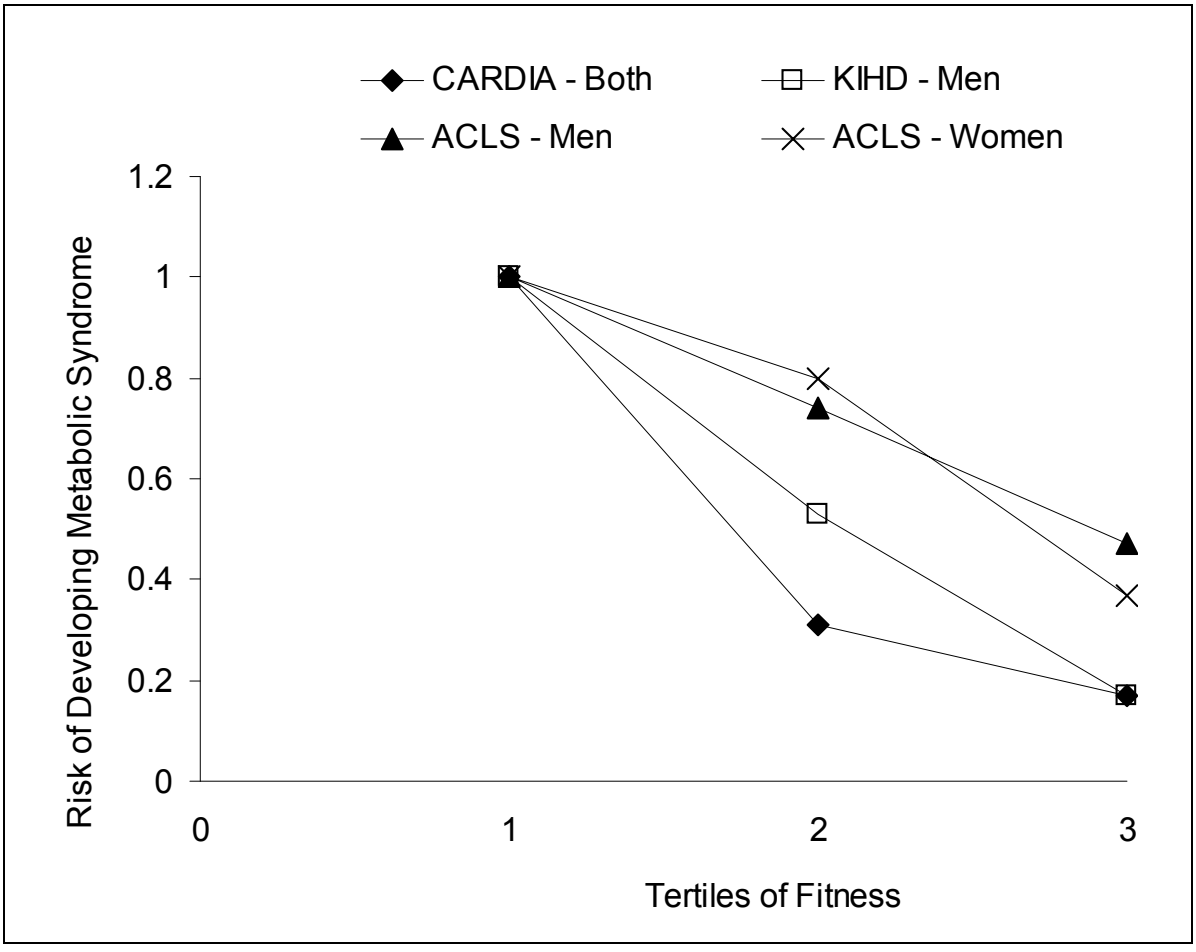
The results were similar to those from the cross-sectional studies. A dose-response relation exists between level of activity and risk of developing metabolic syndrome, with 180 or more minutes per week of moderate intensity physical activity being the minimal amount of time associated with reduced risk of developing metabolic syndrome.

Physical Activity Level Versus Cardiorespiratory Fitness

Laaksonen and colleagues also measured cardiorespiratory fitness and, as depicted in Figure G3.2 and Table G3.A1, the inverse dose-response relationship associated with prevention of metabolic syndrome, is even stronger than that seen with questionnaire-assessed self-report of physical activity (41).

All available prospective studies that measured fitness and categorized participants based on fitness level similarly show a strong inverse dose-response between fitness and risk of developing metabolic syndrome (Figure G3.3) (39;41;46-48) .

Figure G3.3. Summary of Longitudinal Fitness and Metabolic Syndrome Studies That Used Categories of Fitness To Examine Dose-Response Relations



CARDIA, Coronary Artery Risk Development in Young Adults; KIHD, Kuopio Ischemic Heart Disease Risk Factor Study; ACLS, Aerobic Center Longitudinal Study

Thus, despite the methodological differences in assessing physical activity through self-report (questionnaire) vs. measured cardiorespiratory fitness, the association with the prevention of metabolic syndrome is similar for these two modes of activity assessment.

Sex Differences

The available data are composed of men-only studies, women-only studies, and combined-sex studies, with no one type of study comprising the preponderance of the data. As demonstrated in Figure G3.1, the physical activity-metabolic syndrome association is similar in men and women, indicating that both men and women benefit from participating in regular physical activity. As demonstrated in Figure G3.3, the fitness-metabolic syndrome association also is similar in men and women. Thus, no matter whether studies using self-reports of physical activity or objective measures of fitness, it appears that no sex differences exist in regard to the benefits of physical activity in preventing metabolic syndrome.

Youth

Only very limited data are available for youth. These studies, using a variety of methods to quantify physical activity and define metabolic syndrome, are consistent with the findings in adults, namely that higher levels of activity and fitness are associated with reduced risk of metabolic syndrome (Table G3.A5, which summarizes these studies, can be accessed at http://www.health.gov/paguidelines/report/.) (15;44;49;50;50-53). However, this topic is deserving of future study and investigation.

Effect of Race and Ethnicity

The majority of studies with large sample sizes were conducted in Europe or were composed of persons of American or European descent. Though some of the better studies were conducted in populations composed of both African Americans and whites, no studies have examined the physical activity-metabolic syndrome association in an African American or Mexican American population only (11;26;46). Thus, the data on the relationship between physical activity or fitness in terms of preventing metabolic syndrome in non-white populations are limited, and this is clearly an area that needs additional research. It should be noted that in the studies that used study populations composed of both non-Hispanic whites and African Americans, such as the National Health and Nutrition Examination Survey (NHANES) and the Coronary Artery Risk Development in Young Adults (CARDIA) Study, a strong dose-response relation between activity (or fitness) and prevention of metabolic syndrome was evident (26;46).

Prolonged Sitting and Other Sedentary Behaviors

Although regularly participating in physical activity and not leading a sedentary lifestyle may appear to be synonymous, evidence suggests that these two behaviors should be treated as different dimensions of the same pubic health issue. In other words, it is important not only to obtain adequate amounts of aerobic exercise but also to avoid extreme sedentary behaviors, such as prolonged sitting. This is obviously of great importance in today's

environment, in which the typical work day is characterized by long bouts of sitting and most non-work hours are spent watching television. Available data suggest a direct relationship between the prevalence of metabolic syndrome and the time spent watching television or using the computer (23;25;26). For example, using NHANES data (n=1,626 men and women), Ford and colleagues observed that individuals who reported watching television or using the computer 4 or more hours a day had a 2 times greater risk of having metabolic syndrome compared to individuals who reported less than 1 hour a day of television or computer use (26). Given that the current environment in the United States promotes sedentary behavior both within and outside the work place, strategies for reducing sedentary behavior, in addition to promoting exercise, have great potential public health impact.

Role of Physical Activity in Treating Metabolic Syndrome

Numerous studies have examined the benefits of exercise training on individual components of metabolic syndrome, such as blood pressure or fasting glucose. In general, improvements to the variables of interest are noted with exercise training. However, no published studies have been specifically designed to examine the efficacy of exercise training in the reversal of the clinical diagnosis of metabolic syndrome. Two reports have conducted post-hoc analyses to examine the role of exercise in reversing metabolic syndrome. Using data from the HERITAGE study, Katzmarzyk and colleagues report that 20 weeks of aerobic training were associated with improvements in triglycerides, blood pressure, fasting glucose, and waist circumference among 105 participants who had metabolic syndrome at baseline (54). Further, the prevalence of metabolic syndrome decreased 30.5% in this sub-set of participants who received exercise training. However, this study was not controlled, which makes the interpretation of this data challenging. In a recent manuscript using data from the dose-response STTRIDE study, Johnson and colleagues observed an improvement in waist circumference, triglycerides, and blood pressure when the included exercise groups (walking or jogging exercise in varying intensities) (n=130) were combined. None of these variables changed in the control group (n=41) (55). The prevalence of metabolic syndrome also decreased in the combined exercise group from 41% to 27%, with no change in prevalence of metabolic syndrome in the control group (39% to 46%). Although these preliminary data generated from post hoc analyses suggest that exercise training may be an important therapeutic option for the treatment of metabolic syndrome, this area needs additional research. In particular, clinical exercise trials prospectively designed and powered to examine the efficacy of exercise in treating metabolic syndrome are needed.

Resistance Training

Very few studies have examined the role of resistance training or quantified muscular strength in preventing or treating metabolic syndrome (56-58). In both a cross-sectional and longitudinal report from the Aerobic Center Longitudinal Database, greater muscular strength was associated with lower risk of metabolic syndrome (56;57). However, in the report using longitudinal data, the degree of risk reduction associated with greater levels of strength was attenuated (from −34% to −24%) when cardiorespiratory fitness was adjusted

for (57). Given the important role of skeletal muscle in insulin sensitivity, developing a better understanding of the role of resistance training in the prevention and treatment of metabolic syndrome is an area of great interest.

Question 2. Does Physical Activity Have a Role in Preventing and Treating Type 2 Diabetes?

Conclusions

Increased levels of physical activity are associated with significantly decreased risks of developing T2D. Most of the studies addressing T2D prevention have focused on vigorous activity, but a number have included walking at moderate intensity, which has proven efficacious as well. Importantly, two randomized controlled trials (RCTs) and results of observational studies provide empiric evidence to support 150 minutes per week of moderate intensity physical activity for T2D prevention. Several studies have shown that 30 minutes per day of moderate intensity exercise 5 days per week are effective in preventing T2D. Available data do not enable minimal recommendations, although some of the large observational studies show that any amount of increased physical activity is associated with T2D prevention. Recommendations are valid for both men and women. Data are insufficient to clearly show that the benefits are uniform across all ethnicities and racial groups but no data support a lack of benefit and available data do support the benefit in these groups.

Introduction

As noted at the beginning of this chapter, diabetes is a highly significant public health problem in the United States. Available data reveal that physical activity has a strong role in the prevention and treatment of T2D. These data include results from observational studies, and RCTs as well as physiological studies related to physical activity and/or exercise. The relationship between T2D and cardiovascular fitness also is important because population studies reveal a direct correlation between all-cause mortality and reduced fitness in persons with T2D (59;60). Following are data that support the importance of physical activity and exercise in the prevention and treatment of T2D as well as a discussion of the safety of exercise for persons with T2D.

Rationale

Observational Studies of Physical Activity in Preventing Type 2 Diabetes

Large prospective cohort and cross-sectional observational studies that assessed physical activity through the use of questionnaires all show that increased physical activity levels are associated with reduced risk for developing T2D. As with the assessments looking at the relationship between metabolic syndrome and physical activity, it should be noted that these studies used different methods of activity assessment, the activity categories have large ranges, and the cut-points for the activity categories were not generated using the same

statistical methods. In addition, none of the studies was designed or powered to analyze the minimal dose of activity to prevent T2D. Importantly though, however the studies were conducted, the benefit of physical activity in preventing T2D is consistently present. Major prospective cohort studies are described here to illustrate the range of methods used and results obtained. Meta-analyses and structured reviews on this topic are summarized in Table G3.A6, which summarizes these studies and can be accessed at http://www.health.gov/paguidelines/report/. These studies reveal that both moderate and vigorous physical activity can prevent T2D. Dose-response summary information is provided separately below.

In a study by Helmrich and colleagues (61) in 5,990 male alumni of the University of Pennsylvania, incidence rates of T2D decreased as energy expenditure in leisure time physical activity in kilocalories per week increased from less than 500 to 3,500. They found that for each 500 kilocalorie increment in leisure-time physical activity, the age-adjusted risk of T2D was reduced by 6% (relative risk [RR]=0.94, 95% CI= 0.90-0.98) (61). In a study by Manson and colleagues (62) in the Nurses' Health Study cohort (87,252 US women aged 34 to 59 years), the investigators found that women who engaged in vigorous exercise at least once per week had an age-adjusted RR of 0.67 when compared to women who did not exercise (P <0.0001). This significant benefit persisted even after adjustment for body mass index (BMI) although results were somewhat attenuated by this measure (62). Hu and colleagues (63) compared the benefits of walking with benefits of vigorous physical activity on risk of developing T2D in the Nurses' Health Study. Physical activity was divided into quintiles in this study. The authors found that walking (considered a moderate intensity form of exercise) as well as vigorous activity were associated with decreased risk of T2D, with greater physical activity levels providing the most benefit. A study of 5,159 British men revealed a decreased risk for developing T2D that progressively decreased with increasing levels of physical activity (64). Participants were sorted into one of 6 defined levels of physical activity ranging from inactive to vigorously active based on frequency and intensity of the physical activities of each participant. The authors found that the age-adjusted relative risk of T2D decreased progressively with increasing levels of physical activity with even moderate physical activity having a significant effect. In a study of 6,013 Japanese men, Okada and colleagues (65) found that those who engaged in regular physical exercise at least once a week had a relative risk of T2D of 0.75 (95% CI, 0.61-0.93) compared with men not engaging in exercise. In a cohort of 34,257 women aged 55 to 69 years, Folsom and colleagues determined that any level of physical activity was associated with a decreased risk of developing T2D (RR=0.69, 95% CI=0.63, 0.77) when compared with sedentary behavior (66). In a study assessing the effects onT2D of physical activity in 37,918 healthy men where activity levels were classified in metabolic equivalent (MET)-hours per week and considered either moderate or vigorous, relative risks for T2D across increasing quintiles of MET-hours per week were 1.00, 0.78, 0.65, 0.58, and 0.51 (P for trend <.001) (67). Walking pace also was assessed in this study, and walking was found to be efficacious for preventing T2D. Hu and colleagues (68) assessed data from 6,898 Finnish men and 7,392 women ranging in age from 35 to 64 years to evaluate the relationship of occupational, commuting, and leisure-time physical activity with the incidence of T2D.

After adjustment for potential confounders, the hazards ratios of diabetes associated with light, moderate, and active work were 1.00, 0.70, and 0.74 respectively (P=0.020 for trend) and the authors concluded that high or moderate levels of activity were associated with a reduced risk of T2D (68). In a prospective cohort study of 37,878 women, a participant was considered active if she expended more than 1,000 kilocalories on recreational activities per week, with activity levels being divided into quartiles (69). Physical activity was an independent predictor of T2D in this study although BMI was a more powerful predictor. In the Women's Health Initiative Observational Study, Hsia and colleagues (70) found that physical activity across exercise quintiles was associated with a decreased risk of T2D particularly in non-Hispanic white women. This was true for walking (multivariate-adjusted hazard ratios 1.00, 0.85, 0.87, 0.75, 0.74; P for trend <0.001 across exercise quintiles) and total physical activity score (hazard ratios 1.00, 0.88, 0.74, 0.80, 0.67; P=0.002).

These data demonstrate a strong inverse relationship of physical activity across quintiles with diabetes risk in non-Hispanic white women and men. Associations in women of other races and ethnicites are less clear, but the authors of one study (70) note that the study may not have been adequately powered to fully assess data from particular race or ethnic subgroups or possibly that physical activity levels among these groups may not have been intense enough to allow for analyses (see section below).

Physical Activity Level Versus Cardiorespiratory Fitness

Similar to the questionnaire studies, observational studies that assessed physical activity levels using objective measures of cardiorespiratory fitness reported that better fitness is associated with a reduced risk of developing T2D (71-73). Lynch and colleagues (71) found that in a population-based sample of 897 middle-aged Finnish men, higher cardiorespiratory fitness was associated with lower risk of developing T2D compared to sedentary persons. Wei and colleagues (60;72) found that low cardiorespiratory fitness (measured during a maximal exercise test) and physical inactivity (measured by self-report) were associated with risk of impaired fasting glucose and T2D as well as all-cause mortality in men with T2D. In the former study, after adjusting for potential confounders, men in the low-fitness group (the least fit 20% of the cohort) at baseline had a 1.9-fold risk (95% CI, 1.5- to 2.4-fold) of impaired fasting glucose and a 3.7-fold risk (CI, 2.4- to 5.8-fold) of T2D compared with those in the high-fitness group. In another study, in which cardiorespiratory fitness was measured during an exercise test and the 6,249 female participants were divided into thirds by level of fitness, Sui and colleagues (73) found that compared with the least fit third, the adjusted hazard ratio was 0.86 (95% CI=0.59-1.25) for the middle third and 0.61 (95% CI=0.38-0.96) for the upper third of cardiorespiratory fitness. Similar to results from studies using self-report data, results from these studies overall suggest a benefit for achieving and maintaining increased levels of physical activity (64;66;74;75).

Randomized Controlled Trials of Type 2 Diabetes Prevention

The difficulty of evaluating many of the large RCTs looking at the effects of physical activity or exercise on diabetes prevention has been to sort out the effects of diet versus physical activity, as these treatments are commonly combined in large trials. Three large

RCTs have assessed the role of physical activity independently, either using trial design or by analytic means (Table G3.A7, which summarizes these studies, can be accessed at http://www.health.gov/paguidelines/report/.). The Da Qing Impaired Glucose Tolerance and Diabetes Study in China (76) included an exercise-only treatment arm and found that even modest changes in exercise, without change in diet, reduced the risk of developing diabetes. The exercise prescription in this study was 1 or 2 units of exercise a day, with units defined in terms of intensity and duration. One unit was equal to 20 minutes of "mild" exercise (e.g., slow walking, shopping, housekeeping), 20 minutes of "moderate" exercise (e.g., fast walking, cycling), or 10 minutes of "strenuous" exercise (e.g., slow running, stair climbing) or 5 minutes of very strenuous exercise (e.g., skipping, basketball). In this trial, which was randomized by clinic rather than by participant, diabetes risk was reduced 46% in the exercise group, 42% in the diet and exercise group, and 31% in the diet-treated group.

The Diabetes Prevention Study in Finland (77;78) and the Diabetes Prevention Program in the United States (79) have provided clear evidence that intensive lifestyle modifications, including strong diet and physical activity interventions, reduce the risk of developing T2D. Importantly, the role of physical activity is independently beneficial to preventing diabetes. In the Diabetes Prevention Study, 522 middle-aged, overweight men and women with impaired glucose tolerance (IGT) were randomized to either lifestyle modification or a control group (77;78). The physical activity prescription portion of the lifestyle modification (which included a strong dietary component) was for 30 minutes a day of moderate exercise for a total of more than 4 hours per week. Incidence of diabetes was very significantly reduced in the intervention group.

In the Diabetes Prevention Program, 3,234 men and women with IGT and impaired fasting glucose were randomized into control, medication (i.e., metformin, a drug commonly used to treat T2D), or lifestyle modification groups. The physical activity prescription portion of the lifestyle arm (which also had a strong dietary component) was 150 minutes of activity per week. The lifestyle component reduced incident diabetes by 58% and had a more powerful effect than metformin (by 39%). In the Diabetes Prevention Program and Diabetes Prevention Study, weight loss was the dominant predictor of a reduced incidence of diabetes. However, recent analyses from these studies showed that increased levels of physical activity prevented diabetes even after adjusting for confounders (80-82).

Physiological Data Showing Benefits of Exercise in Treating Type 2 Diabetes and Elucidating the Role of Cardiorespiratory Fitness

Type 2 Diabetes is associated with reduced exercise capacity (83;84). Maximal oxygen consumption was approximately 20% lower compared to nondiabetic persons of similar weight and physical activity levels in these studies. These exercise abnormalities are present even in the absence of diabetes-related complications and even in persons with recently diagnosed T2D. The abnormalities are likely associated with cardiac and hemodynamic abnormalities (85-87).

It has been well established that a single bout of moderate exercise has a profound effect on glucose metabolism that may last up to about 18 hours (88). In addition, repeated bouts of exercise appear to have a cumulative beneficial effect on glucose metabolism. A meta-analysis (89) including 14 studies, provides evidence that regular moderate-intensity exercise improves metabolic control in T2D. This meta-analysis shows that exercise significantly improves glycemic control and reduces visceral adipose tissue and plasma triglycerides, although not plasma cholesterol, in people with T2D, even in the absence of weight loss. Exercise training in persons with T2D also has a very significant effect in terms of improving maximal oxygen consumption, measures of submaximal exercise performance, and other measures of fitness (e.g., 90;91). Available data suggest that these findings are true for African American women (92) as well as white women. These findings are further discussed in the section on preventing macrovascular complications of T2D.

Dose-Response Relation

Data on exactly how much physical activity is needed in order to prevent T2D are limited because such studies have not been prospectively designed. Data from observational studies indicate that the amounts of effective physical activity range from any increase over sedentary levels to moderate and vigorous activity levels. It appears, therefore, that any physical activity may be better than none in terms of preventing diabetes, but better results are achieved if individuals engage in higher intensity and more frequent physical activity. Data from several studies support that approximately 30 minutes of moderate intensity exercise at least 5 days per week provides a substantial (25% to 36%) reduction in the risk of T2D according to the Nurses' Health Study (63), the Iowa Women's Health Study (66), the Study of Eastern Finns (68), and the Diabetes Prevention Program (79). Importantly, several of the prospective cohort studies discussed above included walking as a specific modality of physical activity and all of these found that walking was beneficial in terms of preventing T2D compared to sedentary behavior (61;63;67;69;70). Thus, data from observational studies and RCTs support the current recommendation that 2.5 hours per week or typically 30 minutes a day for 5 days a week be performed to prevent T2D. Jeon and colleagues (75) performed a meta-analysis on the prospective cohort studies that assessed the preventive effects of moderate-intensity physical activity that could be analyzed independent of vigorous-intensity physical activity. Moderate-intensity physical activity was defined as an activity requiring 3.0 to 6.0 METs (75). They identified 10 cohort studies that met these criteria. These studies in total included 301,121 participants and 9,367 incident cases. Five of the studies specifically included walking. The summary RR of T2D was 0.69 (95% CI 0.58-0.83) among participants who regularly participated in moderate-intensity exercise compared to sedentary counterparts. The RR for T2D was 0.70 (0.58-0.84) for walking on a regular basis (typically briskly for 2.5 hours per week or more) compared to no walking. However, no data are available to support a specific recommendation for a minimal or even a lesser dose of exercise. In addition, it is not clear how much additional risk reduction is obtained with higher levels of physical activity.

Sex and Race/Ethnicity Differences

In observational studies that included women only, 3 large US cohort studies (67-70) all found that greater physical activity was associated with a lower incidence of diabetes. 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 (70). These findings await confirmation in further studies because the study may not have been powered to detect differences across all race or ethnic groups. Results were based on self report of diabetes in the total population but were confirmed in a subset who also provided blood samples and physician reports.

Data from RCTs as well as observational studies suggest clearly that overall, increased levels of physical activity play a beneficial role in preventing T2D for both women and men. In the Diabetes Prevention Program (93), treatment effects did not differ significantly according to sex, race, or ethnic group. Lifestyle factors addressed in the Program included diet and physical activity, and both had an independent effect on preventing T2D. Although participant numbers became too small for clear results when grouped by ethnicity, it appears that risk reduction compared with placebo was greater for the lifestyle group than for the metformin group in non-Hispanic whites (50% versus 12%, respectively) and Hispanics (57% versus 2%, respectively) (94). African Americans (42% versus 29%) and Native Americans (43% versus 42%), showed similar efficacy for the lifestyle and metformin groups. However, for Asian Americans, metformin showed a nonsignificantly greater reduction than intensive lifestyle intervention (62% versus 30%). Neither lifestyle nor metformin showed significant heterogeneity across the 5 ethnic groups in terms of efficacy. Subsequent studies in India and Japan (95;96), as well as the Da Qing study in Chinese people (76), similarly found an independent effect of physical activity in preventing T2D, and the findings were true for men and women and appeared to be true for all ethnic groups involved.

Thus, overall, acknowledging the limited data available to date, no strong evidence is available to negate the data suggesting that physical activity prevents T2D in men and women of different race and ethnic groups, although further research should explore this important issue.

Youth

Type 2 Diabetes is growing in prevalence in children and adolescents. Alarmingly, unlike youth who do not have T2D, youth with this condition often have CV risk factors, such as hypertension and dyslipidemias as well. Thus, potentially, youth who have T2D may develop CVD at relatively young ages (97;98). Data from RCTs show that increased physical activity improves insulin sensitivity in obese youth, although longitudinal data are limited (99-101) and the effects on CV risk factors are not well established because trials are lacking. A recent review has highlighted the efforts of different interventions to address obesity in youth of various ethnic and racial groups. These interventions focused on lifestyle changes including increased physical activity (102), and several had a physical activity-only component (103;104). Overall findings were encouraging. The studies of both Sallis and

colleagues (103) and Pangrazi and colleagues (104) showed that school-based programs promoting increased physical activity were effective at increasing the physical activity level or cardiorespiratory endurance (although not in reducing BMI) of girls especially.

No RCTs have been completed that show that physical activity or exercise prevents T2D in youth although it is likely give results in aduls. To date, the limited intervention and observation studies suggest that to prevent and manage T2D, daily goals for youth should include less than 60 minutes of daily screen (television, computer or video game) time and 60 to 90 minutes of daily physical activity (105-107). A large multicenter trial (the TODAY study) is currently underway to assess the role of physical activity in preventing T2D in youth (108).

Resistance Training

Resistance training has shown promise as a modality for **treating** diabetes (109;110). Sigal and colleagues (111) found, in a group of 251 individuals with T2D, that both aerobic and resistance training individually improved glycemic control, but improvements were greatest with combined aerobic and resistance training. However, this exercise modality has not been explored for its role in prevention of T2D in large trials, and no data currently exist showing that resistance training plays a role in preventing T2D. Future studies should further investigate the role of resistance training in preventing T2D given the beneficial effects of such training on the metabolism of persons with T2D.

Safety of Physical Activity and Exercise for Persons With Type 2 Diabetes

The consensus is that the benefits of exercise for persons with T2D far outweigh the risks. However, safety concerns about exercise in this group have been voiced. These concerns range from cardiovascular risks associated with physical activity and exercise to caution about hypoglycemia and foot care concerns. The American Diabetes Association (ADA) guidelines on safety (112;113) provide a comprehensive review of safety issues and measures, although the recommendations lack supporting data in some cases.

Question 3. Does Physical Activity Have a Role in Reducing Macrovascular Risks in Type 2 Diabetes?

Conclusions

Strong data support the benefits of physical activity and fitness for CVD protection in T2D and IGT. The data are stronger for hard outcomes, such as CVD events and mortality, than for known CVD risk factors, but this may be an artifact of the relatively short duration of risk factor studies and the potential for small changes in risk factors to have a large cumulative impact on outcomes. These data suggest that a minimum of moderate-intensity aerobic activity for more than 2 hours per week is necessary to achieve significant benefit, and that near maximum benefit may be achieved with moderately vigorous aerobic activity, such as brisk to very brisk walking, for 3 to 7 hours per week (about 12 to 21 MET-hours per week). Combined aerobic and resistance activity appears to have greater benefits than

either type alone when CVD risk factors (and non-CV effects) are considered, but CVD outcome data for activity other than aerobic activity are lacking. In general, the existing data for CVD risk reduction in persons with T2D are consistent with a recommendation of an aerobic activity program with a goal of at least 120 minutes per week and preferably more than 180 minutes per week of moderate to moderately vigorous activity.

Rationale

Several studies have specifically considered the effects of physical activity on CVD risk factors and outcomes in T2D. Observational studies have shown that, among persons with this condition, those who exercise or are more fit have a reduced risk of CV morbidity and mortality than do less active or less fit individuals (67;114-118) (Tables G3.A8 and G3.A9, which summarize these studies, can be accessed at http://www.health.gov/paguidelines/report/.). A study of more than 3,000 Finns with T2D found that all types of physical activity (e.g., recreational and occupational) are beneficial in reducing CV events and mortality (117). Following is a review of the evidence for benefits, dosage, and type of physical activity specifically for reduction of CVD risk and outcomes in T2D.

Cardiovascular Disease Risk Factor Reduction

Many cross-sectional studies have found inverse correlations between physical activity level and various CVD risk factors in T2D populations. Two meta-analyses of these studies have been performed (119;120). One focused on lipid effects and hemoglobin A1c (HbA1c) and found a small (5%) but significant decrease in low-density lipoprotein (LDL) cholesterol (−6.4 mg/dl, range = −11.8 to −1.1) and a strong trend toward improved HbA1c (−0.4%, range = −0.8 to 0.0), but no change in total cholesterol or triglycerides (120). This section focuses on a recent meta-analysis of controlled intervention studies in subjects with T2D that compared different exercise interventions for their effects on CVD risk factors (119). The meta-analysis covers about 1,000 subjects, aged 48-62 years. Exercise interventions were of aerobic, resistance, or combined types. Overall conclusions from the analysis were that all forms of exercise improved insulin sensitivity, with combined types having the greatest effect (especially in men) and resistance alone the least. Combined exercise also had small and moderate benefits on systolic and diastolic blood pressure, respectively, and a small benefit on raising high-density lipoprotein (HDL) levels. Aerobic exercise also benefited triglyceride levels and systolic blood pressure. Resistance exercise did not show significant benefit on any CVD risk factor. Another recent prospective trial with a 6-month, twice weekly, progressive, supervised aerobic program in a population with T2D also demonstrated improved HDL levels (12%) and marked decreases in markers of endothelial dysfunction (ICAM-1 and P-selectin), but no changes in inflammatory markers (hsCRP and TNF-alpha) or LDL levels (121).

Cardiovascular Disease Outcomes

Only one intervention study and no randomized trials have addressed the effect of activity or fitness on hard CVD outcomes. The ongoing Look AHEAD (Action for HEAlth in Diabetes) trial, currently underway, is a randomized long-term study addressing hard CV

outcomes after an intervention (122-124). However, the intervention is targeted at weight loss by a combined program of diet and physical activity and thus will not address the effect of physical activity in isolation. In the one existing interventional trial looking at physical activity alone, Shinji and colleagues followed a small group (n=102) of T2D adults for 17 months after institution of a single, modest, home-based exercise program (walking 20 to 30 minutes, 4 to 6 times per week, at anaerobic threshold) (125). Incident CVD was much higher in "dropouts" than in "completers" even after adjustment for multiple parameters with a RR for incident CVD of 16.5 (95%CI, 1.19-228) for dropouts versus completers. This study suggests that low-level physical activity is beneficial for primary CVD prevention in people with T2D. However, no data were reported or adjustments made for smoking or diet, the "dropouts versus completers" study comparison was nonrandomized, the number of events was very small (n=8), and the confidence interval was very large.

Several prospective cohort studies have found that CV fitness (60;126-128) (Table G3.A8) and physical activity level (60;67;115-118;129;130) (Table G3.A9) are inversely correlated with mortality (all-cause and CVD) and/or CVD event rates in subjects with T2D. Some of these studies have evaluated the effect of frequency, duration, and/or intensity of physical activity on the protective effect. A follow-up of the National Health Interview Survey of 2,896 adults with T2D (115) found that walking for more than 2 hours per week (but not more than 0 hours to 1.9 hours) was associated with a significantly decreased hazard ratio (HR) for CVD mortality (HR = 0.59, 95% CI 0.40 to 0.87, *P* for trend 0.03 after exclusion of disabled subjects, and after adjusting for age, sex, race, BMI, self-rated health, smoking, weight loss approaches, hospitalizations, hypertension or medications, physician visits, limitations caused by CVD or cancer, and extent of functional limitation).

In the Nurses' Health Study of more than 5,000 diabetic women followed for 14 years, subjects were placed in 5 groups based on hours of total moderate-vigorous activity per week, including non-leisure activities (67). RR for CVD events (fatal and nonfatal myocardial infarction or stroke) decreased progressively with increasing weekly volume of moderate to vigorous activity (less than 1, 1 to 1.9, 2 to 3.9, 4 to 6.9, and 7 or more hours per week). Age-adjusted relative risks were 1.0, 0.93 (95% CI, 0.69 to 1.26), 0.82 (95% CI, 0.61 to 1.10), 0.54 (95% CI, 0.39 to 0.76), and 0.52 (95% CI, 0.25 to 1.09) (*P* for trend <0.001). This relationship did not change appreciably after adjustment for smoking, BMI, and other CV risk factors. Among women who primarily walked for exercise, both increased pace (easy pace: 1.0, average pace: 0.52, brisk pace: 0.47, *P* for trend 0.001) and weekly MET walking score were inversely associated with CVD event risk. Among women who did not exercise vigorously in addition to walking, multivariate relative risks across quartiles of MET scores for walking were 1.0, 0.85 (0.62-1.34), 0.63 (0.36-1.10), 0.56 (0.31-1.00) (*P* for trend 0.03) for 0 to 0.5, 0.6 to 2.7, 2.8 to 7.5, and more than 7.5 MET hours per week of walking.

In the Health Professionals follow-up study, Tanasescu and colleagues followed about 2,800 men with T2D for 14 years and assessed incident CVD (fatal or nonfatal MI or stroke) (116). Risk of total and fatal CVD events showed a statistically significant improvement

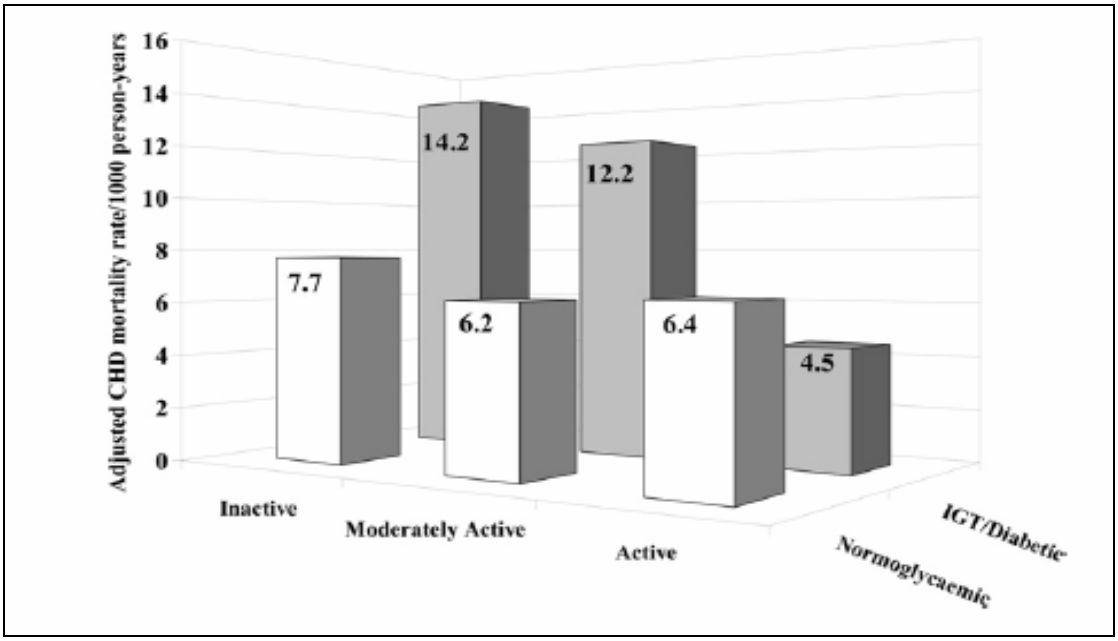
with increasing physical activity after age-adjustment (*P* for trend 0.02, 0.03, respectively) and a strong trend after multivariate analysis (adjusted for alcohol intake; smoking; family history of myocardial infarction; use of vitamin E supplements; duration of T2D; diabetes medication; quintiles of dietary intake of trans fat, saturated fat, fiber, and folate; history of angina and coronary artery bypass graft; and baseline presence of hypertension and high serum cholesterol; *P* for trend 0.07, 0.13, respectively). Additional adjustment for BMI further attenuated the trend (for total CVD events: 1.0, 0.91 [0.63-1.31], 0.68 [0.45-1.02], 0.76 [0.51-1.14], and 0.72 [0.47-1.09] by quintile; *P* for trend 0.14). Their results suggest that physical activity protects from CVD events, especially fatal events, and that for T2D, moderate energy expenditure (3rd quintile, 12 to 22 MET-hours per week, corresponding to about 3 to 5 hours per week of brisk walking) provides the most protection. The authors state that this was not the case in the non-diabetic cohort where a more continuous dose-response was seen. A separate walking intensity multivariate analysis suggests that for those who walked for exercise, the higher the walking speed, the greater the protection. After adjustment for CVD risk factors, walking time, and other vigorous activity, the relative risks for normal pace (2 to 2.9 miles per hour), brisk pace (3 to 3.9 miles per hour), and very brisk pace (more than 4 miles per hour) were 0.82, 0.58, and 0.17 (95% CI 0.04 to 0.71; *P* for trend <0.001) compared to an easy pace (less than 2 miles per hour).

The studies described above suggest that maximum benefit may be achieved with substantial volumes of moderately vigorous exercise, such as brisk to very brisk walking, for 3 to 7 hours per week. It is interesting to speculate that subjects with T2D may differ from non-diabetic subjects in their response to very vigorous exercise, but further studies are needed to fully address the intensity response of CVD risk reduction with physical activity in T2D.

In the Whitehall Study, Batty and colleagues performed a comparative study of the benefits of physical activity in men with T2D or IGT (Table G3.A9) compared to men with normal glucose tolerance (131). After adjustment for other factors, physical activity remained an independent predictor of all-cause, CHD, and other CVD mortality. The gradient for benefit with increasing physical activity was much steeper for the IGT/T2D subjects than for those with normal glucose tolerance, suggesting a greater benefit for metabolically impaired subjects than for the general population. A plot adapted from this data illustrates that the highest level of physical activity actually eliminated the excess CHD mortality associated with IGT and T2D (132) (Figure G3.4).

Others have also found a steeper response of CVD risk to physical activity in diabetic subjects, but most studies have found that CVD risk remains greater in diabetic than non-diabetic subjects even in the most active subgroups (116).

Figure G3.4. Physical Activity/Exercise and Macrovascular Risk Reduction in Type 2 Diabetes



Note: Age-adjusted cardiovascular disease mortality rates by leisure time activity in normoglycemic men (n=6,056) versus men with impaired glucose tolerance/diabetes (n=352) in the Whitehall Study (Adapted by Gill and Malakova 2006, (132) from data from the Whitehall Study). *P*=0.006 for trend in normoglycemic men, *P*=0.003 for trend in men with IGT/diabetes.

Source: Gill JM, Malkova D. Physical activity, fitness and cardiovascular disease risk in adults: interactions with insulin resistance and obesity. Clin Sci (Lond). 2006 Apr;110(4):409-425. Review. Reproduced with permission.

Physical Activity, Cardiovascular Fitness, and Type 2 Diabetes

A recent meta-analysis evaluated the benefits of physical activity for CV fitness in persons with T2D (133). The overall analysis of 9 randomized, controlled, prospective interventional studies had mean exercise characteristics of 3.4 sessions per week and 49 minutes per session for 20 weeks. Mean baseline maximal oxygen consumption of 22.4 ml/kg/min increased 11.8% in the exercise arms and decreased 1.0% in the control arms. Magnitude of improvement in maximal oxygen consumption and in HbA1c correlated better with exercise intensity than with exercise volume. Because fitness and glycemic control appear to benefit overall and CVD mortality, this suggests that more intense exercise would have greater mortality benefits. However, the possibility of a mortality impact of intense exercise in diabetic people cannot be ruled out and is, in fact, suggested by some outcome studies (discussed above). Furthermore, overt nephropathy, peripheral neuropathy, and retinopathy present in many diabetic individuals may be contraindications to very vigorous activity, prolonged stepping activities, and weight-lifting or high-impact activities, respectively,

though these recommendations appear to be based on little experimental evidence (see Question 5. Does Physical Activity Have a Role in Preventing and Treating Diabetic Microvascular Complications?).

Question 4. Does Physical Activity Have Benefits for Type 1 Diabetes?

Conclusions

Data are more limited for type 1 diabetes (T1D) than for T2D, but generally support benefits of exercise for T1D in reducing mortality, CVD risk factors, and microvascular complications. Data are weaker for benefits for glycemic control, and CVD outcomes have not been studied. Data regarding the optimal exercise prescription also are limited. This may still include limiting exercise appropriately in proliferative retinopathy. However, any exercise prescription in T1D also must address the issue of avoiding exercise-induced hypoglycemia. This requires an individualized approach that includes modifying insulin dosing, ingesting additional carbohydrates, and ensuring appropriate details of the exercise prescription.

Rationale

Though T1D is less prevalent than T2D, it remains among the most prevalent chronic, serious diseases of childhood affecting about 1.5/1,000 children in the United States (134). Overall prevalence estimates are increasing now that it has been recognized that a quarter to a half of all T1D develops in adults. Although the metabolic abnormalities associated with insulin resistance have not been considered major factors in this autoimmune form of diabetes, CVD has long been known to be a major cause of morbidity and mortality in T1D. It is now becoming recognized that insulin resistance is also present in T1D and that this may contribute to the associated excess CVD risk. As T1D individuals spend a longer portion of their lives with absolute endogenous insulin deficiency and relative insulin sensitivity, hypoglycemia is a greater safety concern in T1D than in T2D. Effects of physical activity on CVD risk factors and glycemic control and safety concerns are addressed in this section. Microvascular complication effects are addressed in a later section (see Question 5. Does Physical Activity Have a Role in Preventing and Treating Diabetic Microvascular Complications?).

As with T2D and non-diabetic populations, exercise has been shown to be inversely correlated with mortality in T1D. In a cohort study of 548 T1D subjects followed for 7 years in the Pittsburgh Insulin-dependent Diabetes Morbidity and Mortality Study, sedentary males were 3 times as likely to die as active males (135). The relationship did not achieve statistical significance in women.

Physical Activity and Type 1 Diabetes Prevention

No data exist to show that habitual physical activity or exercise plays a role in preventing T1D.

Physical Activity and Type 1 Diabetes Treatment

Glycemic Control

Exercise increases insulin sensitivity and induces non-insulin dependent skeletal muscle glucose uptake. Overweight or otherwise insulin resistant T1D individuals will derive benefit from the improvement in insulin sensitivity that accompanies exercise in the same way that T2D individuals do (see Question 1. Does Physical Activity Have a role in Preventing or Treating Metabolic Syndrome?). Recent evidence suggests that even apparently insulin sensitive diabetic individuals are insulin resistant compared to non-diabetic controls (136;137). Theoretically, therefore, most or all T1D patients might be expected to improve insulin sensitivity with physical activity. As such, it would seem that exercise could improve glycemic control. However, for a T1D patient on a regular dose of insulin, this improved sensitivity comes at the cost of an increased risk of hypoglycemia and resultant hyperglycemia. Furthermore, high-intensity exercise increases catecholamine release and can cause post-exercise hyperglycemia. Thus, studies have had mixed results. Nevertheless, the largest studies have demonstrated improved glycemic control with physical activity in T1D. Interventional studies, most from the 1980s, have all been small (Table G3.A10, which summarizes these studies, can be accessed at http://www.health.gov/paguidelines/report/.). Most have used a moderate aerobic exercise program and have had mixed results, with some negative (138-144) and some modestly positive (145-148) trials. One of the positive trials included a "carbohydrate control" diet intervention in addition to exercise (145). Thus, the improved glycemic control in this study cannot clearly be attributed to exercise. Other positive studies did not include any dietary change or monitoring. Some negative trials followed caloric intake and noted an increase in calories in the exercise group (139). Few studies have looked at resistance training. Two studies with resistance interventions were split, one with improvement in HbA1c (148), the other without (143). Larger cross-sectional studies have also been split (Table G3.A11, which summarizes these studies, can be accessed at http://www.health.gov/paguidelines/report/.). Ligtenberg studied 200 subjects and found no correlation between self-reported activity and HbA1c (149). The FinnDiane study of 1,030 T1D subjects found a sex-based difference in that self-reported physical activity did correlate with improved HbA1c in women, but not in men (150). The effect on HbA1c in women was an 0.5% decrease in both the moderately active (10 to 40 MET-hours per week) and active groups (more than 40 MET-hours per week). In contrast, in men, insulin doses were decreased to a greater extent in the more active populations. In the largest study to date, Herbst and colleagues studied more than 23,000 subjects with T1D and found a small, but highly significant improvement in HbA1c (0.3%) in the 2 active groups (exercise 1 to 2 times a week and 3 or more times a week) compared to the sedentary group (151). Only one study compared resistance to aerobic training and found no benefit for glycemic control in either arm (143). Overall, good evidence for a significant role for exercise alone in glycemic control is limited. Existing evidence suggests

that a modest improvement in glycemic control occurs with small amounts of activity and does not increase with more frequent or more intense exercise. More studies are needed to further clarify the role of physical activity in T1D because many of the studies are relatively old.

Macrovascular Complications

CVD risk factors. The FinnDiane study found that low physical activity correlated with the presence of metabolic syndrome in TID, especially the waist circumference component (152). Lehman and colleagues found significant improvements in insulin sensitivity, LDL, HDL, blood pressure, and waist-to-hip ratio with a self-monitored increase in physical activity of about 150 minutes per week without an increase in severe hypoglycemic events (153). Few studies have investigated the effect of different doses or types of exercise on CVD risk factors in TID. In one 12-week intervention study, Ramalho and colleagues compared the effects of thrice weekly 40 minutes of moderate aerobic training to resistance training (143). Neither group improved lipid profiles, but the aerobic group had improved waist circumference while the resistance group did not.

CVD outcomes. No data exist on the effect of physical activity on actual CV outcomes specifically in T1D.

Physical Activity, Type 1 Diabetes, and Risk of Hypoglycemia

Whatever the benefits of exercise in T1D, it is clear that they come at the expense of an increased risk of hypoglycemia, both during and up to 30 hours after exercise. However, the ADA Position Statement on Physical Activity and Exercise states the "all levels of physical activity, including leisure activities, recreational sports, and competitive professional performance, can be performed by people with T1D who do not have complications and are in good glucose control"(154, p.61). This is because it is possible, with a good understanding of the physiologic responses to exercise, to manage exercise and post-exercise blood sugars. Guidelines for hypoglycemia control have been published, although they are not always strongly data-based and therefore are outside the scope of this section. (155-162).

Question 5. Does Physical Activity Have a Role in Preventing and Treating Diabetic Microvascular Complications?

Conclusions

Physical activity may prevent the development of diabetic neuropathy and diabetic nephropathy (primary prevention) in those with T1D and T2D. Though uncontrolled observational studies suggest physical activity may treat diabetic neuropathy and nephropathy, RCTs are necessary to confirm this. Other observational studies suggest no effect of physical activity on either the prevention or treatment of diabetic retinopathy in T1D subjects. No data are available on sex differences or dose-response of physical activity.

Moderate-intensity physical activity appears safe for all individuals with diabetes even those with existing diabetic microvascular complications, although vigorous-intensity activity, high-impact exercise, or weight-bearing exercise may possibly lead to adverse outcomes in those with existing proliferative retinopathy, severe nephropathy with renal osteodystrophy, or severe neuropathy, respectively. Exercise stress testing is not recommended before starting a moderate-intensity exercise regimen and is of controversial benefit before initiating a vigorous intensity aerobic exercise program.

Introduction

Persons with diabetes have a highly increased prevalence of microvascular complications, which are associated with substantial morbidity. In this section, the role of physical activity in preventing and treating microvascular complications in those with T1D and T2D will be discussed. For the purpose of this document, microvascular complications of diabetes are defined to include neuropathy (based either on symptoms, physical examination, or abnormal electromyogram findings consistent with this diagnosis), nephropathy (defined as microalbuminuria, macroalbuminuria, or decreased calculated glomerular filtration rate), and retinopathy (defined as non-proliferative or proliferative retinopathy diagnosed by an ophthalmologist using retinal photographs).

To date, no large RCTs have investigated the role of exercise training or physical activity in preventing or treating diabetic microvascular complications. One small RCT and some observational studies have suggested a possible relationship between physical activity and both the primary prevention and treatment (tertiary prevention) of diabetic microvascular complications. One meta-analysis (119) has evaluated the impact of physical activity on a surrogate intermediate marker (HbA1c) for progression to diabetic microvascular complications, and showed convincingly that physical activity interventions lower HbA1c. Because better glycemic control has been shown to decrease the incidence of diabetic microvascular complications in subjects with T1D (163) and T2D (164), it is possible that exercise training could reduce microvascular complications solely due to its general improvement of glycemic control. However, the overall lack of studies in this area means that the role of physical activity in preventing microvascular complications remains inconclusive. Specific gaps in the literature that warrant further research are large studies to determine the exercise dose-response curve for prevention or treatment of microvascular complications, and determining whether differences exist by subject race/ethnicity, sex, T1D vs. T2D, or exercise modality.

The next three sections will summarize what is known regarding the role of physical activity in preventing and treating 1) diabetic neuropathy, 2) diabetic nephropathy, and 3) diabetic retinopathy. Safety concerns for exercise in these populations also will be discussed.

Rationale

Observational studies provide most of the existing data, which are of limited scope and quality, to determine the role of physical activity in primary prevention of diabetic

nephropathy, neuropathy, and retinopathy. Observational studies of lesser quality (often uncontrolled) have been performed to address the role of physical activity for treatment of diabetic nephropathy, neuropathy, and retinopathy. To determine the safety of physical activity with existing microvascular complications, small observational studies have been performed and clinical standards of care also have been discussed when appropriate to supplement the scarce amount of safety data.

Diabetic Neuropathy

One small RCT (165), one cross-sectional study (166), and one retrospective cohort study (167) have evaluated the impact of physical activity on primary prevention of diabetic neuropathy (Table G3.A12, which summarizes these studies, can be accessed at http://www.health.gov/paguidelines/report/.). From these limited data, no firm conclusions may be drawn but it does appear that physical activity may possibly have some role in preventing diabetic neuropathy. The RCT data, although only based on 78 participants (73% with T2D), revealed a reduction in both motor and sensory neuropathy from 4 years of moderate-intensity exercise despite no significant weight loss (165). Of the 2 cross-sectional studies performed in T1D subjects addressing neuropathy, one showed physical activity significantly benefited males only (166), while the other had no effect (167).

Treatment of Diabetic Neuropathy

No studies have evaluated the use of physical activity to treat diabetic neuropathy. One study evaluated 12 months of physical activity in conjunction with a dietary intervention for prediabetic neuropathy (Table G3.A13, which summarizes these studies, can be accessed at http://www.health.gov/paguidelines/report/.), using a pre-post study design in 40 subjects with prediabetes to show significant differences in nerve fiber density at the proximal portion of the leg (P <0.05), and non-significant improvement in neuropathic pain and nerve fiber density at the distal portion of the leg (168).

With respect to diabetic ulcer prevention in a group with diabetic neuropathy, no significant improvement in the surrogate outcome of dorsal foot cutaneous perfusion was found after either a 10-week aerobic exercise (169) or 8-week resistance exercise program (170). Although significant differences were initially described in dorsal foot cutaneous perfusion between physically active individuals with T2D as compared with sedentary individuals with T2D who had a higher mean HbA1c (171), no differences were evident when this study was repeated with similar HbA1c levels between groups (172). This area requires further study.

Safety of Exercise With Diabetic Neuropathy

Three different aspects of safety of exercise with comorbid neuropathy are at issue: (1) Safety of exercise with autonomic neuropathy, (2) Ulcer risk with existing neuropathy, (3) Fall risk with existing neuropathy.

Safety of exercise with autonomic neuropathy. Existing guidelines are not based on data and are therefore are outside the scope of this chapter. Graham and Lasko-McCarthy and Sigal and colleagues provide further information on this topic (112;173).

Ulcer risk with existing neuropathy. Two studies observed an inverse relationship between physical activity and ulcer incidence (174;175). However, 2 other studies have suggested that abrupt increases in activity may increase the short-term risk of ulceration. Armstrong and colleagues found a significantly greater coefficient of variation in the group with recurrent ulcer (174) and Lemaster and colleagues (175) found a significant unadjusted increased risk of ulcer with increased short-term activity. Ulcer risk was increased with greater intensity and duration of loading pressure on the feet while walking (176;177) possibly showing a clinical benefit to protective diabetic footwear in this population.

Risk of falls with existing neuropathy. Several studies have evaluated the degree to which gait is altered by diabetic neuropathy (suggesting attendant increased fall risk), with one study showing a targeted intervention may improve balance in this population. Dingwell and colleagues as well as other researchers have performed studies showing decreased walking speeds or decreased gait variability (176;178-180) in those with diabetic peripheral neuropathy versus non-diabetic controls. Giacomozzi and colleagues also showed those with diabetic neuropathy and a prior foot ulcer had even greater gait variability than those with neuropathy and no prior ulcer (176). Mueller and colleagues showed that the peak torque generated during plantar flexion and the range of motion of dorsiflexion at the ankle are strongly correlated ($r = 0.78$) and contribute to the power generated from the ankle joint during ambulation (181). These data suggest that decreased ankle dorsiflexion range of motion and/or plantar flexion strength are associated with decreased step length and speed during walking (181). Novak and colleagues (182) reported that 30 individuals with T2D and associated diabetic neuropathy described worse foot pain and walked shorter distances than subjects with T2D without neuropathy and non-diabetic controls, with strong correlation between pain level and walking distance ($r = -0.45$, $P < 0.001$) (182).

The data presented here generally support the pragmatic exercise precautions recommended in clinical practice guidelines (Table G3.A14, which summarizes these studies, can be accessed at http://www.health.gov/paguidelines/report/.). Those with **severe** peripheral neuropathy should use non-weight bearing activities to avoid foot ulceration or Charcot joint destruction (112;173), and all individuals with diabetes should use appropriate footwear and inspect their feet daily to reduce injury risk (183).

Diabetic Nephropathy

Four cross-sectional studies (150;152;166;184) and 1 retrospective cohort study (167) have evaluated the impact of physical activity on diabetic nephropathy prevention in subjects with T1D (Table G3.A12). These data are not available in patients with T2D. From these limited data, no firm conclusions may be drawn but they suggest physical activity may prevent diabetic nephropathy. In 2 separate cross-sectional analyses of slightly different subsets of a Finnish population with T1D, less physical activity was associated with greater prevalence

of nephropathy (150;152). A significant association was observed between greater leisure-time physical activity and decreased nephropathy in men only, with no increased risk in women with T1D (166). The other 2 observational studies performed showed neither harm nor benefit in prevention of diabetic nephropathy (167;184).

Physical Activity To Treat Diabetic Nephropathy

A pre-post analysis (185) evaluated the effect of 3 weeks of physical activity and low-calorie diet in treating existing nephropathy (Table G3.A13) in subjects with T2D. Although albuminuria was reduced, the dietary intervention and/or associated weight loss may have confounded these results. These data are somewhat promising but inconclusive.

Safety of Physical Activity With Existing Nephropathy

The relevant literature appears to show that exercise does not worsen resting proteinuria (186-188). In a cohort of 373 subjects with T1D, a strong correlation between overnight albumin excretion rate (AER) and post-exercise AER existed ($r = 0.74$, $P < 0.001$), and 52% of subjects had an elevated overnight AER preceding an elevated post-exercise AER (186). In a smaller cross-sectional study, Groop and colleagues (187) showed exercise did not increase protein excretion in 17 subjects newly diagnosed with T1D, but that 17 subjects with long-standing T1D had a significant increase in post-exercise excretion of albumin, β2-microglobulin, Kappa light chains, and IgG independent of whether resting AER was elevated (n=7) or normal (n=10). A small cohort study found no significant difference in time for nephropathy progression in 6 subjects with "good" unrestricted physical activity as compared with 7 subjects with "self-restricted" physical activity (188).

Despite hypothetical adverse effects of increased proteinuria immediately after exercise (189), existing data show no progression of nephropathy with exercise and, in fact, increasing physical activity may decrease existing albuminuria, as described earlier in this section (185;190;191). In the absence of primary data for other safety considerations in those with diabetic nephropathy, a review of these issues is outside the scope of this discussion, although guidelines exist (112;173).

Diabetic Retinopathy

One moderate-sized prospective cohort study (192), and several cross-sectional (150;152;166;184;193) and retrospective (167;194) observational studies have evaluated the impact of physical activity on diabetic retinopathy (Table G3.A12) in T1D. These limited data suggest that physical activity does not influence the risk of developing diabetic retinopathy. The moderately sized cohort study (192) observed no difference in the incidence of retinopathy over 6 years in 606 T1D subjects with respect to current physical activity or historical participation in team sports, in contrast to an earlier cross-sectional analysis (193) in a subset of the same cohort population where a decreased prevalence of retinopathy in women who played team sports (OR 0.46, $P < 0.05$) or who reported current strenuous physical activity (OR 0.34, $P < 0.05$) was previously observed. Two cross-sectional analyses of slightly different subsets of a Finnish population with T1D found no

association between physical activity and retinopathy (150;152) despite an association between physical activity and less nephropathy in those same studies (150;152). Of the 4 other cross-sectional studies performed, none showed any benefit or harm of physical activity in the prevention of diabetic retinopathy (166;167;184;194).

Treatment of Diabetic Retinopathy

A large cohort study reported no impact of self-reported current or historical physical activity measurements on retinopathy in a large cohort of T1D subjects with both non-proliferative and proliferative retinopathy at baseline measurement (192).

Safety of Physical Activity With Existing Diabetic Retinopathy

Although existing data raise concerns about the plausible causality of exercise-induced vitreous hemorrhages individuals with diabetic retinopathy, existing data have not conclusively shown a risk of moderate-intensity exercise in those with this condition (195).

The 2 prospective studies evaluating the safety of exercise in humans with existing retinopathy have not shown an increased risk of retinopathy progression or of vitreous hemorrhage in this population. The prospective cohort study analysis by Cruickshanks and colleagues showed no risk of worsened retinopathy in those with T1D who were more physically active over a 6-year period as compared with their more sedentary counterparts, including a very small subset of self-described weight lifters (192). A pre-post exercise intervention study in 30 subjects with T1D or T2D and existing proliferative diabetic retinopathy (90% or greater) or diabetic macular edema observed no newly documented vitreous hemorrhages attributable to a 12-week supervised exercise training program, although the study was under-powered to definitively determine vitreous hemorrhage risk (196).

Given the preceding evidence, clinical providers have generally recommended moderate-intensity exercise but advised against vigorous exercise regimens for those with proliferative retinopathy (112;173;183;197) and severe nonproliferative retinopathy (112) due to the theoretical (yet unproven) increased risk for vitreous hemorrhage and retinal detachments with vigorous exercise.

Cardiovascular Safety of Physical Activity With Existing Microvascular Complications

Despite a lack of studies evaluating this practice, the most recent published standards of care suggest that diabetic subjects with more than a 10% 10-year risk for CV disease by the United Kingdom Prospective Diabetes Study risk calculator (198) should **consider** exercise stress testing to screen for latent ischemia before initiating vigorous aerobic exercise regimens that exceed the “demands of everyday living” (199).

Question 6: Do Physical Activity and Exercise Have a Role In Preventing Gestational Diabetes?

Conclusions

Although no RCTs have been performed to demonstrate that physical activity can prevent gestational diabetes (GDM), data from observational studies support that concept. Available studies suggest that approximately 30 minutes per day of moderate-intensity physical activity is likely a sufficient dose to decrease the GDM risk (200). However, this suggestion is based on relatively few studies, and further studies should directly address the issue of dose-response.

Introduction

Gestational diabetes is defined as diabetes first identified during pregnancy. Overall, prevalence rates of GDM have increased from 1.9% in 1989-1990 to 4.2% in 2003-2004, a relative increase of 122% (201). The prevalence of GDM is 17% in obese women, and overweight women have a significantly greater risk of developing GDM than do non-overweight women (202). It is estimated that up to 60% of women with GDM will develop T2D within 4 years of delivery (203). GDM can give rise to many adverse outcomes both to mother and infant. It is associated with a greater likelihood of Caesarean section deliveries and other birth complications (204). Women with GDM also are more likely to have a difficult labor and delivery. Babies of women with GDM are at increased risk of obesity and diabetes later in life as well as other comorbid conditions at birth (205).

Given that women who develop GDM are at highly increased risk of developing T2D, understanding how to prevent and treat GDM is very important. The role of physical activity in preventing and treating GDM has not been as well studied as for T2D. Indeed, no RCTs have assessed whether GDM can be prevented by regular physical activity. However, observational epidemiologic studies suggest overall that this may be the case (Table G3.A15, which summarizes these studies, can be accessed at http://www.health.gov/paguidelines/report/.).

Rationale

Data From Observational, Epidemiological Studies

Several studies have shown that physical activity is associated with a significantly reduced risk of GDM (200). These studies reported that increased levels of physical activity (assessed by questionnaire) before pregnancy or during the first 20 weeks of pregnancy was associated with reductions in risk of GDM. Overall the reduction in risk is about 50% when active women are compared to inactive women.

Dose-Response Data

No RCTs have evaluated prospectively whether physical activity can prevent GDM or what doses might be effective for such a response. Such trials would be of great value to establish

the role of exercise and physical activity in GDM. Available studies suggest that approximately 30 minutes per day of moderate intensity physical activity is likely a sufficient dose to decrease the GDM risk (200). However, this suggestion is based on relatively few studies, and further studies should directly address the issue of dose-response.

Overall Summary and Conclusions

In summary, physical activity and exercise play a key role in preventing and treating metabolic syndrome and T2D. The evidence for T2D are the clearest because RCTs have been conducted to corroborate the findings of many observational trials, although, as mentioned previously, 2 of the 3 RCTs combined physical activity and diet in their lifestyle intervention. (The post-hoc findings on effects of physical activity in the absence of weight change, although consistent and strong, are therefore not considerd strong RCT data but rather are equivalent to the quality of prospective cohort study data.) The role of physical activity and exercise in treating T1D is still being established. Current evidence suggests that benefits are likely, perhaps most of all in the area of reducing mortality, CVD risk factors, and microvascular complications. For both T1D and T2D, physical activity may prevent the development of diabetic neuropathy and diabetic nephropathy. Finally, it appears likely that physical activity and exercise may help prevent and treat gestational diabetes although more research is needed to establish these findings. The amount of exercise that appears to be the most well accepted and documented across the conditions included in this section to date is 30 minutes of moderate physical activity 5 days per week. However, it is clear that benefits are obtained with even lower volumes of physical activity. Walking is a beneficial form of physical activity and has been especially well documented as effective in T2D (where it has been most extensively studied). In the next section, the extensive research needs for further study in the area of Metabolic Health are documented.

Research Needs

Although a considerable body of literature exists on the role of physical activity in promoting and maintaining metabolic health, a number of questions remain unanswered and require additional research:

- Available data indicate that regular physical activity is associated with reduced risk of metabolic syndrome. However, it is not clear whether physical activity and exercise can be used in treating or reversing metabolic syndrome, and additional studies will help to clarify this issue.

- Research is needed in diverse populations to determine whether the effects of physical activity across the range of metabolic health issues, including metabolic syndrome, T2D, T1D, and gestational diabetes, differ with race and ethnicity.

- Further examination of the effects of physical activity on metabolic syndrome and T2D also is warranted to determine whether and how its effect differ in youth and adults.

- Additional research evaluating dose-response patterns of exercise in preventing diabetes and cardiovascular outcomes in diabetes would make a valuable contribution to the metabolic health literature.

- RCTs are needed to examine the effects of exercise on treating T1D in children and adults. Good cardiovascular outcome data in response to physical activity in T1D is lacking and could potentially be obtained in adult-onset T1D.

- Clinical studies in post-exercise hypoglycemia are needed to further study the intermittent high-intensity exercise approach to prevention and to compare extra carbohydrate versus lower insulin dosing approaches to treating T2D.

- Research is needed on several issues related to gestational diabetes. For example, RCTs are needed to determine whether physical activity can prevent gestational diabetes. It also would be useful to have additional dose-response data on the role of exercise and physical activity in treating gestational diabetes.

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