Exercise is Medicine – The Importance of Physical Activity, Exercise Training, Cardiorespiratory Fitness and Obesity in the Prevention and Treatment of Type 2 Diabetes

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Abstract

Type 2 diabetes has reached epidemic proportions worldwide and is associated with increased risk of cardiovascular diseases and premature mortality. Diet and physical activity (PA)-based lifestyle interventions have been shown to prevent progression to type 2 diabetes in patients at high risk. Regular PA substantially reduces the risk of type 2 diabetes and a high level of PA is associated with a substantial reduction in type 2 diabetes risk. In addition, there is strong evidence suggesting a steep inverse relationship between both PA and cardiorespiratory fitness (CRF) and mortality in patients with type 2 diabetes. Of particular concern is the dramatic, steep increase in mortality among patients with low CRF. An important point is that obese individuals who are at least moderately fit have a lower mortality risk than those who are normal weight but unfit. A large body of evidence demonstrates that exercise improves glycaemic control in type 2 diabetes; the greatest improvements are achieved with combined aerobic and resistance training. A primary goal of public health strategies is to promote PA and move patients out of the least fit, high-risk cohort by increasing PA among the least active. Any plan to deal with the global epidemic of type 2 diabetes must give major attention to low PA and how this can be reversed in the general population.

Keywords

Fitness, mortality, physical activity, exercise, type 2 diabetes

Disclosure: The authors have no conflicts of interest to declare.

Received: 21 March 2013 **Accepted:** 26 April 2013 **Citation:** *European Endocrinology*, 2014;10(1):18–22 *DOI:10.17925/EE.2014.10.01.18*

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Support: The publication of this article was supported by The Coca-Cola Company. The views and opinions expressed are those of the authors.

Globally, type 2 diabetes has reached epidemic proportions and is associated with an increased risk of cardiovascular disease (CVD) and premature mortality. The total number of people with diabetes worldwide is projected to rise from 366 million in 2012 to 552 million in 2030.[1] In 2012, type 2 diabetes imposed direct and indirect costs of an estimated $245 billion in the US.[2] It is estimated that low levels of physical activity (PA) causes 7 % of the global burden of disease from type 2 diabetes, and that inactivity causes more deaths than smoking.[3]

In addition to type 2 diabetes, low PA has been demonstrated to contribute to obesity, coronary heart disease (CHD)/myocardial infarction (MI), stroke, hypertension (HTN), dyslipidaemia, osteoporosis and cancer (colon, breast and bowel).[4,5] As a result, sedentary lifestyles are one of the most significant public health problems of the 21st century. Low PA was directly responsible for 3 % of disability adjusted life–years in the UK in 2002.[6] Furthermore, it has been estimated that low cardiorespiratory fitness (CRF) was the cause of approximately 16 % of deaths in the Aerobics Center Longitudinal Study, which was more than the combined number of deaths due to smoking, obesity and diabetes in this population.[7] Despite the known risks of low PA, there have been substantial declines in PA over the past decades. Over the last 50 years in the US, it has been estimated that daily occupation-related PA has decreased by more than 100 calories,[8] and household management PA has fallen by well over this amount.[9] In addition to the effects of PA on morbidity and mortality, there are clear economic reasons to improve PA: a US cohort study (8,000 health plan members and national population percentage estimates derived from the National Health Interview Survey) found that low PA, overweight and obesity were associated with 23 % of health plan healthcare charges and 27 % of national healthcare charges.[10]

Low PA can initiate and accelerate the pathogenesis of type 2 diabetes and subsequent morbidity and mortality.[11] The American Diabetes Association (ADA) recommends that individuals with type 2 diabetes perform at least 150 minutes of moderate-intensity aerobic exercise training (ET) or at least 75 minutes of vigorous aerobic ET per week.[12]

However, a recent population-based study found that only 28 % of people with type 2 diabetes achieve these recommendations.[13] The majority of people with type 2 diabetes have low PA. As a proof of this statement, a US study of 23,263 adults found that 39 % of adults with type 2 diabetes were physically active versus 58 % of adults without type 2 diabetes.[14] In addition to PA, low CRF has been associated with type 2 diabetes.[15–18]

This article aims to review evidence for the relative roles of PA, CRF and obesity in the primary prevention and secondary control of type 2 diabetes, to examine other health benefits of PA, and discuss current approaches to integrate ET into clinical practice.

Which is More Important – Cardiorespiratory Fitness or Physical Activity?

Quantification of the strength and nature of the relationship between PA and type 2 diabetes in population studies is dependent on the accurate quantification of PA. Much of the evidence in which PA recommendations have been based has been obtained from self-report questionnaires. Self-report methods have poor reliability owing to recall and response bias and the inability to capture the absolute level of PA.[19] In addition, PA questionnaires do not take into account everyday activities such as standing, moving around and fidgeting. While energy expenditure associated with PA can be quantitatively assessed by a number of methods, these tend to be expensive and impractical for large-scale studies. By contrast, the assessment of CRF is objective and reproducible. The principal behavioural determinant of CRF is PA. Therefore, it has been suggested that CRF reflects PA patterns and may be a more useful parameter than PA in the evaluation of the health impacts of fitness.[20] Some studies have assessed CRF as an objective marker of PA.[21] However, CRF is influenced by other factors, including age, sex, health status and genetics, raising the question of whether PA has similar effects in fit and unfit individuals.

CRF is commonly assessed by time and workload on treadmill or cycle ergometer as a metabolic equivalent of calorie expenditure (MET) or, occasionally, as peak or maximal oxygen consumption (VO_2 peak). Participants usually exercise to at least 85 % of their age-predicted maximum heart rate or to volitional exhaustion.[22] One MET is defined as the energy expended at a resting state, which is equivalent to a body oxygen consumption of approximately 3.5 ml per kilogramme of bodyweight per minute for an average adult, assuming an average surface area for an adult of 1.8 m^2. Thus, a greater amount of total METs achieved during exercise testing represents a higher CRF level. The importance of measuring rather than estimating CRF must be stressed. In a study of cardiac rehabilitation profiles, commonly used prediction equations overestimated aerobic exercise capacity by up to 51 % compared with precise measurements using cardiopulmonary testing.[23]

Although some consider that CRF is simply a more accurate, less-biased estimate of PA, others consider them as independent factors. Several studies suggest that CRF is more important than PA in predicting CV and all-cause mortality.[24,25] A large cohort study (31,818 men and 10,555 women) found that CRF was more strongly associated with all-cause mortality than was PA. The authors concluded that the stronger associations with CRF were most likely due to inherent error and misclassification in self-reported PA.[26] However, a meta-analysis of 23 sex-specific cohorts of PA or CRF (representing 1,325,004 person–years of follow up) attempted to correlate PA and CRF and concluded that while the two are related, there is a poor correlation between PA and CRF, particularly at low fitness levels. The study found a dramatic, steep increase in mortality among patients with very low CRF, where individuals below the 25th percentile of the CRF distribution were at substantially higher risk than those in the higher percentiles.[24] The authors concluded that CRF was a risk factor for mortality, distinct from PA and worthy of screening and intervention. In summary, CRF and PA are related, but are distinct risk factors for health outcomes. Some of the greater strength of association between CRF and health outcomes compared with PA may be attributed to the precision with which it is measured. However, population studies do not always made clear distinctions between CRF and PA, and the two will be discussed in parallel.

The Role of Cardiorespiratory Fitness or Physical Activity in Cardiovascular Mortality in Patients with Type 2 Diabetes

A strong inverse relationship exists between CRF level and CV mortality[27] and studies have shown that every 1-MET increase in treadmill performance was associated with a 12–13 % decrease in mortality.[28,29] The association between low CRF and higher mortality is particularly applicable to patients with type 2 diabetes, who have a substantially elevated risk of CVD and all-cause mortality, and commonly present with a low CRF. Two studies have demonstrated a steep inverse relationship between both PA and CRF and mortality in patients with type 2 diabetes. In a prospective cohort study of 1,263 men with type 2 diabetes, men in the low-CRF group had a 2.1-fold increase in all-cause mortality over 12 years compared with fit men. Men who reported low PA had an adjusted risk of mortality that was 1.7-fold higher than that in men who reported higher PA, independently of weight status.[30] In an observational cohort study of 2,196 men with type 2 diabetes, mortality risk was 4.5-, 2.8- and 1.6-fold higher in the lowest three quartiles of CRF compared with the highest CRF quartile ($p<0.0001$). This inverse relationship was independent of body mass index (BMI).[31]

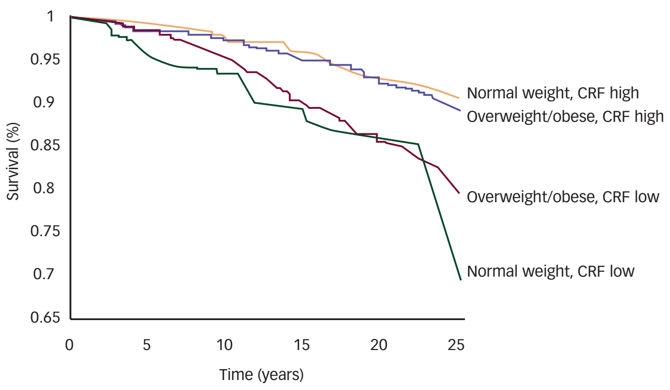
A more recent study examined the association between electrocardiogram (ECG) responses during exercise and mortality in 2,854 men with type 2 diabetes who had no previous CVD event at baseline. Abnormal exercise ECG responses were associated with higher risk of all-cause, CVD and CHD mortality. Compared with the low CRF cohort, all-cause, CVD and CHD mortality was reduced by 54 %, 53 % and 57 %, respectively, in those with moderate CRF and by 66 %, 68 % and 70 %, respectively, in those with high CRF.[32]

The Role of Adiposity in Type 2 Diabetes

Although independent associations have been reported for CRF and obesity in diabetes, the relative contribution of CRF/PA and fatness to the risk of developing type 2 diabetes and mortality and morbidity within type 2 diabetes is controversial. Obesity and CRF are associated, but obese individuals may have a moderate or high level of CRF.[33] A study found that the magnitude of risk of developing type 2 diabetes contributed by obesity is much greater than that imparted by lack of PA.[34] However, whereas some studies of CVD have found no difference between CRF and fatness in predicting mortality,[35,36] several reports from the Aerobics Center Longitudinal Study (ACLS) suggest that CRF can greatly modify the association of adiposity with mortality.

Two large studies have demonstrated the importance of CRF rather than weight as a predictor of mortality. In an observational study of 25,714

Figure 1: Cardiovascular Mortality by Fitness and Obesity Levels in Men with Type 2 Diabetes



CRF = cardiorespiratory fitness. Source: Church et al., 2005.[38]

adult men, low CRF was a strong and independent predictor of CVD and all-cause mortality in all BMI groups.[37] In an 8-year observational study of 21,925 men, unfit (low CRF), normal weight men had double the risk of all-cause mortality compared with fit, normal weight men (relative risk [RR] 2.07; p=0.01). Unfit, normal weight men also had double the risk (RR 2.2; p=0.008) of all-cause mortality compared with fit, obese men. The all-cause mortality rate of fit, obese men was not significantly different from that of fit, normal weight men.[33] The study concluded that health benefits of normal weight are limited to fit men, and that being fit may reduce the hazards of obesity.

The contribution to mortality of CRF compared with weight has also been demonstrated in individuals with type 2 diabetes. A study comprising 2,316 men with no history of stroke or MI and who were diagnosed as having type 2 diabetes found that a low CRF level was associated with a higher risk of CVD mortality within normal weight, overweight and class 1 obese weight categories. A 2.7-fold increased risk of mortality was observed in men with a low CRF level who were normal weight, 2.7-fold risk in overweight men and 2.8-fold increased risk in class 1 obese men compared with normal weight men with a high CRF level (see *Figure 1*).[38]

A more recent review found that the risk of all-cause and CV mortality was lower in individuals with high BMI and good CRF compared with individuals with normal BMI and poor CRF. By contrast, having a high BMI even with high PA was a greater risk of the incidence of type 2 diabetes and the prevalence of CV and type 2 diabetes risk factors compared with normal BMI with low PA.[39]

An analysis of baseline data from Look AHEAD, a study of 5,145 overweight or obese individuals with type 2 diabetes, revealed evidence to suggest that both CRF and fatness influence different CV risk factors. When the CRF and BMI categories were examined together in the same model, CRF had a stronger association than fatness with glycated haemoglobin (HbA_{1c}), ankle/brachial index and Framingham risk score. By contrast, BMI had a stronger association with systolic blood pressure.[40]

Both CRF and fatness are related to the prevention and control of type 2 diabetes.[15–18] However, CRF seems to play a greater role in protecting individuals with type 2 diabetes from CVD. Thus, the primary emphasis on patients with type 2 diabetes should be on improving CRF, rather than reducing weight.

Cardiorespiratory Fitness or Physical Activity in the Primary Prevention of Type 2 Diabetes

There is clear scientific evidence to support the role of regular PA and CRF in the primary prevention of diabetes, though few studies have drawn distinctions between the two as independent risk factors. Studies have focused on increasing PA. In a Finnish study of 2,017 men and 2,352 women, PA was observed to reduce the risk of developing type 2 diabetes in subjects with an excessive BMI and elevated glucose levels.[41] In an observational study of over 87,000 female nurses followed over an average of 8 years, women who reported vigorous ET at least once per week had a significantly lower age and BMI-adjusted risk of developing type 2 diabetes compared with women reporting no ET (RR 0.84; p=0.005).[42] In a population-based cohort study comprising 114,996 men and 92,483 women, the adjusted odds ratio (OR) for new-onset type 2 diabetes in those undertaking regular PA was 0.76 for men and 0.77 for women.[43]

Other studies have assessed CRF as an objective measure of PA in the prevention of type 2 diabetes: in a population-based prospective study of 8,633 men without diabetes, men in the low-CRF group (the least fit 20 % of the cohort) at baseline had a 1.9-fold risk of impaired fasting glucose and a 3.7-fold risk of type 2 diabetes compared with those in the high-CRF group (the most fit 40 % of the cohort; *Figure 2*).[21] Another study of 23,444 men independently assessed CRF and PA: men who participated in a walking/jogging/running programme or a sport/fitness group had a 40 % and 28 % lower risk of developing diabetes compared with sedentary men, respectively (both p<0.05). In the assessment of CRF, moderate and high CRF had a 38 % and 63 % lower risk of developing diabetes compared with the low CRF group (p<0.0001).[15]

Impaired glucose tolerance is an intermediate category between normal glucose tolerance and type 2 diabetes. Individuals with impaired glucose tolerance have an increased risk of type 2 diabetes and therefore form an important target group for studies aimed at preventing diabetes. In a Chinese study involving 577 adults with impaired glucose tolerance, lifestyle intervention involving increased ET led to a 31 % (p<0.03) reduction in the risk of developing type 2 diabetes.[44] In a follow up to this study, it was found that increased ET could prevent or delay type 2 diabetes for up to 14 years after the active intervention.[45] In a study involving 523 subjects with impaired glucose tolerance, a lifestyle intervention involving changes in diet and ET reduced the overall incidence of type 2 diabetes by 58 %.[46] Associations have been found between both PA and CRF in the development of the metabolic syndrome, a known risk factor for type 2 diabetes. The authors concluded that high-risk men participating in recommended levels of PA were less likely to develop the metabolic syndrome than sedentary men. CRF was also a strongly protective factor, although its effect may not be independent of other risk factors.[47]

The type of ET has also been studied in relation to prevention of type 2 diabetes. A recent prospective cohort study of 32,002 men from the Health Professionals Follow-up Study observed from 1990 to 2008 found that resistance ET was associated with a significantly lower risk of type 2 diabetes, independent of aerobic ET. Engaging in resistance or aerobic ET for at least 150 minutes per week was independently associated with a lower risk of type 2 diabetes of 34 % and 52 %, respectively. Men who engaged in both aerobic and weight ET for at least 150 minutes per week had the greatest reduction in type 2 diabetes risk (59 %).[48]

Although obesity and low PA independently contribute to the development of type 2 diabetes, there is evidence to suggest that the magnitude of risk contributed by obesity is greater than that imparted by lack of PA. In a study to examine the individual and joint association of obesity and PA with the development of type 2 diabetes in 68,907 female nurses who had no history of diabetes, CVD or cancer at baseline, 4,030 incident cases of type 2 diabetes were reported in the 16-year study period. The RRs of developing type 2 diabetes were 16.75 for women who were obese (BMI ≥30 kg/m^2) and inactive (exercise <2.1 MET hours/week), 10.74 for women who had high PA but were obese and 2.08 for women who were lean but inactive.[34]

In summary, available evidence suggests a strong role for both CRF and PA in the prevention and delay of onset of type 2 diabetes, with a combination of aerobic and resistance ET showing the strongest reduction in risk. Obesity is also a strong, independent risk factor for the development of type 2 diabetes.

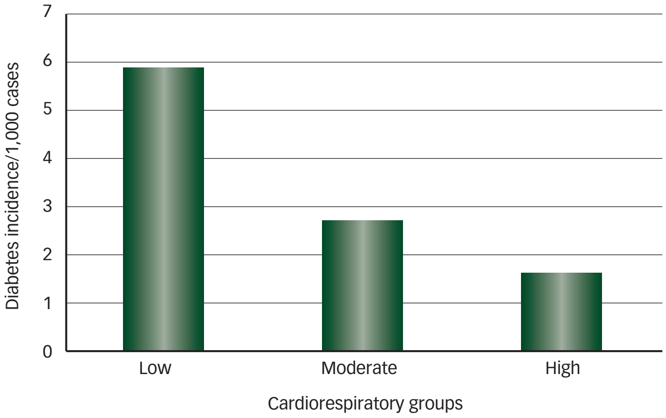
Cardiorespiratory Fitness or Physical Activity in the Control of Type 2 Diabetes

Studies investigating the role of PA and CRF in the control of type 2 diabetes have included different types of PA and several parameters of disease control. HbA_{1c} is the most widely used indicator of glycaemic control in individuals with type 2 diabetes. Even 1 week of aerobic ET can improve whole body insulin sensitivity in individuals with type 2 diabetes.[49] Aerobic and resistance ET have also been shown to improve insulin action,[50] fat oxidation and storage in muscle,[51] as well as other major CVD risk factors.[12]

Comparative studies have shown that aerobic and resistance ET, if maintained over a period of several months, are similarly effective in reducing HbA_{1c} levels in patients with diabetes, but the improvements are greatest with combined aerobic and resistance ET.[52–55] Numerous studies have demonstrated that the combination of aerobic and resistance ET reduces HbA_{1c} levels in type 2 diabetes patients.[53,54,56–58] A randomised controlled trial in which 262 sedentary men and women with type 2 diabetes and HbA_{1c} levels of 6.5 % to 11 % (inclusive) were enrolled in 9 months of either aerobic, resistance or a combination ET programme or a non-exercise control group found that only the combination ET group resulted in significant reductions in HbA_{1c} levels. Furthermore, cumulative benefit across all outcomes (which included measures of anthropometry and fitness.) were greater in the combination training group compared with either aerobic or resistance ET alone.[59]

A recent systematic review found that behavioural interventions increased PA in patients with type 2 diabetes and produced clinically significant improvements in long-term glucose control.[60] The Look AHEAD trial compared an intensive lifestyle intervention with type 2 diabetes support and education on 4-year change in CRF and PA and enrolled 3,942 overweight or obese adults with type 2 diabetes. Participants in the education group received standard care plus information three times per year related to diet, PA and social support. Participants in the intervention group received weekly intervention contact for 6 months that was reduced over the 4-year period. Although the intervention did not reduce the occurrence of MI or strokes during the 4-year study period, a significant difference in CRF between intervention and education groups after adjustment for baseline CRF and change in weight (3.70 versus 0.94 %; p<0.01) was observed. At 4 years, PA increased by 348 kcal/week in the intervention group versus 105 kcal/week in the education group (p<0.01). The change in CRF was also associated with improvements in glycaemic control.[61] In summary, patients with type 2 diabetes may derive substantial benefits from glycaemic control, body composition and CVD risk factors by combining aerobic and resistance ET. As a result, many organisations recommend the combination of aerobic and resistance ET in all adults with type 2 diabetes.[12,55,62]

Figure 2: Type 2 Diabetes Incidence Rates by Fitness Groups



Source: Wei M, et al., Ann Int Med, *1999.*[21]

Box 1: Recommendations of the Exercise is Medicine Initiative in Individuals with Type 2 Diabetes

- Exercise prescriptions must be tailored to a medication schedule and the presence and severity of any diabetic complications, as well as specific goals for your exercise programme.
- For every 1 hour of exercise, consume an additional 15 g of carbohydrates before or after your workout.
- Daily exercise is highly recommended. Minimally, perform moderate–intensity cardiovascular exercise for 20 to 60 minutes at least 4 days per week.
- On 2 days per week, consider doing a lower-resistance, lower-intensity strength-training programme with one set of exercises for the major muscle groups, with 10 to 15 repetitions.
- Start slowly and gradually progress the intensity and duration of your workouts.
- Take frequent breaks during activity if needed.

Source: Exercise is Medicine.[71]

Current Approaches and Future Strategies to Improve Physical Activity

Although nutritional counselling is standard practice in the clinical setting, an individualised prescription for PA is much less likely to occur. Since the lower mortality rates associated with moderate to high CRF are greatest for those with very low baseline CRF, ET should be an achievable goal for most individuals. A report by the American Heart Association concluded that: "The greatest potential for reduced mortality is in the sedentary who become more active."[63] Most policies for promoting PA should therefore aim to move patients out of the least fit, high-risk cohort by increasing PA among the least active.

The overarching goal should be to reverse low PA at the population level. A recent review found that participation in cardiac rehabilitation and ET (CRET) programmes was associated with improvements in CRF, levels of low-density lipoprotein (LDL)-cholesterol, fat distribution, obesity and on the overall level psychological stress, including levels of depression, hostility and anxiety. Furthermore, participation in CRET programmes is associated with lower mortality.[64] The benefits of ET as preventative medicine are not limited to type 2 diabetes. Individuals with adequate levels of PA, about 7 hours per week, based on epidemiological data, would have a 40 % lower risk of premature death compared with those who are active for less than 30 minutes per week.[65] Regular PA or high CRF have been shown to be effective in the prevention of CVD,[66] cancer,[67] HTN,[68] dyslipidaemia,[69] and can benefit cognition and mental health.[70]

In 2007, the American College of Sports Medicine, in collaboration with the American Medical Association, initiated a campaign known as Exercise is Medicine® to promote ET as a health strategy for the general public and to promote collaborations between healthcare providers and ET professionals. The primary aim is to make PA and ET a standard part of a global disease prevention and treatment medical paradigm. Exercise Is Medicine is a programme that encourages healthcare providers to assess and review each patient's PA at every visit. The Exercise Is Medicine recommendations for ET in type 2 diabetes are given in *Box 1*.[71]

Summary and Concluding Remarks

Low PA, low CRF and obesity are associated with a high risk of the development of type 2 diabetes as well as poor glycaemic control and greater CV mortality risk in individuals with type 2 diabetes. Although PA, CRF and obesity are important predictors of developing type 2 diabetes, PA and CRF greatly modify the association of obesity with CVD and mortality. Strategies to reduce CVD and mortality should emphasise increasing PA and undertaking ET that combines aerobic and resistance training. The benefits of ET in the prevention and management of type 2 diabetes are supported by a large body of scientific evidence. It is imperative that individuals with type 2 diabetes or who have risk factors for type 2 diabetes understand the risks of a sedentary lifestyle and the importance of increasing PA and ET in treating and preventing type 2 diabetes. It is also important that clinicians and healthcare systems make as large a commitment to modifying PA behaviours in their patients as they make to adherence to medications. ■

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