Type 2 Diabetes in Singapore: The Role of Exercise Training for its Prevention and Management

J G Lim, H J Kang, K J Stewart

ABSTRACT

The prevalence of type 2 diabetes has been increasing in Singapore and is a major risk factor for cardiovascular disease. Exercise training is an important therapeutic modality for managing glycaemic control and improving cardiovascular health among persons with type 2 diabetes. It may also help to prevent or delay the onset of this harmful condition. This review examines the evidence and possible mechanisms by which exercise training produces these benefits, and gives a brief review of appropriate exercise activities.

Keywords: diabetes mellitus, exercise, metabolic syndrome, pre-diabetes, type 2 diabetes

Singapore Med J 2004 Vol 45(2):62-68

INTRODUCTION

Type 2 diabetes mellitus, a complex metabolic disorder, leads to a variety of complications that include nephropathy, retinopathy, and cerebrovascular and cardiovascular disease. The rapid economic development and the associated adverse lifestyle changes in Singapore have resulted in significant increases in the prevalence of coronary heart disease (CHD), which is now among the top three leading causes of death among Singaporeans[1]. Singapore is similar to other industrialised nations in that diabetes is an important risk factor for the development of CHD. In the Singapore Cardiovascular Cohort Study[2], one-third of patients who developed CHD had type 2 diabetes at baseline. Individuals with type 2 diabetes are also at increased risk of mortality compared with non-diabetics, with heart disease contributing to about three out of every four deaths among persons with diabetes[3].

According to the 1998 National Health Survey (NHS)[4], among Singaporeans aged 18 - 64 years of age, the prevalence of diabetes and impaired glucose tolerance (IGT) was approximately 9% and 15%, respectively. In this survey, 62% of patients diagnosed with diabetes were previously undiagnosed. Globally, this places Singapore among countries with a high rate of diabetes[5]. There are marked ethnic differences in the prevalence of diabetes in Singapore. The highest rate is seen among Indians (15.8%), followed by Malays (11.3%), and is lowest in Chinese (8.0%)[4]. The rate of increase in the prevalence of diabetes is occurring in both sexes and is particularly marked among the Chinese, with the prevalence doubling from 4.7% in 1984 to 8.0% in 1998[4,6,7]. Singaporean Indian (15.8%) and Chinese (8.0%) are also at higher risk of developing diabetes than their counterparts from rural India (2.7%) and China (1.6%)[6].

Several factors may account for the higher prevalence of diabetes in Singapore. Although the molecular basis for type 2 diabetes is still poorly understood, both insulin resistance and beta-cell dysfunction are well documented[8,9] and is likely a result of both environmental influences and genetic factors[10,11]. The ageing population in Singapore, increasing prevalence of obesity and a sedentary lifestyle parallel the rise in diabetes, and are likely contributors to this metabolic abnormality[4].

The National Healthy Lifestyle Programme was launched in 1992, with its principal aim being to promote healthy lifestyles and disease prevention. This programme has resulted in increases in regular exercise rates among Singaporeans (13.6% in 1992 vs 16.9% in 1998) and a leveling off in the prevalence rates of diabetes (8.6% in 1992 vs 9.0% in 1998). However, more than one-half of all Singaporeans still report no leisure time physical activity. The lowest physical activity rates were seen among those aged 30 - 49 years, which is also the age range for which the incidence for development of new onset type 2 diabetes begins to rise rapidly[4]. In addition, obesity rates among Singaporean children are now estimated at about 12%[7]. These prevalence rates of obesity in children will certainly increase the future rate of type 2 diabetes unless sweeping interventions are implemented.

PRE-DIABETES AND METABOLIC SYNDROME

Pre-diabetes refers to a metabolic stage that is intermediate between normal glucose homeostasis and diabetes. These conditions refer to patients who

Department of Medicine
Division of Cardiology
Johns Hopkins Bayview Medical Center
Johns Hopkins University School of Medicine
4940 Eastern Ave
Baltimore, Maryland 21224, USA

J G Lim, MBChB, MRCP
Fellow

H J Kang, MS
Doctoral Student

K J Stewart, EdD
Associate Professor and Director, Johns Hopkins Heart Health

Correspondence to:
Dr Kerry J Stewart
Tel: (410) 550 0870
Fax: (410) 550 7727
Email: kstewart@jhmi.edu

have either impaired fasting glucose (IFG) or impaired glucose tolerance (IGT) (See Table I for diagnostic criteria)[12,13]. Patients with either IGT or IFG have about a 10% risk of developing overt type 2 diabetes over the ensuing 6.5 years[14]. Patients with IFG also have a 40% greater risk of mortality from all causes, even after adjusting for other cardiovascular disease risk factors[15].

Many of the risk factors for cardiovascular disease are known to cluster in certain individuals. This clustering has been called the metabolic syndrome[16], and consists of hypertension, low high-density lipoprotein (HDL) cholesterol levels, high triglyceride levels, high plasma glucose concentrations, and abdominal obesity. The clinical criteria for diagnosis of the metabolic syndrome based on The Third Report of the National Cholesterol Education Program Adult Treatment Panel (ATP III)[17] is shown in Table II. Although the pathophysiological mechanism of the metabolic syndrome has not been fully elucidated, a major underlying abnormality is insulin resistance[16,18,19]. To our knowledge, there are no published data on the prevalence of the metabolic syndrome in Singapore. Although it remains to be determined if the same exact diagnostic criteria as adopted by the ATP III can be applied to our local population, many Singaporeans are clearly at risk for type 2 diabetes and cardiovascular disease.

Exercise and the pre-diabetic state

The evidence for physical inactivity as a risk factor for the development of the metabolic syndrome and type 2 diabetes comes from epidemiological observational studies and prospective intervention trials. Laaksonen et al[20] demonstrated that Finnish men who engaged in more than three hours per week of moderate or vigorous leisure time physical activity were half as likely as their sedentary counterparts to develop the metabolic syndrome over a follow-up period of four years.

A recent study also showed the strong association between sedentary behaviours in relation to the development of obesity and type 2 diabetes among women[21]. During a six-year follow-up period, every two-hour per day increment in television watching was associated with an increased risk of developing obesity by 23% and type 2 diabetes by 14%, respectively. Conversely, each one-hour per day spent doing brisk walking was associated with a reduction in the risk of developing obesity by 24% and type 2 diabetes by 34%, respectively. Hsueh et al[11] showed that the prevalence of type 2 diabetes was lower in the Amish than the general U.S. Caucasian population although the prevalence of IGT was similar. Of note, the more physically active lifestyle of the Amish was a key difference between these populations that could account for the differences in the development of type 2 diabetes. The hypothesis that regular physical activity protects against overt type 2 diabetes is further supported by follow-up glucose tolerance tests two to five years later in more than 100 Amish individuals with IGT [22]. It is thought that the low incidence of progression to the diabetic state was related to the increased physical activity among these individuals.

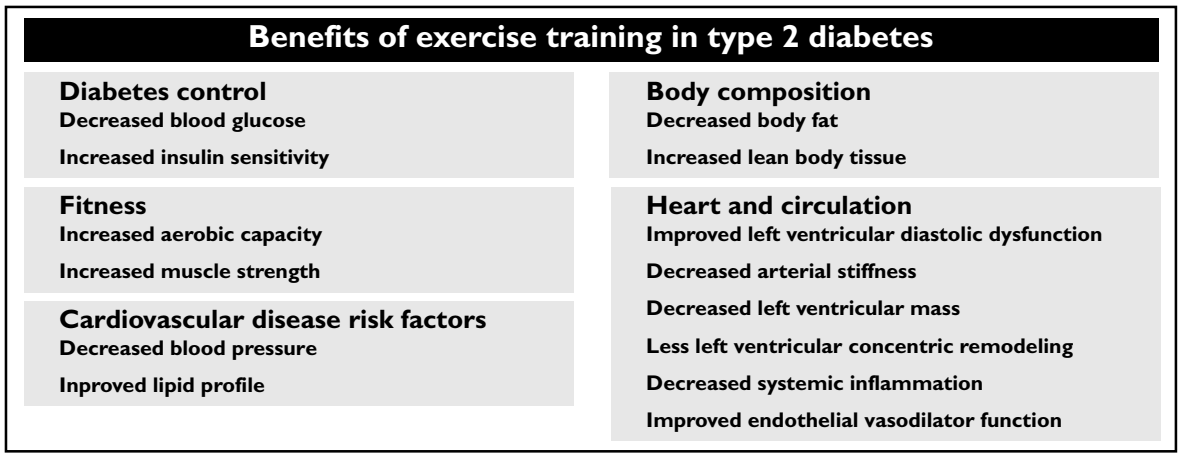
There are also prospective studies that have established the efficacy of lifestyle interventions such as diet and exercise to reduce the incidence of type 2 diabetes amongst people with IGT[23-25]. In the Da Qing study, Pan et al[23] placed subjects on dietary restrictions, an exercise program or both interventions. All of these interventions reduced the incidence of diabetes when compared to a control group. In the Diabetes Prevention Program Research Group Study[25], which enrolled subjects in the United States with IGT, the intensive lifestyle intervention reduced the incidence of developing type 2 diabetes by 58% whereas metformin reduced the incidence by 31%, as compared with placebo. The lifestyle intervention therefore was significantly more effective than metformin. The intensive lifestyle program included at least 30 minutes of moderate physical activity every day.

Among persons with pre-diabetes, exercise can also reduce the risk of cardiovascular mortality. In the Malmo Prevention Trial[26], among patients with IGT who participated in a diet and exercise program, overall mortality during a 12-year follow-up period was similar to patients with normal glucose tolerance (6.5 vs 6.2 per 1,000 person-years) and significantly lower than a matched group of patients with IGT on routine management (6.5 vs 14.0 per 1,000 person-years). Of equal importance was the finding that between the two matched groups of patients with IGT, lifestyle intervention but not body mass index, systolic blood pressure, smoking or cholesterol levels predicted overall mortality. Together, the findings from these large epidemiological and intervention studies highlight the importance of regular exercise and other lifestyle treatments for preventing type 2 diabetes and reducing mortality and morbidity among persons who are at an increased risk of developing the disease.

BENEFICIAL EFFECTS OF EXERCISE ON DIABETES

Physical inactivity and poor physical fitness have been associated with increased mortality among persons with established type 2 diabetes[27]. A recent study by Tanasescu et al[28] demonstrated that physical activity was associated with a reduced risk of both cardiovascular and total mortality among men with type 2 diabetes.

Fig. 1 Mechanisms by which exercise training may improve health in persons with type 2 diabetes.



In addition, there was a 58% reduction in the risk of all-cause mortality when the walking pace was at a rate of 4 mph (6.5 km/h) or higher compared with an easy pace of 2 mph (3.2 km/h). This effect of walking speed was independent of the total number of hours walked per week, suggesting that increased exercise intensity is a determinant of cardiovascular disease risk. There are many plausible ways by which exercise training can improve metabolic and cardiovascular health of persons with type 2 diabetes (Fig. 1).

Exercise and glycaemic control

A meta-analysis of 14 trials found that exercise training reduces haemoglobin A1c levels by 0.66%, and this reduction was independent of changes in body weight[29]. This effect is in part due to long-term adaptations in skeletal muscle, hepatic glucose metabolism and body composition[30], in addition to shorter term changes in glucose transport. Glucose decreases after a single bout of exercise, and this is likely secondary to augmented uptake into skeletal muscles via the increased translocation of GLUT4 glucose transporters to the plasma membrane[31]. It is important to engage in exercise on a frequent basis as favourable changes in glucose tolerance and insulin sensitivity appear to be partially related to the last bout of exercise[32]. It has also been demonstrated that acute exercise enhances insulin stimulated glucose uptake more in trained than untrained muscle, suggesting the importance of regular exercise[30].

Exercise and hypertension

Hypertension is commonly seen in persons with type 2 diabetes. In a population-based survey in Singapore conducted by Hughes et al[33], the prevalence of hypertension among men was found to be 43% in those with type 2 diabetes, compared to 21% without the condition. Among women, the prevalence of hypertension was 57% versus 24%, respectively. The sixth report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure[34] concluded that diabetes increases cardiovascular disease risk at any stage of hypertension. In the United Kingdom Prospective Diabetes Study (UKPDS) trials, blood pressure reduction resulted in a significant benefit on cardiovascular disease risk reduction over and above that achieved by tight glycaemic control[35]. The role of exercise in the management of patients with hypertension is well documented[36]. Although there are no randomised clinical trials examining the efficacy of exercise to reduce blood pressure in persons with type 2 diabetes, it is likely that exercise training would produce benefits in such patients[36].

Exercise and left ventricular function

Type 2 diabetes is associated with abnormalities in left ventricular diastolic function[37]. Increased glucose levels, even when they fall below the threshold for the diagnosis of type 2 diabetes, was independently associated with impaired left ventricular diastolic function[38]. Exercise training has been shown to improve diastolic filling in animal models[39], among hypertensive persons[40] and reverses age-related diastolic filling patterns[41]. Although it can be expected that exercise training would also improve left ventricular diastolic dysfunction among persons with type 2 diabetes, further randomised studies in this area are needed to confirm this view.

Exercise and endothelial function

Impaired endothelial function is a common finding among patients with type 2 diabetes and pre-diabetes[42,43]. Impaired endothelial vasodilator function in the coronary arteries and micro-vasculature may be an important contributor to myocardial ischaemia. Exercise has been shown to reduce myocardial perfusion defects in patients with CAD, even in the absence of significant plaque regression, and this is believed to be secondary to improved endothelial function[44].

Table I. Criteria for diagnosis of diabetes mellitus (Clinical Practice Guidelines: Diabetes Mellitus, Ministry of Health, Singapore, 1999).

Classification	Normal	Impaired Fasting Glucose (IFG)	Impaired Glucose Tolerance (IGT)	Diabetes
Fasting	<6.1 mmol/L	6.1 to <7.0 mmol/L	6.1 to <7.0 mmol/L	≥7.0 mmol/L
2 hours (after 75 g glucose load)	<7.8 mmol/L	<7.8 mmol/L	7.8 to <11.1 mmol/L	≥11.1 mmol/L or Casual glucose level ≥11.1 mmol/L and symptoms

For asymptomatic individuals who have plasma glucose in the diabetic range, a second glucose sample should be measured on a separate occasion in order to confirm the diagnosis of diabetes mellitus.

Table II. Definition of metabolic syndrome (based on NCEP ATP III).

Individuals with three or more of the following are defined as having the metabolic syndrome

1. Abdominal obesity. Waist circumference >102 cm in men and >88 cm in women
2. Hypertriglyceridaemia >1.69 mmol/L
3. Low high density lipoprotein (HDL). Men <1.04 mmol/L and women <1.29 mmol/L
4. Hypertension. Blood pressure >130/85 mmHg
5. High fasting glucose >6.1 mmol/L

Studies which utilise changes in reactive hyperaemic brachial artery vasodilatation as an index of endothelial health have shown that exercise training restores endothelial function among subjects with type 2 diabetes as well as those with the metabolic syndrome[45,46]. Hosokawa et al[47] measured coronary endothelial function directly by infusing acetylcholine into the coronary arteries of patients (both diabetic and non-diabetic) who had suffered a recent myocardial infarction. They also measured artery diameter by contrast angiography. They demonstrated that six months of exercise training improved coronary endothelial response to acetylcholine, independent of type 2 diabetes, smoking status, use of statins or calcium channel blockers, and lipid lowering. Exercise-induced improvements in endothelial function are thought to be secondary to the elevated shear stress that occurs during exercise on vessel walls, which results in up-regulation of endothelium-derived nitric oxide, leading to improved smooth muscle relaxation and vasodilatation.

EXERCISE AND OBESITY

Obesity, and especially intra-abdominal fat, is strongly associated with insulin resistance, glucose intolerance, diabetes mellitus and is a growing problem in Singapore[48]. Contributory to this is the westernisation of traditional Asian diets, with fruits, vegetables, and whole grains being replaced by readily-accessible fast foods, which are high in saturated fat, sugars and refined carbohydrates. The 1998 Singapore NHS[4] (based on WHO criteria[49]) found that among adults (aged 18 - 64), 24.4% were overweight (Body mass index (BMI) ≥25) and 6% were obese (BMI ≥30). However, Deurenberg-Yap et al [50,51], showed that Singaporeans have a higher percentage body fat for the same BMI as Caucasians. Even among Singaporeans with a BMI of 22 -24, which would be classified as normal by WHO criteria, the prevalence of diabetes was increased over those with a BMI <22 in both sexes (In men 4.6% vs 2.5%, in women 7.1% vs 2.9%). The authors have therefore recommended different cut-off points from the WHO definition, with overweight being defined as a BMI ≥23 and obesity being defined as a BMI of ≥27. This definition would increase the prevalence of obesity in Singapore to over 15% (compared to 6% based on WHO criteria).

Among Singaporeans who have already developed type 2 diabetes, their BMI, waist hip ratio and abdominal girth were also found to be significantly higher than in persons without diabetes[33]. Of concern is the finding that intra-abdominal obesity in persons with type 2 diabetes is independently associated with increased coronary artery calcium scores on electron-beam computed tomographic studies[52], which suggests a higher burden of atherosclerotic coronary disease. In an observational study of overweight diabetics by Williamson et al[53], intentional weight loss resulted in a 25% lower total mortality and a 28% reduction in cardiovascular and diabetes-related mortality. The greatest mortality reduction (of 33%) was seen among subjects who lost 10 - 15% of their initial weight.

In a randomised controlled trial, Irwin et al[54] examined the effects of regular aerobic exercise without significant dietary modification in previously sedentary middle-aged women. After 12 months, persons in the exercise intervention had modest decreases in body weight (-1.3 kg vs + 0.1 kg from baseline) and considerable reductions in intra-abdominal fat (-8.5 g/cm^2 vs + 0.1 g/cm^2 from baseline), compared to controls. There was also a significant dose response for greater fat loss with increasing amounts of exercise. Progressive resistance training has also been shown to

result in improvements in body composition. Twice-weekly resistance training without additional aerobic activity for a period of six months has been shown to result in improvements in body composition (increases in fat free mass and decreases in percent body fat), even though total body weight remained the same[55].

Exercise and inflammation

Obese persons have been found to have higher levels of high sensitivity-C reactive protein (CRP)[56]. Adipose tissue is an important source of cytokines, called adipokines, which contribute to systemic and vascular inflammation[57]. This in turn results in endothelial dysfunction, increased atherosclerotic risk and insulin resistance. Studies have shown that CRP levels are associated with many components of the metabolic syndrome[58] and predict risk of development of type 2 diabetes[59]. Kopp et al[60] demonstrated that significant weight loss among obese individuals resulted in a parallel decreases in both insulin resistance and CRP levels. Studies among non-diabetic populations have shown that regular exercise results in lower concentrations of several inflammatory markers[61,62]. Although there is no direct evidence yet that exercise training reduces inflammatory levels amongst diabetics, exercise-induced weight loss is a plausible mechanism by which inflammation could be attenuated.

Exercise and lipoproteins

In Singapore, fasting serum triglycerides, but not HDL and LDL cholesterol levels, were found to be higher among persons with type 2 diabetes than in those without diabetes[33]. However, patients with type 2 diabetes have a dyslipidaemia characterised by increases in atherogenic small dense LDL sub-fractions and decreases in HDL-2 cholesterol. Exercise training results in improvement of the LDL sub-fractions, with a decrease in the small dense particles[63], and may therefore protect against CHD, despite a lack of reduction of total or LDL cholesterol. Because the amount of exercise training rather than the intensity of exercise may be a more important determinant of improvements in lipids, it is important for patients to engage in frequent and regular exercise[64].

Exercise and PPARs

The peroxisome proliferator-activated receptors (PPARs) are ligand-activated receptors that control gene expression[65]. PPARs modulate risk factors associated with the metabolic syndrome[66]. Three isoforms are described, namely: PPARα, PPARδ and PPARγ. PPARα is the receptor for the action of fibrates, which results in lowering of LDL cholesterol, triglycerides and elevation of HDL cholesterol. PPARγ is the receptor for the thiazolidinedione class of drugs (glitazones), which results in recovery of insulin sensitivity among type 2 diabetics[65]. Limited studies have shown that exercise training may result in up-regulation of PPARα. Horowitz et al[67] demonstrated that 12 weeks of endurance training resulted in increased skeletal muscle PPARα protein content among women. In an animal study by Iemtisu[68], ageing induced decreases in PPARα levels in senescent rats were improved by exercise training. Additional research in this area is needed but these recent findings suggest that increased PPAR expression and action may be an additional and important beneficial feature of the exercise training response.

PRESCRIBING EXERCISE

Patient evaluation

Both the American Diabetes Association and the ATP III guidelines consider diabetes as a coronary artery disease risk equivalent. The prevalence of silent myocardial ischaemia in persons with type 2 diabetes can be as high as 20 - 25%, especially amongst those over the age of 65 years[69], if the duration of diabetes exceeds 10 years and if there is the presence of other cardiovascular risk factors[70]. The Singapore Clinical Practice Guidelines on Diabetes Mellitus[12] suggest that a graded exercise test with electrocardiographic monitoring should be performed in patients over 40 years of age and/or with high risk of coronary heart disease, before participation in a moderate to vigorous intensity physical activity program.

Exercise prescription

A review of exercise training guidelines and precautions for persons with diabetes can be found in the Clinical Practice Guidelines on Diabetes Mellitus published by the Ministry of Health[12]. In addition, both the American Diabetes Association[71] and the American College of Sports Medicine[72] advise a combination of both aerobic and resistive training as part of the exercise prescription for most afflicted persons. Although resistive exercise is often neglected in such exercise programs, this mode of exercise is generally safe and improves HBA1C levels and increases lean body mass[73,74].

Among frail elderly patients, aerobic type exercises may not be practical, due to concomitant cardiovascular and arthritic limitations. In these instances, light intensity resistance exercises can be a safe and effective alternative. Among such patients, resistance training has additional benefits aside from improving insulin sensitivity and glycaemic control, including enhancing strength, mobility and counteracting age related sarcopenia[75]. In terms of the amount of exercise to be performed, a goal of a 1,000 kcal/week expended in aerobic-type exercise is considered to be a minimum for reducing cardiovascular disease risk whereas the expenditure of more calories is required to produce significant weight loss[76].

Factors such as a person's initial level of fitness, age, other co-morbidities and goals must be considered when formulating an exercise prescription. When progressing the level of exercise as the individual improves, the duration and frequency of exercise should be increased first. Any increases in intensity should be done more gradually so as to minimise the risk of injury, pain, non-compliance and complications. Since the majority of cardiovascular benefit occurs at moderately-intense exercise levels, higher intensity levels of exercise are probably unnecessary.

CONCLUSION

Exercise training is an essential component in both the medical management of patients with type 2 diabetes and in preventing the development of diabetes among those at risk. Exercise contributes to glycaemic control and blood pressure reduction, and may improve several of the cardiovascular consequences of type 2 diabetes such as impaired endothelial function and left ventricular diastolic dysfunction. It is particularly important for physicians to recognise patients at risk of diabetes or those who have already developed the pre-diabetic state, as intervention in terms of exercise and other lifestyle changes will reap the greatest benefits at this stage.

Despite the preponderance of evidence of the benefits for exercise, there is still a lack of participation among patients who are at risk of or who have type 2 diabetes. The reasons for the under-participation in regular exercise include patients' lack of knowledge about the benefits of exercise, a lack of motivation, and a lack of clear recommendations from health care professionals. Clinicians should view the need to encourage such patients to exercise regularly as an essential part of management of their condition. Specific instructions should be given to patients rather than general advice, which does not increase compliance. Furthermore, there are exercise programs available in most hospitals in Singapore. These can be a useful way to introduce patients to exercise and in so doing, act as a springboard for patients to initiate their own exercise program in the long term. One such resource is the cardiac rehabilitation program, which will be an ideal setting for initiating exercise for such patients.

While a great amount of resources and attention have centered on "gene" therapy, this mode of therapy holds promise for future generations and is not yet ready for "prime-time". On the other hand "gym" therapy, which is cost effective and widely available, should be implemented as part of standard management of such patients.

REFERENCES

1. Health Facts Singapore 2002, Principle causes of death. Ministry of Health, Singapore.
2. Lee J, Heng D, Chia KS, Chew SK, Tan BY, Hughes K. Risk factors and incident coronary heart disease in Chinese, Malay and Asian Indian males: the Singapore Cardiovascular Cohort Study. Int J Epidemiol 2001; 30:983-8.
3. Muller WA. Diabetes mellitus: long time survival. J Insur Med 1998; 30:17-27.
4. National Health Survey 1998. Ministry of Health, Singapore.
5. Zimmet PZ, McCarty DJ, de Courten MP. The global epidemiology of non-insulin-dependent diabetes mellitus and the metabolic syndrome. J Diabetes Complications 1997; 11:60-8.
6. Tan CE, Emmanuel SC, Tan BY, Jacob E. Prevalence of diabetes and ethnic differences in cardiovascular risk factors. The 1992 Singapore National Health Survey. Diabetes Care 1999; 22:241-7.
7. Lee WR. The changing demography of diabetes mellitus in Singapore. Diabetes Res Clin Pract 2000; 50 Suppl 2:S35-9.
8. Porte D, Jr., Kahn SE. Mechanisms for hyperglycemia in type II diabetes mellitus: therapeutic implications for sulfonylurea treatment – an update. Am J Med 1991; 90:8S-14S.
9. Kahn CR. Banting Lecture. Insulin action, diabetogenes, and the cause of type II diabetes. Diabetes 1994; 43:1066-84.
10. Kahn CR, Vicent D, Doria A. Genetics of non-insulin-dependent (type-II) diabetes mellitus. Annu Rev Med 1996; 47:509-31.
11. Hsueh WC, Mitchell BD, Aburomia R, Pollin T, Sakul H, Gelder Ehm M, et al. Diabetes in the Old Order Amish: characterization and heritability analysis of the Amish Family Diabetes Study. Diabetes Care 2000; 23:595-601.
12. Clinical Practice Guidelines: Diabetes Mellitus. Ministry of Health, Singapore, 1999.
13. Report of the expert committee on the diagnosis and classification of diabetes mellitus. Diabetes Care 2003; 26 Suppl 1:S5-20.
14. de Vegt F, Dekker JM, Jager A, Hienkens E, Kostense PJ, Stehouwer CD, et al. Relation of impaired fasting and postload glucose with incident type 2 diabetes in a Dutch population: The Hoorn Study. JAMA 2001; 285:2109-13.
15. Saydah SH, Loria CM, Eberhardt MS, Brancati FL. Subclinical states of glucose intolerance and risk of death in the U.S. Diabetes Care 2001; 24:447-53.
16. Brotman DJ, Girod JP. The metabolic syndrome: a tug-of-war with no winner. Cleve Clin J Med 2002; 69:990-4.
17. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). JAMA 2001; 285:2486-97.
18. Ferrannini E, Haffner SM, Mitchell BD, Stern MP. Hyperinsulinaemia: the key feature of a cardiovascular and metabolic syndrome. Diabetologia 1991; 34:416-22.
19. DeFronzo RA, Ferrannini E. Insulin resistance. A multifaceted syndrome responsible for NIDDM, obesity, hypertension, dyslipidemia, and atherosclerotic cardiovascular disease. Diabetes Care 1991; 14:173-94.
20. Laaksonen DE, Lakka HM, Salonen JT, Niskanen LK, Rauramaa R, Lakka TA. Low levels of leisure-time physical activity and cardiorespiratory fitness predict development of the metabolic syndrome. Diabetes Care 2002; 25:1612-8.
21. Hu FB, Li TY, Colditz GA, Willett WC, Manson JE. Television watching and other sedentary behaviors in relation to risk of obesity and type 2 diabetes mellitus in women. JAMA 2003; 289:1785-91.
22. Snitker S, Mitchell BD, Shuldiner AR. Physical activity and prevention of type 2 diabetes. Lancet 2003; 361:87-8.
23. Pan XR, Li GW, Hu YH, Wang JX, Yang WY, An ZX, et al. Effects of diet and exercise in preventing NIDDM in people with impaired glucose tolerance. The Da Qing IGT and Diabetes Study. Diabetes Care 1997; 20:537-44.
24. Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med 2002; 346:393-403.
25. Tuomilehto J, Lindstrom J, Eriksson JG, Valle TT, Hamalainen H, Ilanne-Parikka P, et al. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. N Engl J Med 2001; 344:1343-50.
26. Eriksson KF, Lindgarde F. No excess 12-year mortality in men with impaired glucose tolerance who participated in the Malmo Preventive Trial with diet and exercise. Diabetologia 1998; 41:1010-6.
27. Wei M, Gibbons LW, Kampert JB, Nichaman MZ, Blair SN. Low cardiorespiratory fitness and physical inactivity as predictors of mortality in men with type 2 diabetes. Ann Intern Med 2000; 132:605-11.
28. Tanasescu M, Leitzmann MF, Rimm EB, Hu FB. Physical activity in relation to cardiovascular disease and total mortality among men with Type 2 diabetes. Circulation 2003; 107:2435-9.

29. Boule NG, Haddad E, Kenny GP, Wells GA, Sigal RJ. Effects of exercise on glycemic control and body mass in type 2 diabetes mellitus: a meta-analysis of controlled clinical trials. JAMA 2001; 286:1218-27.
30. Borghouts LB, Keizer HA. Exercise and insulin sensitivity: a review. Int J Sports Med 2000; 21:1-12.
31. Dela F, Ploug T, Handberg A, Petersen LN, Larsen JJ, Mikines KJ, et al. Physical training increases muscle GLUT4 protein and mRNA in patients with NIDDM. Diabetes 1994; 43:862-5.
32. Schneider SH, Amorosa LF, Khachadurian AK, Ruderman NB. Studies on the mechanism of improved glucose control during regular exercise in type 2 (non-insulin-dependent) diabetes. Diabetologia 1984; 26:355-60.
33. Hughes K, Choo M, Kuperan P, Ong CN, Aw TC. Cardiovascular risk factors in non-insulin-dependent diabetics compared to non-diabetic controls: a population-based survey among Asians in Singapore. Atherosclerosis 1998; 136:25-31.
34. The sixth report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure. Arch Intern Med 1997; 157:2413-46.
35. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. UK Prospective Diabetes Study Group. Br Med J 1998; 317:703-13.
36. Stewart KJ. Exercise training and the cardiovascular consequences of type 2 diabetes and hypertension: plausible mechanisms for improving cardiovascular health. JAMA 2002; 288:1622-31.
37. Uusitupa MI, Mustonen JN, Airaksinen KE. Diabetic heart muscle disease. Ann Med 1990; 22:377-86.
38. Holzmann M, Olsson A, Johansson J, Jensen-Urstad M. Left ventricular diastolic function is related to glucose in a middle-aged population. J Intern Med 2002; 251:415-20.
39. Brenner DA, Apstein CS, Saupe KW. Exercise training attenuates age-associated diastolic dysfunction in rats. Circulation 2001; 104:221-6.
40. Kelemen MH, Effron MB, Valenti SA, Stewart KJ. Exercise training combined with antihypertensive drug therapy. Effects on lipids, blood pressure, and left ventricular mass. JAMA 1990; 263:2766-71.
41. Forman DE, Manning WJ, Hauser R, Gervino EV, Evans WJ, Wei JY. Enhanced left ventricular diastolic filling associated with long-term endurance training. J Gerontol 1992; 47:M56-8.
42. Williams SB, Cusco JA, Roddy MA, Johnstone MT, Creager MA. Impaired nitric oxide-mediated vasodilation in patients with non-insulin-dependent diabetes mellitus. J Am Coll Cardiol 1996; 27:567-74.
43. Caballero AE, Arora S, Saouaf R, Lim SC, Smakowski P, Park JY, et al. Microvascular and macrovascular reactivity is reduced in subjects at risk for type 2 diabetes. Diabetes 1999; 48:1856-62.
44. Gielen S, Hambrecht R. Effects of exercise training on vascular function and myocardial perfusion. Cardiol Clin 2001; 19:357-68.
45. Maiorana A, O'Driscoll G, Cheetham C, Dembo L, Stanton K, Goodman C, et al. The effect of combined aerobic and resistance exercise training on vascular function in type 2 diabetes. J Am Coll Cardiol 2001; 38:860-6.
46. Lavrencic A, Salobir BG, Keber I. Physical training improves flow-mediated dilation in patients with the polymetabolic syndrome. Arterioscler Thromb Vasc Biol 2000; 20:551-5.
47. Hosokawa S, Hiasa Y, Takahashi T, Itoh S. Effect of regular exercise on coronary endothelial function in patients with recent myocardial infarction. Circ J 2003; 67:221-4.
48. Pi-Sunyer FX. Comorbidities of overweight and obesity: current evidence and research issues. Med Sci Sports Exerc 1999; 31:S602-8.
49. WHO. Obesity: Preventing and managing the global epidemic. Report of a WHO consultation on obesity, Geneva, 3-5 June 1997. Geneva: WHO, 1998.
50. Deurenberg-Yap M, Chew SK, Deurenberg P. Elevated body fat percentage and cardiovascular risks at low body mass index levels among Singaporean Chinese, Malays and Indians. Obes Rev 2002; 3:209-15.
51. Deurenberg-Yap M, Schmidt G, van Staveren WA, Deurenberg P. The paradox of low body mass index and high body fat percentage among Chinese, Malays and Indians in Singapore. Int J Obes Relat Metab Disord 2000; 24:1011-7.
52. Arad Y, Newstein D, Cadet F, Roth M, Guerci AD. Association of multiple risk factors and insulin resistance with increased prevalence of asymptomatic coronary artery disease by an electron-beam computed tomographic study. Arterioscler Thromb Vasc Biol 2001; 21:2051-8.
53. Williamson DF, Thompson TJ, Thun M, Flanders D, Pamuk E, Byers T. Intentional weight loss and mortality among overweight individuals with diabetes. Diabetes Care 2000; 23:1499-504.
54. Irwin ML, Yasui Y, Ulrich CM, Bowen D, Rudolph RE, Schwartz RS, et al. Effect of exercise on total and intra-abdominal body fat in postmenopausal women: a randomized controlled trial. JAMA 2003; 289:323-30.
55. Schmitz KH, Jensen MD, Kugler KC, Jeffery RW, Leon AS. Strength training for obesity prevention in midlife women. Int J Obes Relat Metab Disord 2003; 27:326-33.
56. Yudkin JS, Stehouwer CD, Emeis JJ, Coppack SW. C-reactive protein in healthy subjects: associations with obesity, insulin resistance, and endothelial dysfunction: a potential role for cytokines originating from adipose tissue? Arterioscler Thromb Vasc Biol 1999; 19:972-8.
57. Lyon CJ, Law RE, Hsueh WA. Minireview: adiposity, inflammation, and atherogenesis. Endocrinology 2003; 144:2195-200.
58. Tamakoshi K, Yatsuya H, Kondo T, Hori Y, Ishikawa M, Zhang H, et al. The metabolic syndrome is associated with elevated circulating C-reactive protein in healthy reference range, a systemic low-grade inflammatory state. Int J Obes Relat Metab Disord 2003; 27:443-9.
59. Pradhan AD, Manson JE, Rifai N, Buring JE, Ridker PM. C-reactive protein, interleukin 6, and risk of developing type 2 diabetes mellitus. JAMA 2001; 286:327-34.
60. Kopp HP, Kopp CW, Festa A, Krzyzanowska K, Kriwanek S, Minar E, et al. Impact of Weight Loss on Inflammatory Proteins and Their Association With the Insulin Resistance Syndrome in Morbidly Obese Patients. Arterioscler Thromb Vasc Biol 2003.
61. Geffken DF, Cushman M, Burke GL, Polak JF, Sakkinen PA, Tracy RP. Association between physical activity and markers of inflammation in a healthy elderly population. Am J Epidemiol 2001; 153:242-50.
62. Mattusch F, Dufaux B, Heine O, Mertens I, Rost R. Reduction of the plasma concentration of C-reactive protein following nine months of endurance training. Int J Sports Med 2000; 21:21-4.
63. Halle M, Berg A, Garwers U, Baumstark MW, Knisel W, Grathwohl D, et al. Influence of 4 weeks' intervention by exercise and diet on low-density lipoprotein subfractions in obese men with type 2 diabetes. Metabolism 1999; 48:641-4.
64. Kraus WE, Houmard JA, Duscha BD, Knetzger KJ, Wharton MB, McCartney JS, et al. Effects of the amount and intensity of exercise on plasma lipoproteins. N Engl J Med 2002; 347:1483-92.
65. Vamecq J, Latruffe N. Medical significance of peroxisome proliferator-activated receptors. Lancet 1999; 354:141-8.
66. Barbier O, Torra IP, Duguay Y, Blanquart C, Fruchart JC, Glineur C, et al. Pleiotropic actions of peroxisome proliferator-activated receptors in lipid metabolism and atherosclerosis. Arterioscler Thromb Vasc Biol 2002; 22:717-26.
67. Horowitz JF, Leone TC, Feng W, Kelly DP, Klein S. Effect of endurance training on lipid metabolism in women: a potential role for PPARalpha in the metabolic response to training. Am J Physiol Endocrinol Metab 2000; 279:E348-55.
68. Iemitsu M, Miyauchi T, Maeda S, Tanabe T, Takanashi M, Irukayama-Tomobe Y, et al. Aging-induced decrease in the PPAR-alpha level in hearts is improved by exercise training. Am J Physiol Heart Circ Physiol 2002; 283:H1750-60.
69. Inoguchi T, Yamashita T, Umeda F, Mihara H, Nakagaki O, Takada K, et al. High incidence of silent myocardial ischemia in elderly patients with non insulin-dependent diabetes mellitus. Diabetes Res Clin Pract 2000; 47:37-44.
70. Janand-Delenne B, Savin B, Habib G, Bory M, Vague P, Lassmann-Vague V. Silent myocardial ischemia in patients with diabetes: who to screen. Diabetes Care 1999; 22:1396-400.
71. American Diabetes Association: Diabetes mellitus and exercise (Position Statement). Diabetes Care 2000; 23 Suppl 1:S50 -54.
72. Albright A, Franz M, Hornsby G, Kriska A, Marrero D, Ullrich I, et al. American College of Sports Medicine position stand. Exercise and type 2 diabetes. Med Sci Sports Exerc 2000; 32:1345-60.
73. Dunstan DW, Daly RM, Owen N, Jolley D, De Courten M, Shaw J, et al. High-intensity resistance training improves glycemic control in older patients with type 2 diabetes. Diabetes Care 2002; 25:1729-36.
74. Castaneda C, Layne JE, Munoz-Orians L, Gordon PL, Walsmith J, Foldvari M, et al. A randomized controlled trial of resistance exercise training to improve glycemic control in older adults with type 2 diabetes. Diabetes Care 2002; 25:2335-41.
75. Willey KA, Singh MA. Battling Insulin Resistance in Elderly Obese People With Type 2 Diabetes: Bring on the heavy weights. Diabetes Care 2003; 26:1580-8.
76. Fletcher GF, Balady G, Blair SN, Blumenthal J, Caspersen C, Chaitman B, et al. Statement on exercise: benefits and recommendations for physical activity programs for all Americans. A statement for health professionals by the Committee on Exercise and Cardiac Rehabilitation of the Council on Clinical Cardiology, American Heart Association. Circulation 1996; 94:857-62.