

## Review

# Evidence for prescribing exercise as therapy in chronic disease

B. K. Pedersen<sup>1,2</sup>, B. Saltin<sup>2</sup>

<sup>1</sup>The Centre of Inflammation and Metabolism, Department of Infectious Diseases, <sup>2</sup>The Copenhagen Muscle Research Centre, Rigshospitalet, Faculty of Health Sciences, University of Copenhagen, Copenhagen, Denmark.

Corresponding author: Bente Klarlund Pedersen, Centre of Inflammation and Metabolism, Rigshospital–Section 7641, Blegdamsvej 9, DK-2100, Copenhagen, Denmark. Tel: 45 35 45 77 97, Fax: 45 35 45 76 44, E-mail: bkp@rh.dk

Accepted for publication 12 December 2005

Considerable knowledge has accumulated in recent decades concerning the significance of physical activity in the treatment of a number of diseases, including diseases that do not primarily manifest as disorders of the locomotive apparatus. In this review we present the evidence for prescribing exercise therapy in the treatment of metabolic syndrome-related disorders (insulin resistance, type 2 diabetes, dyslipidemia, hypertension, obesity), heart and pulmonary diseases (chronic obstructive pulmonary disease, coronary heart disease, chronic heart failure, intermittent claudica-

tion), muscle, bone and joint diseases (osteoarthritis, rheumatoid arthritis, osteoporosis, fibromyalgia, chronic fatigue syndrome) and cancer, depression, asthma and type 1 diabetes. For each disease, we review the effect of exercise therapy on disease pathogenesis, on symptoms specific to the diagnosis, on physical fitness or strength and on quality of life. The possible mechanisms of action are briefly examined and the principles for prescribing exercise therapy are discussed, focusing on the type and amount of exercise and possible contraindications.

Over the past decades, considerable knowledge has accumulated concerning the significance of exercise in the treatment of a number of diseases, including diseases that do not primarily manifest as disorders of the locomotive apparatus. Today, exercise is indicated in the treatment of a large number of medical disorders (Oldridge, 2003; Roberts & Barnard, 2005). In the medical world, it is traditional to prescribe the evidence-based treatment known to be the most effective and entailing the fewest side effects or risks. The evidence suggests that in selected cases exercise therapy is just as effective as medical treatment – and in special situations more effective – or adds to the effect. In this context, exercise therapy does not represent a paradigm change – it is rather that the accumulated knowledge is now so extensive that it has to be implemented.

In selecting diagnoses for inclusion in this review, we have taken into account both the frequency of the diseases and the relative need for exercise therapy. Borderline cases exist between physical training as prophylaxis and physical training as actual therapy. The review includes diagnoses for which there is a tradition or consensus to offer pharmacotherapy, for example hypertension, hyperlipidemia, insulin resistance and obesity. We exclusively describe the foundation for exercise therapy in the form of endurance training, metabolic training or strength conditioning. Thus, the review does not examine other forms of

therapy such as pharmacotherapy, dietary modification or smoking cessation. The aim of this review is to provide the evidence for exercise as therapy. We also suggest how such therapy can be prescribed. However, the specific recommendations are only evidence-based for some few diseases. Nevertheless, based on evidence, experience and common sense, we have included suggestions for specific training modes in an attempt to make this review also of practical use.

## Methods

A comprehensive literature search was carried out for each diagnosis in the Cochrane Library and MEDLINE databases (search terms: exercise therapy, training, physical fitness, physical activity, rehabilitation and aerobic). In addition, we sought literature by examining reference lists in original articles and reviews. We have primarily identified systematic reviews and thereafter identified additional controlled trials. We then selected studies in which the intervention was aerobic exercise or strength conditioning and have accorded priority to randomized-controlled trials. Non-controlled trials and controlled trials in which the randomization was uncertain have been included in cases where the other literature was sparse, or where these studies contained important information, for example concerning the form of exercise. Exercise therapy can have clinical effects, either by directly affecting the disease pathogenesis (e.g. intermittent claudication, coronary heart disease) by improving dominant symptoms of the underlying disease (e.g. chronic obstructive pulmonary disease) or

by enhancing physical fitness, strength and hence quality of life in patients weakened by disease (e.g. cancer). The goal is that all patients should exercise so that they benefit from the positive effect of prevention of other diseases. It was considered important to emphasize the strength of the scientific evidence. The review of each diagnosis thus includes a figure grading the evidence for physical exercise: A = strong scientific documentation, i.e. many relevant studies of high quality are available; B = moderate scientific documentation, i.e. at least one study of high quality or several of moderate quality are available; C = limited scientific documentation, i.e. at least one relevant study of moderate quality is available; and D = no scientific documentation for (1) effects on disease pathogenesis, (2) symptoms specific to the diagnosis, (3) physical fitness or strength or (4) quality of life.

**Metabolic syndrome-related disorders**

**Insulin resistance (Fig. 1)**

*Background*

Insulin resistance causes impaired glucose tolerance. 40% of persons with impaired glucose tolerance develop type 2 diabetes within 5–10 years, while some will remain insulin resistant and others will regain normal glucose tolerance. The frequency of other risk factors, e.g. overweight, hypertension and dyslipidemia, is high in patients with impaired glucose tolerance (Kannel & McGee, 1979; Goldbourt et al., 1993; Stamler et al., 1993). Moreover, impaired glucose tolerance is associated with a high prevalence of coronary heart disease.

*Evidence for physical training*

Few studies have examined the isolated effect of training on the prevention of diabetes in patients with impaired glucose tolerance, but there is good evidence for a beneficial effect of combined physical training and dietary modification. A Chinese study (Pan et al., 1997) subdivided 577 persons with impaired glucose tolerance into four groups: diet alone, physical exercise, diet+physical exercise and

control, and followed them for 6 years. The risk of diabetes was reduced by 31% ( $P < 0.03$ ) in the diet group, by 46% ( $P < 0.0005$ ) in the exercise group and by 42% ( $P < 0.005$ ) in the diet+exercise group.

In a Swedish study, 6956 men aged 48 years underwent health screening. Persons with impaired glucose tolerance were subdivided into two groups: (1) Diet+exercise ( $n = 288$ ) or (2) Routine treatment ( $n = 135$ ), and followed for 12 years (Eriksson & Lindgarde, 1998). The mortality rate was the same in the intervention group as in the men in the study who had normal glucose tolerance (6.5% vs 6.2%) and lower than in the routine treatment group (6.5% vs 14%). In the two groups with impaired glucose tolerance taken together, mortality was predicted by the intervention, but not by body mass index (BMI), systolic blood pressure, smoking, cholesterol or the glucose level.

Two randomized-controlled trials including persons with impaired glucose tolerance have found that lifestyle modification protects against the development of type 2 diabetes. A Finnish trial randomized 522 overweight middle-aged persons with impaired glucose tolerance to physical training combined with diet or to control and followed them for 3.2 years (Tuomilehto et al., 2001). The risk of type 2 diabetes was reduced by 58% in the intervention group.

An American trial randomized 3234 persons with impaired glucose tolerance to either treatment with metformin, lifestyle modification entailing dietary change and at least 150 min of physical exercise weekly, or placebo, and followed them for 2.8 years (Knowler et al., 2002). The lifestyle modification reduced the risk of type 2 diabetes by 58%. The reduction was thus the same as in the Finnish trial (Tuomilehto et al., 2001), while treatment with metformin only reduced the risk of diabetes by 31%.

These all-over impressive effects were obtained although full compliance to exercise and diet habits was not obtained in all individuals (Tuomilehto et al., 2001; Knowler et al., 2002). The effect was greatest in the patients who made the greatest lifestyle modification (Lindstrom et al., 2003a, b).

It is not possible to determine the isolated effect of exercise in these three trials (Eriksson & Lindgarde, 1998; Tuomilehto et al., 2001; Knowler et al., 2002), where the intervention was combined exercise and diet, but the weight loss in the intervention groups was only modest. In the Finnish trial, the weight loss after 2 years was 3.5 kg in the intervention group vs 0.8 kg in the control group (Tuomilehto et al., 2001). BMI in the intervention group decreased from approximately 31 to approximately 30 in the Finnish trial (Tuomilehto et al., 2001) and from 34 to 33 in the American trial (Knowler et al., 2002).

Positive effect of training on:	Evidence level			
	Strong evidence A	Moderate evidence B	Limited evidence C	No evidence D
Pathogenesis				
Symptoms specific to the diagnosis				
Physical fitness or strength				
Quality of life				

Fig. 1. Insulin resistance.

*Type and amount of training*

Most of the information available concerns aerobic training of moderate intensity over a long period of time, but strength conditioning with many repetitions enhances insulin sensitivity in experimental situations and is probably effective in the prevention of type 2 diabetes (Holten et al., 2004). Moreover, muscular strength and cardiorespiratory fitness are known to have independent and joint inverse associations with the prevalence of metabolic syndrome (Jurca et al., 2004).

A recent randomized clinical trial assessed the effect of the volume and intensity of exercise training in 154 sedentary overweight/obese men and women with dyslipidemia (Houmard et al., 2004). The subjects were randomly assigned to a control group or to 6 months of physical training entailing either high-volume-high-intensity exercise (32 km jogging/week at 65–80% of peak oxygen uptake ( $VO_{2max}$ ), low-volume-high-intensity exercise (19 km jogging/week at 65–80% of  $VO_{2max}$ ) or low-volume-moderate-intensity exercise (19 km walking/week at 40–55% of  $VO_{2max}$ ). The study did not address high-volume-moderate-intensity exercise.

The actual duration of training in the three groups was 167, 114 and 171 min, respectively. The subjects were encouraged to maintain their baseline body weight. Despite this there were small but significant weight losses in the control group and two of the exercise groups. Insulin sensitivity was investigated using the 3 h intravenous glucose tolerance test (IVGTT) at the beginning and the end of the study. All three exercise regimens increased insulin sensitivity significantly. However, an exercise prescription that incorporated approximately 170 min of exercise/week improved insulin sensitivity more substantially than a program utilizing approximately 115 min of exercise/week, regardless of exercise intensity and volume.

These findings have not yet been confirmed by other studies.

*Possible mechanisms*

Physical training enhances insulin sensitivity in the exercised muscle and enhances muscle contraction-induced glucose uptake in the muscle. The mechanisms include increased postreceptor insulin signalling (Dela et al., 1993), GLUT4 mRNA and protein (Dela et al., 1994), increased glycogen synthase activity (Ebeling et al., 1993), increased hexokinase activity (Coggan et al., 1993), decreased release and enhanced clearance of free fatty acids (Ivy et al., 1999), and enhanced influx of glucose to the muscles due to enhanced muscle capillarization and blood flow (Saltin et al., 1977; Mandroukas et al., 1984). Physical activity also has a beneficial effect on the

endothelial dysfunction seen in patients with insulin resistance. Physical activity increases blood flow and hence shear stress on the blood vessel wall, which is considered to be the stimulus for endothelium-derived nitric oxide, which induces smooth muscle relaxation and vasodilatation (McAllister et al., 1995).

*Prescription*

Many patients with insulin resistance develop chronic complications in the locomotive apparatus (e.g. painful osteoarthritis) or symptomatic ischemic cardiovascular disease. The recommendations therefore need to be highly individualized, although the prescription should follow the general recommendations for the population. The goal is at least 30 min of moderate-intensity exercise (Borg 12–13 with short periods at Borg 15–16) daily or 3–4 h/week in the form of brisk walking, cycling, jogging, swimming, rowing, golf, etc.

*Contraindications*

There are no general contraindications, but the training should take into account comorbidities. Patients with coronary heart disease should refrain from short intensive exercise situations (Borg 15–16). Patients with hypertension should perform strength conditioning with light weights and a low contraction rate.

Diabetes, type 2 (Fig. 2)

*Background*

Type 2 diabetes is a metabolic disease characterized by hyperglycemia and abnormal glucose, fat and protein metabolism (Beck-Nielsen et al., 2000). The disease is a result of insulin resistance in the striated muscle tissue and a  $\beta$ -cell defect, which prevent the insulin resistance from being compensated for by

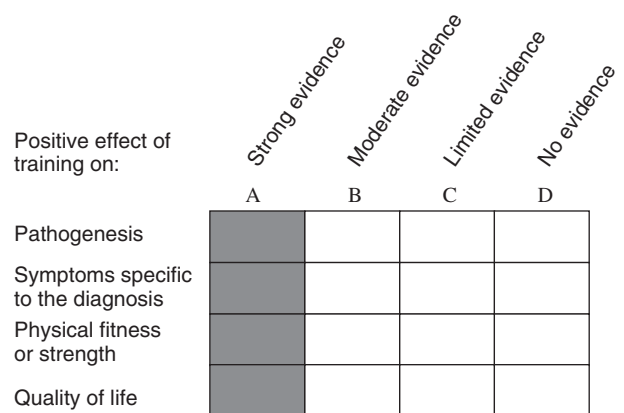


Fig. 2. Diabetes type 2.

enhanced insulin secretion. Type 2 diabetes has nearly always been present for several years before the diagnosis is made, and more than half of all newly diagnosed diabetics exhibit signs of late diabetic complications. In particular, these include macrovascular disease in the form of coronary heart disease, stroke and lower extremity ischemia, although microvascular complications such as nephropathy and retinopathy (especially diabetic maculopathy) also frequently occur. In patients with newly diagnosed type 2 diabetes, the prevalence of peripheral arteriosclerosis is 15%, coronary heart disease 15%, stroke 5%, retinopathy 5–15% and microalbuminuria 30%. Furthermore, the prevalence of other risk factors is high. Thus, 80% are overweight, 60–80% have hypertension and 40–50% have dyslipidemia. The mortality is two- to fourfold that of the population in general, with approximately 75% of the deaths being due to cardiovascular disease (Kannel & McGee, 1979; Goldbourt et al., 1993; Stamler et al., 1993). Intensive multifactorial intervention prevents late diabetic complications (Gaede et al., 2003).

#### *Evidence for physical training*

**Effect on glycemic control.** The beneficial effect of training in patients with type 2 diabetes is very well documented, and there is international consensus that physical training comprises one of the three cornerstones of the treatment of diabetes together with diet and medicine (Joslin et al., 1959; Albright et al., 2000; American Diabetes Association, 2002).

A meta-analysis published in 2001 examined the effect of at least 8 weeks of physical training on glycemic control (Boule et al., 2001). The meta-analysis included 14 controlled clinical trials (Fujii et al., 1982; Ronnema et al., 1986; Kaplan et al., 1987; Wing et al., 1988; Vanninen et al., 1992; Raz et al., 1994; Lehmann et al., 1995; Agurs-Collins et al., 1997; Dunstan et al., 1997; Honkola et al., 1997; Mourier et al., 1997; Dunstan et al., 1998; Tessier et al., 2000) encompassing a total of 504 patients. Twelve of the trials examined the effect of aerobic training (mean (SD); 3.4 (0.9) times/week for 18 (15) weeks), while two examined the effect of strength conditioning (mean (SD); 10 (0.7) exercises, 2.5 (0.7) sets, 13 (0.7) repetitions, 2.5 (0.4) times/week for 15 (10) weeks). A recent small study encompassing 22 patients with type 2 diabetes found that strength training was more effective than endurance training in improving glycemic control (Cauza et al., 2005). No differences could be identified between the effect of aerobic training and strength conditioning. Neither could any dose–response effect be demonstrated relative to either the intensity or the duration of training. Post-intervention HbA1c was lower in

the exercise groups than in the control groups (7.65% vs 8.31%; weighted mean difference, 0.66%;  $P < 0.001$ ). In comparison, intensive glycemic control with metformin reduced HbA1c by 0.6%, but reduced the risk of diabetes-related complications by 32% and the risk of diabetes-related mortality by 42% (UK Prospective Diabetes Study (UKPDS) Group, 1998). A meta-analysis encompassing 95 783 non-diabetic individuals showed that cardiovascular morbidity is strongly correlated to fasting blood glucose (Coutinho et al., 1999). The effect of physical training on HbA1c is thus clinically relevant.

In the 2001 meta-analysis (Boule et al., 2001), 8 weeks of physical training had no effect on body mass. There are several possible explanations for this: the training period was relatively short, the patients overcompensated for their energy consumption by eating more, or the patients lost fat but increased their lean body mass. There are grounds for believing that the latter explanation is the most important. It is known that inactive persons who begin to exercise increase their lean body mass (Brooks et al., 1995; Foxx & Keteyian, 1998). Only one of the studies included in the meta-analysis investigated the abdominal fat by means of magnetic resonance (MR) scanning (Mourier et al., 1997). The aerobic training program used (45 min cycling twice/week and intermittent exercise once/week for 2 months) reduced abdominal subcutaneous adipose tissue (227.3–186.7 cm<sup>2</sup>;  $P < 0.05$ ) and visceral adipose tissue (156.1–80.4 cm<sup>2</sup>;  $P < 0.05$ ), but did not have any effect on body weight.

**Effect on fitness and strength.** Poor fitness is an independent prognostic marker for death in patients with type 2 diabetes (Kohl et al., 1992; Wei et al., 1992; Myers et al., 2002). A meta-analysis (Boule et al., 2003) has assessed the effect of at least 8 weeks of physical training on peak oxygen uptake (VO<sub>2max</sub>). In all, 266 patients with type 2 diabetes were included in the meta-analysis. The mean training consisted of 3.4 sessions/week, 49 min/session for 20 weeks at an intensity of 50–75% of VO<sub>2max</sub>. Overall, there was an 11.8% increase in VO<sub>2max</sub> in the exercise group vs a 1% decrease in the control group.

In a trial in which elderly patients with type 2 diabetes ( $n = 31$ ) were randomized to a strength-conditioning program for 24 months, muscle strength for all muscle groups increased by 31% after the first 6 months of training, and the strength gains were retained for the duration of the training intervention but remained unchanged in the control group (Brandon et al., 2003). There was also a group and time effect for mobility as performance increased by 8.6% and 9.8%. Thus, in patients with type 2

diabetes, both fitness and strength can be improved by physical training.

**Motivation.** Patients with type 2 diabetes can be motivated to change their physical activity habits by exercise consultation (Kirk et al., 2003). A total of 70 inactive persons with type 2 diabetes were given standard information that “regular physical activity promotes health”. They were thereafter randomized to either no consultation or a 30-min individual consultation providing information/instruction about physical activity based on the transtheoretical model (Marcus & Simkin, 1994). Compared with the control group, the level of physical activity after 6 months was significantly higher in the intervention group, and both systolic blood pressure and HbA1c were significantly lower.

“The First Step Program” (FSP) was developed in collaboration with a number of diabetes associations (Yamanouchi et al., 1995; Tudor-Locke et al., 2000, 2001, 2002). The program aims to enhance patient understanding of the importance of walking in daily life and at work. A pedometer is used to monitor daily activity and as feedback and encouragement to increase the number of steps taken in daily life. FSP was used as the intervention in a group of diabetes patients (Tudor-Locke et al., 2004). Overweight patients with type 2 diabetes ( $n = 47$ ) were randomized to FSP or control. In the FSP group, the amount of walking increased by 3000 steps/day ( $P < 0.0001$ ).

As a physical activity-induced increase in insulin sensitivity (Bogardus et al., 1984; Trovati et al., 1984; Krotkiewski et al., 1985; Dela et al., 1995; Yamanouchi et al., 1995; Mourier et al., 1997) entails that a greater amount of glucose can be taken up by the insulin-sensitive tissues using less insulin, the above-mentioned decrease in glycemic level is not unexpected. Moreover, clinical experience has indicated that increased insulin sensitivity due to weight loss and/or physical training must be accompanied by a reduction in treatment with oral antidiabetics or insulin. A reduction in the hyperinsulinemia – in cases where this is present – has also been demonstrated, both with (Bogardus et al., 1984; Yamanouchi et al., 1995; Halle et al., 1999; Proctor et al., 1999) and without (Trovati et al., 1984; Vanninen et al., 1992; Di et al., 1993; Dela et al., 1995) dietary intervention. In some other studies, however, the insulin level remained high and unchanged following training (Ruderman et al., 1979; Reitman et al., 1984; Schneider et al., 1984; Krotkiewski et al., 1985; Ronnema et al., 1986; Allenberg et al., 1988; Wing et al., 1988; Hornsby et al., 1990; Vanninen et al., 1992; Lehmann et al., 1995, 2000; Dunstan et al., 1997; Mourier et al., 1997; Eriksson et al., 1998; Walker et al., 1999), but never increased. A decrease

in hyperinsulinemia is desirable as it is a risk factor for atherosclerosis and hypertension.

Physical training also has a number of other well-documented effects of significance for patients with type 2 diabetes (Stewart, 2002). As mentioned above, hypertension occurs in 60–80% of patients with type 2 diabetes. The beneficial effect of exercise on hypertension is well documented in non-diabetic persons (Stewart, 2001; Whelton et al., 2002). A recent meta-analysis encompassing 54 randomized trials found that aerobic training reduced systolic blood pressure by a mean of 3.8 mmHg. Subgroup analysis revealed a 4.9 mmHg reduction in systolic blood pressure in hypertensive patients. In another meta-analysis encompassing 47 trials (Kelley et al., 2001a), exercise was found to reduce systolic blood pressure by 6 mmHg in hypertensive persons vs 2 mm in normotensive persons. Patients with type 2 diabetes are affected by diastolic left ventricular dysfunction (Takenaka et al., 1988; Yasuda et al., 1992; Tarumi et al., 1993; Robillon et al., 1994), endothelial dysfunction (McVeigh et al., 1992; Johnstone et al., 1993; Clarkson et al., 1996) and chronic low-grade inflammation with raised levels of C-reactive protein, etc. (Pradhan et al., 2001). The latter is of poor prognostic value (Duncan & Schmidt, 2001; Abramson et al., 2002). Physical training increases left ventricular diastolic filling (Kelemen et al., 1990; Levy et al., 1993), increases endothelium-dependent vasodilatation (Higashi et al., 1999a, b) and induces anti-inflammatory effects (Febbraio & Pedersen, 2002).

### *Type and amount of training*

Experience is greatest with aerobic training, although strength conditioning involving many repetitions has also been shown to be effective.

The above-mentioned meta-analysis (Boule et al., 2003) evaluating the effect of at least 8 weeks of physical training showed that there was a good correlation between exercise intensity and post-intervention change in HbA1c ( $r = -0.91$ ,  $P = 0.002$ ) but not between the amount of exercise and change in HbA1c ( $r = -0.46$ ,  $P = 0.26$ ). These correlations, to some extent, conflict with the results of an intervention study showing that regular physical training enhanced insulin sensitivity in sedentary, overweight/obese non-diabetics, with the effect being greatest in those who exercised most, irrespective of the intensity of exercise (Houmard et al., 2004).

In consideration of insulin treatment and adjustment and regulation of diet, the training should optimally be planned and daily.

### *Possible mechanisms*

The literature on the effects of physical training on type 2 diabetes is comprehensive, but the mechan-

isms involved will only be dealt with briefly here. Physical training enhances insulin sensitivity in the exercised muscle and enhances muscle contraction-induced glucose uptake in the muscle. The mechanisms include increased postreceptor insulin signalling (Dela et al., 1993), GLUT4 mRNA and protein (Dela et al., 1994), increased glycogen synthase activity (Ebeling et al., 1993), increased hexokinase activity (Coggan et al., 1993), decreased release and enhanced clearance of free fatty acids (Ivy et al., 1999), enhanced  $\beta$ -cell function (Dela et al., 2004) and enhanced influx of glucose to the muscles due to enhanced muscle capillarization and blood flow (Saltin et al., 1977; Mandroukas et al., 1984). Strength conditioning increases insulin-mediated glucose uptake, GLUT4 content and insulin signalling in skeletal muscle in patients with type 2 diabetes (Holten et al., 2004). Physical exercise increases blood flow and hence shear stress on the blood vessel wall, which is considered to be the stimulus for endothelium-derived nitric oxide, which induces smooth muscle relaxation and vasodilatation (McAllister et al., 1995). The antihypertensive effect is believed to be mediated by reduced sympathetic vasoconstriction in the trained state. Supervised physical training reduces the amount of very low-density lipoprotein (VLDL) in persons with type 2 diabetes (Alam et al., 2004).

#### *Prescription*

The majority of patients with type 2 diabetes can exercise without taking special precautions. However, it is important that patients being treated with sulfonylurea, postprandial regulators or insulin are instructed regarding precautions to prevent hypoglycemia. The precautions include blood glucose monitoring, dietary modification and adjustment of the insulin dose. The advice given below is in line with the Danish Endocrine Society recommendations and Danish Diabetes Association guidelines ([www.diabetesforeningen.dk](http://www.diabetesforeningen.dk)).

In order to prevent hypoglycemia, 10–15 g carbohydrate should be consumed 30 min prior to exercise provided the blood glucose is satisfactory. During prolonged physical activity a 10–20 g carbohydrate snack (fruit, juice or a soft drink) should be consumed for each 30 min of exercise.

When beginning a specific training program patients should measure their blood glucose frequently during and after the training session in order to learn their individual response to a given amount of exercise of a given duration. If hypoglycemia nevertheless still occurs, the dose of insulin or peroral antidiabetic will have to be reduced. The insulin should be injected in a region that is not active during the training (Koivisto et al., 1991), and the

performance of exercise immediately after administration of regular insulin or a rapidly acting analogue cannot be recommended (Tuominen et al., 1995).

Many patients with type 2 diabetes develop chronic complications in the locomotive apparatus (e.g. painful osteoarthritis) and ischemic cardiovascular disease. If neuropathy is present, special footwear should be recommended before starting an exercise program. The recommendations should therefore be individualized, but both endurance training and strength conditioning can be recommended, either in combination or separately.

The goal is at least 30 min of moderate-intensity exercise (Borg 12–13 with short periods at Borg 15–16) daily or 3–4 h/week in the form of brisk walking, cycling, jogging, swimming, rowing, golf, etc. Raising the intensity of the physical activity probably has a beneficial effect, but specific guidelines must await the outcome of more studies specifically aimed at determining the significance of the amount and intensity of exercise.

Attention should be paid to the presence of autonomic neuropathy where the Borg scale is particularly well suited for assessing the intensity of the exercise, in contrast to the heart rate. Strength conditioning should include many repetitions. The training program should also include 5–10 min warming up, 5–10 min cooling down after training and the intake of carbohydrate.

#### *Contraindications/precautions*

Generally speaking, the danger associated with not exercising is greater than that associated with exercising, although special precautions apply.

If blood glucose is  $>17$  mmol/L, exercise should be postponed until it is corrected. The same applies if blood glucose is  $<7$  mmol/L.

In patients with hypertension and active proliferative retinopathy, high-intensity training or training involving Valsalva-like maneuver should be avoided. Strength conditioning should be carried out only using light weights and with a low contraction rate.

Patients with neuropathy and incipient foot ulcers should refrain from activities entailing the bearing of the patient's own body weight. Repeated strain on neuropathic feet can lead to ulceration and fractures. Treadmills, long walks/jogs and step exercises are advised against, while non-body-weight-bearing exercises such as cycling, swimming and rowing are recommended.

One should be aware that patients with autonomic neuropathy can have severe ischemia without ischemic symptoms (silent ischemia). These patients typically have resting tachycardia, orthostatism and poor thermoregulation. They are at risk of sudden

Positive effect of training on:	Evidence level			
	Strong evidence A	Moderate evidence B	Limited evidence C	No evidence D
Pathogenesis				
Symptoms specific to the diagnosis				
Physical fitness or strength				
Quality of life				

Fig. 3. Dyslipidemia.

cardiac death. Referral to a cardiologist, exercise ECG or myocardial scintigraphy should be considered. The patients should be instructed to avoid exercising in cold/warm temperatures and to ensure adequate hydration when exercising.

### Dyslipidemia (Fig. 3)

#### Background

Dyslipidemia is a group of disorders of lipoprotein metabolism entailing elevated blood levels of certain forms of cholesterol and triglyceride. Primary dyslipidemias caused by environmental and genetic factors are by far the most frequent, accounting for 98% of all cases. Isolated hypercholesterolemia and combined dyslipidemia are the most frequent types of dyslipidemia, and are due to excessive intake of fat in most people. These types of dyslipidemia entail an elevated risk of atherosclerosis. Isolated hypercholesterolemia is characterized by elevation of only LDL cholesterol, while combined dyslipidemia is characterized by elevated triglyceride, elevated LDL, IDL and VLDL cholesterol and lowered HDL cholesterol. When the concentration of LDL is high, the particles are pressed into the intima where they are oxidized and taken up by macrophages. This leads to the formation of fat lesions and subsequently to atherosclerosis with intra- and extracellular cholesterol deposition, fibrosis, cell death and actual occlusive disease. Triglyceride elevation with a concomitant slight cholesterol elevation also entails elevation of IDL and VLDL particles in the blood. These particles are trapped in the intima, possibly even more easily than LDL particles, and thereby also promote the development of atherosclerosis. The low concentration of HDL particles probably entails that the removal of cholesterol from the blood is reduced, thereby indirectly enhancing atherosclerosis.

The consensus is that physical activity protects against the development of cardiovascular disease (National Heart, 1998; Brown et al., 2001), and it has been proposed that one of the many mechanisms could be a beneficial effect of exercise on the blood lipid profile (Prong, 2003; National Institutes of Health Consensus Development Panel, 1993).

#### Evidence for physical training

There is currently considerable evidence that independent of the resultant weight loss, physical training has beneficial effects on the blood lipid profile. A number of review articles summarize this aspect (Tran et al., 1983; Tran & Weltman, 1985; Lokey & Tran, 1989; Leon, 1991; Armstrong & Simons-Morton, 1994; Durstine & Haskell, 1994; Stefanick & Wood, 1994; US Department of Health & Human Services, 1996; Crouse et al., 1997; Stefanick et al., 1998b; Leon, 1999; Leon & Sanchez, 2001; Prong, 2003).

A 2001 meta-analysis (Leon & Sanchez, 2001) encompassed 51 studies, of which 28 were randomized-controlled trials (4700 persons). In the majority of the studies, the intervention consisted of aerobic exercise training of moderate to hard intensity 30 min/session 3–5 times a week for more than 12 weeks. In training studies in which the diet was kept constant, there was a mean 4.6% increase in HDL ( $P < 0.05$ ), a 3.7% decrease in triglyceride concentration ( $P < 0.05$ ) and a 5% decrease in LDL ( $P < 0.05$ ), but no change in total cholesterol. The meta-analysis is characterized by some heterogeneity among the studies and the inclusion of some non-randomized trials. A few of the studies compared different levels of exercise intensity, but none of the studies compared different amounts of exercise, and a possible dose–response relationship could not be evaluated. Supervised physical training reduces the amount of VLDL in persons with type 2 diabetes (Alam et al., 2004).

A recent randomized-controlled trial has examined the effect of the amount and intensity of training in 111 sedentary, overweight men and women with mild-to-moderate dyslipidemia (Kraus et al., 2002). The subjects were randomly assigned to a control group or to 8 months of physical training entailing either high-amount–high-intensity exercise (32 km jogging/week at 65–80% of peak oxygen uptake ( $VO_{2max}$ ), low-amount–high-intensity exercise (19 km jogging/week at 65–80% percent of  $VO_{2max}$ ) or low-amount–moderate-intensity exercise (19 km walking/week at 40–55% of  $VO_{2max}$ ). This study is notable in that it evaluates an extensive lipoprotein profile that includes the size of the lipoprotein particles. The subjects were encouraged to maintain their baseline body weight, and those who lost

considerable weight were excluded. Despite this, there were small but significant weight losses in the exercise groups. Beneficial effects on the lipoprotein profile were detected in all three exercise groups compared with the control group. However, there was no marked difference in effect between the two low-amount exercise groups despite the fact that fitness improved more in the group that performed high-intensity exercise. High-amount exercise had a significantly better effect than low-amount exercise as regards virtually all lipid and lipoprotein variables despite the fact that the improvement in fitness was the same in the two groups with high-intensity exercise. There was no effect on total cholesterol. High-amount-high-intensity exercise lowered the concentrations of LDL, IDL and small LDL particles and raised the size of the LDL particles and the concentration of HDL. Beneficial effects on the concentrations of triglyceride and VDL triglyceride and on the size of the VLDL particles were recorded in all three exercise groups. Thus, the effects were clearly related to the amount of exercise but not to the intensity of the exercise.

The effect of physical activity on HDL is clinically relevant, although it is smaller than the effect that can be achieved through the use of lipid-lowering drugs (Knopp, 1999). It is estimated that each time HDL increases 0.025 mmol/L, the cardiovascular risk decreases by 2% for men and by at least 3% for women (Pasternak et al., 1990; Nicklas et al., 1997). Physical training induced a mean increase in HDL of 0.125 mmol/L (Kraus et al., 2002).

*Type and amount of training*

The amount of physical training should be high, but the intensity can be either moderate or high.

*Possible mechanisms*

Exercise enhances the ability of the muscles to burn fat to a greater extent instead of glycogen. This is mediated by activation of a number of enzymes in the skeletal muscles that are necessary for lipid metabolism (Saltin & Helge, 2000).

*Prescription*

Many patients with dyslipidemia have hypertension or symptomatic ischemic cardiovascular disease. The recommendations therefore need to be highly individualized. The prescription follows the general recommendations for the population, but the amount of exercise should be increased. The exercise intensity can be either moderate or high. The patient should aim to walk or run at least 20 km/week, preferably 30 km. Performing two of these sessions daily will

Positive effect of training on:	Strong evidence A	Moderate evidence B	Limited evidence C	No evidence D
Pathogenesis				
Symptoms specific to the diagnosis				
Physical fitness or strength				
Quality of life				

Fig. 4. Hypertension.

have an extremely beneficial effect on the blood lipid profile.

*Contraindications*

There are no general contraindications, but the training should take into account comorbidities. Patients with coronary heart disease should refrain from intensive exercise (Borg 15–16). Patients with hypertension should perform strength conditioning with light weights and a low contraction rate.

**Hypertension (Fig. 4)**

*Background*

Hypertension is an important risk factor for stroke, acute myocardial infarction, cardiac insufficiency and sudden death. The boundary between high and normal blood pressure is not sharp as the frequency of the above-mentioned cardiovascular diseases starts to increase with the blood pressure level at a relatively low blood pressure. A newly published meta-analysis encompassing 61 prospective studies (1 million persons) showed that the risk of cardiovascular death decreased linearly with decreasing blood pressure until a systolic blood pressure of less than 115 mmHg and a diastolic blood pressure of less than 75 mmHg (Lewington et al., 2002). A 20 mmHg decrease in systolic blood pressure or a 10 mmHg decrease in diastolic blood pressure halves the risk of cardiovascular death. For example, a person with a systolic blood pressure of 120 mmHg has half the risk of cardiovascular death as a person with a systolic blood pressure of 140 mmHg (Lewington et al., 2002). Treatment-demanding hypertension is defined as systolic blood pressure >140 mmHg and diastolic blood pressure >90 mmHg. According to this definition, approximately 20% of the population has hypertension or take antihypertensive medication (Burt et al., 1995).



*Evidence for physical training*

*Effect on resting blood pressure (normotensive and hypertensive).* The beneficial effect of physical training on blood pressure is well documented (Stewart, 2001; Whelton et al., 2002; Pescatello et al., 2004). This is further confirmed in a recent meta-analysis (Cornelissen & Fagard, 2005) which involved 72 trials, 105 study groups, and 3936 participants (Mann et al., 1969; Gettman et al., 1976; Myrtek & Villinger, 1976; Lansimies et al., 1979; De Plaen & Detry, 1980; Kukkonen et al., 1982; Duncan et al., 1985; Jennings et al., 1986; Nelson et al., 1986; Urata et al., 1987; Fortmann et al., 1988; Vroman et al., 1988; Hagberg et al., 1989; Tanabe et al., 1989; Van Hoof et al., 1989a; Martin et al., 1990; Meredith et al., 1990; Suter et al., 1990; Oluseye, 1990a; Blumenthal et al., 1991; Cononie et al., 1991; Duncan et al., 1991; King et al., 1991; Meredith et al., 1991; Albright et al., 1992; de Geus et al., 1992; Hamdorf et al., 1992; Posner et al., 1992; Hellenius et al., 1993; Kingwell & Jennings, 1993; Marceau et al., 1993; Braith et al., 1994; Lindheim et al., 1994; Reid et al., 1994; Wijnen et al., 1994; Anderssen et al., 1995; Arroll & Beaglehole, 1995; Kokkinos et al., 1995; Wang et al., 1995; Anshel, 1996; Cox et al., 1996; Leon et al., 1996; Ready et al., 1996; Rogers et al., 1996; Tanaka et al., 1997; Wang et al., 1997; Duey et al., 1998; Jessup et al., 1998; Murphy & Hardman, 1998; Sakai et al., 1998; Stefanick et al., 1998a; Hamdorf & Penhall, 1999; Higashi et al., 1999a,b; Blumenthal et al., 2000; Cooper et al., 2000; Ross et al., 2000; Ferrier et al., 2001; Hass et al., 2001; Kraemer et al., 2001; Marshall et al., 2001; Moreau et al., 2001; Staffileno et al., 2001; Wood et al., 2001; Miyai et al., 2002; Tsai et al., 2002a,b; Asikainen et al., 2003; Santa-Clara et al., 2003; Tsuda et al., 2003). After weighting for the number of trained participants and using a random-effects-model training induced significant net reductions of resting and daytime ambulatory blood pressure of, respectively, 3.0/2.4 mmHg ( $P < 0.001$ ) and 3.3/3.5 mmHg ( $P < 0.01$ ). The reduction of resting blood pressure was more pronounced in the 30 hypertensive study groups ( $-6.9/-4.9$ ) than in the others ( $-1.9/-1.6$ ;  $P < 0.001$  for all).

A meta-analysis (Whelton et al., 2002) encompassing 54 randomized controlled trials (2419 persons) (Jennings et al., 1986; Nelson et al., 1986; Urata et al., 1987; Jones et al., 1989; Van Hoof et al., 1989b; Akinpelu, 1990; Martin et al., 1990; Meredith et al., 1990; Suter et al., 1990; Oluseye, 1990b; Blumenthal et al., 1991; Duncan et al., 1991; King et al., 1991; Meredith et al., 1991; Albright et al., 1992; Hamdorf et al., 1992; Posner et al., 1992; Radaelli et al., 1992; Kingwell & Jennings, 1993; Braith et al., 1994; Lindheim et al., 1994; Wijnen et al., 1994; Arroll &

Beaglehole, 1995; Potempa et al., 1995; Leon et al., 1996; Okumiya et al., 1996; Ready et al., 1996; Rogers et al., 1996; Gordon et al., 1997; Wang et al., 1997; Duey et al., 1998; Murphy & Hardman, 1998; Sakai et al., 1998; Wing et al., 1998; Higashi et al., 1999a,b; Blumenthal et al., 2000; Cooper et al., 2000) found that aerobic exercise (for at least 2 weeks) led to a mean decrease in systolic blood pressure of 3.84 mmHg (95% CI  $-4.97$  to  $-2.72$ ;  $P < 0.001$ ) and in diastolic blood pressure of 2.58 mmHg (95% CI  $-3.35$  to  $-1.81$ ;  $P < 0.001$ ). The effect of training increased upon the exclusion of trials in which blood pressure was not the primary end point, upon exclusion of trials in which the training was not supervised, and upon exclusion of trials with multiple interventions. The amount of exercise had a significant effect on blood pressure, while the intensity of exercise did not. Neither the initial weight nor any weight loss associated with the training had isolated effects on blood pressure.

Another meta-analysis (Fagard, 2001) extracted 44 randomized-controlled trials of aerobic exercise (for at least 4 weeks) and found that in the whole group ( $n = 1529$ ), training led to a 3.4 mmHg decrease in systolic blood pressure and a 2.4 mmHg decrease in diastolic blood pressure. The two meta-analyses (Fagard, 2001; Whelton et al., 2002) overlap considerably, which explains the considerable agreement between their findings.

A meta-analysis of 16 mixed randomized and non-randomized trials assessed the effect of walking and found that this moderate form of physical activity induced a 3 mmHg decrease in systolic blood pressure and a 2 mmHg decrease in diastolic blood pressure in normotensive individuals (Kelley et al., 2001c).

A meta-analysis (Kelley & Kelley, 2000) of 10 randomized-controlled trials assessing the effect of at least 6 weeks of strength conditioning found a 3 mmHg decrease in both systolic and diastolic blood pressure in a mixed group of normotensive and hypertensive adults. Only 20% of the subjects were classified as hypertensive based on their systolic blood pressure and only 13% based on their diastolic blood pressure. No information is available about the effect of strength conditioning on the hypertensive subjects alone.

*Effect on resting blood pressure (hypertensive patients).* A position stand by the American College of Sports Medicine (ACSM) (Pescatello et al., 2004) based on data extracted from 16 trials encompassing persons with hypertension (systolic blood pressure  $> 140$  mmHg; diastolic blood pressure  $> 90$  mmHg) concluded that physical training reduced systolic blood pressure by 7.4 mmHg and diastolic blood pressure by 5.8 mmHg. It is a common finding that

the blood pressure-lowering effect of physical training is greatest in the patients most in need of it. 24 h blood pressure monitoring was performed in 11 of the studies (Pescatello et al., 2004) and showed the same effect of physical training as mentioned above.

We have identified a number of other systematic review articles (Ebrahim & Smith, 1998; Petrella, 1998; Cleroux et al., 1999; Fagard, 1999; Kelley, 1999; Kelley & Kelley, 1999; Kelley & Sharpe, 2001; Krummel et al., 2001; Houde & Melillo, 2002) concerning the effect of physical training that will not be mentioned here, either: (1) because there is considerable overlap with those already mentioned, (2) because it has not been possible to identify the randomized trials or (3) because there is little or no information about persons with hypertension.

#### *Acute effect of physical activity*

Physical activity induces a decrease in blood pressure that typically lasts 4–10 h after cessation of exercise, but that may last 22 h. The blood pressure decrease averages 15 mmHg systolic and 4 mmHg diastolic (Pescatello et al., 2004). Persons with hypertension can thus achieve normotensive values during much of the day, which is considered to be of major clinical significance (Pescatello et al., 2004).

All in all, it is well documented that physical training of hypertensive persons induces a blood pressure decrease of 7.4 mmHg systolic and 5.8 mmHg diastolic. This blood pressure decrease is clinically relevant. Conventional therapy with antihypertensive agents typically lowers diastolic blood pressure by the same amount (Collins et al., 1990; Collins & MacMahon, 1994; Gueyffier et al., 1997; Blood Pressure Lowering Treatment Trialists' Collaboration, 2000), and in the long term is estimated to reduce death from stroke by 30% and the risk of death from ischemic heart disease by 30%. The new meta-analysis encompassing 1 million persons calculated that a decrease in systolic blood pressure of just 2 mmHg will reduce death from stroke by 10% and death from ischemic heart disease by 7% among middle-aged persons (Lewington et al., 2002). These calculations are in accordance with older analyses (Collins et al., 1990; Cook et al., 1995). A recent study found that the antihypertensive effect of regular training given as monotherapy was maintained for as long as 3 years (Ketelhut et al., 2004).

#### *Type and amount of training*

All patients with hypertension (both those in pharmacotherapy and those not receiving treatment) benefit from physical training. The exercise should primarily consist of aerobic exercise of moderate intensity. In patients with mild hypertension it is reasonable to try non-pharmacological treatment in

the form of physical activity, dietary modification and smoking cessation for a period of 3–6 months before deciding upon pharmacological treatment. The duration of the blood pressure reduction persists up to 24 h after exercise (Park et al., 2005) and daily exercise is required.

#### *Possible mechanisms*

The blood pressure-lowering effect of physical training is considered to be multifactorial, but seems to be independent of weight loss and energy expenditure (Padilla et al., 2005). The mechanisms include neurohumoral, vascular and structural adaptation. The antihypertensive effect is believed to be mediated via reduced sympathetically induced vasoconstriction in the trained state (Esler et al., 2001), and decreased catecholamine levels. Hypertension often occurs together with insulin resistance and hyperinsulinemia (Zavaroni et al., 1999; Galipeau et al., 2002). Physical training enhances insulin sensitivity in the trained muscle and thereby reduces the hyperinsulinemia. The mechanisms include increased postreceptor insulin signalling (Dela et al., 1993), GLUT4 mRNA and protein (Dela et al., 1994), increased glycogen synthase activity (Ebeling et al., 1993) and increased hexokinase activity (Coggan et al., 1993), decreased release and enhanced clearance of free fatty acids (Ivy et al., 1999) and enhanced input of glucose to the muscles due to enhanced muscle capillarization and blood flow (Saltin et al., 1977; Mandroukas et al., 1984; Coggan et al., 1993).

Many patients with hypertension are affected by diastolic left ventricular dysfunction (Takenaka et al., 1988; Yasuda et al., 1992; Tarumi et al., 1993; Robillon et al., 1994) and chronic low-grade inflammation with raised levels of C-reactive protein, etc. (Pradhan et al., 2001). The latter is of poor prognostic value (Duncan & Schmidt, 2001; Abramson et al., 2002). Physical training augments left ventricular diastolic filling (Kelemen et al., 1990; Levy et al., 1993), augments endothelium-dependent vasodilatation (Higashi et al., 1999a,b) and induces anti-inflammatory effects (Febbraio & Pedersen, 2002). Moreover, increased walking frequency over a 24-month period reduces vascular stiffness (Havlik et al., 2005).

Patients with hypertension often also have endothelial dysfunction. Physical exercise increases blood flow and hence shear stress on the blood vessel wall, which is considered to be the stimulus for endothelium-derived nitric oxide, which induces smooth muscle relaxation and vasodilatation (McAllister et al., 1995). Patients with hypertension often also have dyslipidemia. Physical activity and exercise have beneficial effects on the blood lipid profile (Kraus et al., 2002).

*Prescription*

Many patients with hypertension have symptomatic ischemic cardiovascular disease. The recommendations therefore need to be highly individualized, but the prescription should follow the general recommendations for the population. The goal is at least 30 min of moderate intensity exercise (Borg 12–13 with short periods at Borg 15–16) daily. One can also replace the endurance training with strength conditioning twice/week.

*Contraindications*

According to the ACSM guidelines, individuals with a blood pressure >180/105 should begin pharmacotherapy before regular physical activity is initiated (relative contraindication) (American College of Sports Medicine, 1993; Pescatello et al., 2004). There is no evidence for an enhanced risk of sudden death or stroke in physically active persons with hypertension (American College of Sports Medicine, 1993; Tipton, 1999; Pescatello et al., 2004). The ACSM recommends caution when performing very intensive dynamic exercise or strength conditioning with very heavy weights. During heavy strength conditioning, very high pressures can be attained in the left ventricle of the heart (>300 mmHg), which can be potentially dangerous. Patients with left-sided cardiac hypertrophy should be particularly cautious about heavy strength conditioning.

Patients with coronary heart disease should refrain from short intensive exercise situations (Borg 15–16).

Obesity (Fig. 5)

*Background*

Overweight is a condition in which an abnormally large proportion of the body mass consists of fat. In the routine clinical situation, the diagnosis is usually made by determining the body mass index (BMI),

which is the weight in kilograms divided by the square of the height in metres (Dansk Selskab for Adipositasforskning & Dansk Kirurgisk Selskab, 2001; Svendsen et al., 2001). In most cases, BMI is relatively closely associated with the body's fat mass. Internationally, overweight is subdivided into various degrees according to the magnitude of the BMI. It is important to emphasize that changes in body composition, e.g. in the direction of more muscle mass and less fat mass, do not necessarily entail changes in body weight or BMI. The amount and distribution of fat can be assessed using various forms of scanning (CT, MR, DXA).

From medical examinations of young men called up for military service it is known that the prevalence of overweight has increased considerably during recent years. Danes became more overweight in the 10-year period of 1982–1992, during which the prevalence of obesity among the middle aged (30–60 years) increased by 30% (Dansk Selskab for Adipositasforskning & Dansk Kirurgisk Selskab, 2001). Among the young, the prevalence of obesity has increased around fivefold since World War II. Of the whole adult population in Denmark, 10–12% are obese (BMI >30) (Dansk Selskab for Adipositasforskning & Dansk Kirurgisk Selskab, 2001), corresponding to 400 000 persons. To this should be added the more frequent abdominal obesity, which is estimated to affect 30% of adult males and a smaller proportion of adult females. Mortality is only slightly raised in overweight persons, while it is increased twofold in obese persons (BMI >30) compared with persons of normal weight (Dansk Selskab for Adipositasforskning & Dansk Kirurgisk Selskab, 2001). The increased mortality is predominantly attributable to an increased prevalence of cardiovascular disease. In a group aged 25–30 years, the excess mortality associated with extreme obesity (BMI >40) was 10–12-fold (Dansk Selskab for Adipositasforskning & Dansk Kirurgisk Selskab, 2001).

*Evidence for physical training*

The significance of physical activity for weight loss assessed as body weight or BMI is controversial, but physical training causes a reduction in fat mass and abdominal fat and counteracts loss of muscle mass during dieting. Strong evidence exists that physical activity is important for preventing weight increase generally, including for maintaining body weight after weight loss.

*Physical training as a means of weight loss.* A meta-analysis (Ross & Janssen, 2001) of studies encompassing persons with a BMI >25 (overweight or obese) in which it was possible to determine the isolated effect of physical training on obesity identi-

Positive effect of training on:	Strong evidence A	Moderate evidence B	Limited evidence C	No evidence D
Pathogenesis				
Symptoms specific to the diagnosis				
Physical fitness or strength				
Quality of life				

Fig. 5. Obesity.

fied nine randomized-controlled trials (Sopko et al., 1985; Wood et al., 1988; Posner et al., 1992; Hinkleman & Nieman, 1993; Ready et al., 1995; Binder et al., 1996; Kohrt et al., 1997; Mourier et al., 1997; Ross et al., 2000) and 22 non-randomized trials. In short-term trials (<16 weeks) ( $n = 20$ ) involving exercise regimens that increased energy expenditure by 2200 kcal/week, exercise-induced weight loss was found to be positively related to reduction in total fat in a dose-response manner. There was insufficient evidence to determine a dose-response relationship between exercise and the reduction in abdominal and visceral fat.

In a recent randomized-controlled trial (Slentz et al., 2004) completed by 120 sedentary overweight men and women with dyslipidemia (aged 40–65 years), the subjects were randomized to (1) a control group or 8 months of physical training entailing either (2) low-volume-moderate-intensity exercise, (3) low-volume-high-intensity exercise or (4) high-volume-high-intensity exercise. The subjects did not diet during the study. All three training regimens had beneficial effects on body weight, fat mass and central obesity. The changes were greatest with the high-volume-high intensity regimen, while exercise intensity had no effect.

In a study (Ross et al., 2000) in which 52 obese men were randomly assigned to diet-induced weight loss, exercise-induced weight loss, exercise without weight loss and control and followed for 3 months, body weight decreased by 7.5 kg in both weight loss groups and did not change in the other two groups. The peak oxygen uptake ( $VO_{2max}$ ) increased in both exercise groups. The decrease in fat mass was 1.3 kg greater in the weight loss group that exercised. The abdominal obesity decreased in both exercise groups.

In another study (Kraemer et al., 1999), 35 overweight men were randomized to either a control group ( $n = 6$ ), a diet-only group ( $n = 8$ ), a diet group that performed aerobic exercise ( $n = 11$ ), or a diet group that performed both aerobic training and strength conditioning ( $n = 10$ ). After 12 weeks the weight loss in the three intervention groups was 9.64 kg, 8.99 kg and 9.90 kg, respectively, of which 69%, 78% and 97%, respectively, were accounted for by fat loss. The diet-only group also demonstrated a significant reduction in fat-free mass. This same study has also been performed on 31 overweight women (Kraemer et al., 1997), but in this case there was no difference between the three intervention groups as regards the reductions in body mass and percentage body fat, and fat-free mass remained unchanged in all three groups. In both studies (Kraemer et al., 1997, 1999), fitness increased in the exercise groups, and muscle strength increased in the group that also performed strength conditioning.

A Danish study (Svendsen et al., 1993) in which 121 overweight postmenopausal women were randomized to diet-only or diet+physical training found an overall weight loss of 9.5 kg vs 10.3 kg in the two groups. However, the diet-only group lost 7.8 kg fat, while the diet+physical training group lost 9.6 kg fat.

*Physical training as a means of maintaining body weight.* A 2001 meta-analysis (Anderson et al., 2001) included six non-randomized trials (Sikand et al., 1988; Pavlou et al., 1989; Holden et al., 1992; Flynn & Walsh, 1993; Hartman et al., 1993; Ewbank et al., 1995) ( $n = 492$ ) providing information on the effects of exercise on weight-loss maintenance. The initial weight loss was 21 kg in the physically active group and 22 kg in the physically inactive group. After 2.7 years, the weight loss was 15 kg in the physically active group and 7 kg in the physically inactive group.

A Danish follow-up study (Svendsen et al., 1994) examined 118 overweight post-menopausal women, who 6 months previously, had completed a randomized weight-loss trial in which they were assigned to 12 weeks of either diet-only or diet+physical training or control. There were no long-term effects of the 12 weeks of training, but marked effects on body weight and fat mass if the women continued to train.

Observational studies generally find a good correlation between the amount of physical activity and weight-loss maintenance after a diet (Rissanen et al., 1991; Williamson et al., 1993; Haapanen et al., 1997; Barefoot et al., 1998), apart from one study (Heitmann et al., 1997). Persons who increase their physical activity after a diet are better able to maintain their weight (Owens et al., 1992; Williamson et al., 1993; Taylor et al., 1994; Haapanen et al., 1997; Coakley et al., 1998; Guo et al., 1999; Fogelholm & Kukkonen-Harjula, 2000). Only a few studies do not find any such correlation (Bild et al., 1996; Crawford et al., 1999). Non-randomized weight-loss studies with prospective follow-up find that persons who are highly physically active put on less weight than persons who do not exercise (Hoiberg et al., 1984; Kayman et al., 1990; Holden et al., 1992; Hartman et al., 1993; Haus et al., 1994; DePue et al., 1995; Ewbank et al., 1995; Walsh & Flynn, 1995; Grodstein et al., 1996; Sarlio-Lahteenkorva & Rissanen, 1998; Andersen et al., 1999; Crawford et al., 1999; McGuire et al., 1999). Only one study did not find such a relationship (Sarlio-Lahteenkorva et al., 2000).

The effect of physical activity on weight maintenance has been assessed in three studies (Perri et al., 1988; Leermakers et al., 1999; Fogelholm et al., 2000) in which the patients were randomized to physical training or control ( $n = 672$ ). The patients who exercised put on 4.8 kg as compared with 6 kg in the controls. A number of studies (Perri et al., 1986;

Sikand et al., 1988; King et al., 1989; Pavlou et al., 1989; van Dale et al., 1990; Wadden et al., 1998) have assessed patients ( $n = 475$ ) who were randomized to a weight-loss program with or without physical training. After 1–2 years, the training group had put on an average of 4.8 kg as compared with 6.6 kg in the control group. Corresponding data were extracted in a 1997 meta-analysis (Miller et al., 1997) encompassing 493 moderately obese adults. After 15 weeks of diet or diet+training the weight loss in both groups was 11 kg. The weight loss maintained at 1-year follow-up was 6.6 kg in the diet group and 8.6 kg in the diet+training group.

*Physical training – other effects.* Obesity is often accompanied by hypertension, dyslipidemia and insulin resistance. The effect of physical training on these risk markers is described in the sections dealing with these diagnoses. Chronic exercise without caloric restriction or weight loss is a useful strategy for fat reduction in obese individuals with and without type 2 diabetes (Lee et al., 2005), decreasing visceral, subcutaneous and total abdominal fat (Slentz et al., 2005). Daily exercise without caloric restriction is associated with substantial reductions in total fat, abdominal fat, visceral fat and insulin resistance in women. Exercise without weight loss was also associated with a substantial reduction in total and abdominal fat (Ross et al., 2004).

Erectile dysfunction is common in obesity, and physical training reduces the risk of erectile dysfunction (Derby et al., 2000). In a randomized-controlled trial (Esposito et al., 2004) in which 55 obese men aged 35–55 years with erectile dysfunction were instructed in weight loss through dietary modification and physical activity, the erectile function index 2 years later was significantly better in the intervention group than in the control group. Multivariate analysis revealed independent effects of both weight loss and physical activity on erectile function.

*Children.* With children, the result is basically the same as for adults. Training has little effect on weight loss assessed as body weight, but has a good effect on fat mass and a good effect as regards maintenance of weight after a weight loss (Epstein & Goldfield, 1999; Rowlands et al., 2000; Campbell et al., 2001; Campbell et al., 2002; LeMura & Maziekas, 2002; Reilly et al., 2002).

In considering the evidence for physical training, it should be kept in mind that many other risk factors are associated with obesity. The beneficial effects of physical training on insulin resistance, dyslipidemia and hypertension are well documented (see the sections dealing with these diagnoses). It is therefore important to inform overweight patients that physical training has beneficial effects – also even if an

effect cannot immediately be measured on body weight.

### *Type and amount of training*

The training should preferably consist of large amounts of moderate-intensity aerobic training, preferably combined with strength conditioning.

### *Possible mechanisms*

Physical training increases energy consumption and induces lipolysis, thereby reducing the fat mass provided that the energy consumption is not compensated for by increased calorie intake.

Physical training enhances endothelial function, a possible mechanism whereby physical activity enhances erectile function.

### *Prescription*

It should be highlighted that weight loss requires a negative calorie balance and that weight loss is not achieved if the energy expenditure during exercise is overcompensated for by food intake. Many patients with overweight or obesity concomitantly have hypertension or symptomatic ischemic cardiovascular disease. The recommendations therefore need to be highly individualized, although the prescription should follow the general recommendations for the population. The goal is at least 30 min of moderate-intensity exercise (Borg 12–13 combined with short periods at Borg 15–16) daily. If the training is to affect body weight markedly, it is necessary to aim for 1 h of exercise daily. The training can be performed as walking/running on a treadmill or in the open, or as cycling on a bicycle ergometer.

### *Contraindications*

There are no general contraindications, but the training should take into account comorbidities. Patients with coronary heart disease should refrain from short intensive exercise situations (Borg 15–16). Patients with hypertension should perform strength conditioning with light weights and a low contraction rate.

## **Heart and pulmonary diseases**

Chronic obstructive pulmonary disease (Fig. 6)

### *Background*

Chronic obstructive pulmonary disease (COPD) is characterized by irreversible reduction in pulmonary function (Lange & Vestbo, 2002). In the advanced stage, COPD is characterized by a protracted and agonizing course of gradually worsening and eventually debilitating dyspnea. Interest in COPD has

Positive effect of training on:	Strong evidence		Moderate evidence		Limited evidence		No evidence	
	A	B	C	D	A	B	C	D
Pathogenesis								
Symptoms specific to the diagnosis								
Physical fitness or strength								
Quality of life								

Fig. 6. Chronic obstructive pulmonary disease.

increased in recent years in line with the increasing incidence of the disease. A number of recommendations have been put forward concerning its diagnosis and treatment (American Thoracic Society, 1995; European Respiratory Society, 1995; Dansk Lunge-medicinsk Selskab & Dansk Selskab for Almen Medicin, 1998) and more recently also concerning rehabilitation (2001a).

The current international consensus is that rehabilitation is an important component of the treatment of COPD. This is in concert with the acknowledgement that pharmacotherapy of the disease is inadequate. With increasing severity of COPD, the functional level decreases. The increasing dyspnea eventually makes the patients anxious about moving around and results in them becoming extremely sedentary. This leads to loss of fitness and muscular atrophy, which further exacerbates the dyspnea. A vicious circle thus arises, whose the main components are loss of fitness, dyspnea, anxiety and social isolation. Rehabilitation breaks this vicious circle through physical training, psychological support and the establishment of networks among the COPD patients.

*Evidence for physical training*

The beneficial effects of physical training in patients with COPD are well documented. A 2002 Cochrane Review (Lacasse et al., 2002) encompassing 23 randomized-controlled trials (McGavin et al., 1977; Cockcroft et al., 1981; Cockcroft et al., 1982; Booker, 1984; Guyatt et al., 1984; Reid & Warren, 1984; Guyatt et al., 1985; Jones et al., 1985; Schantz, 1986; Busch & McClements, 1988; Jones, 1988; Feinleib et al., 1989; Jaeschke et al., 1989; Lake et al., 1990; McDowell et al., 1991; Donner & Howard, 1992; Guyatt et al., 1992; Simpson et al., 1992; Weiner et al., 1992; Goldstein et al., 1994; Wijkstra et al., 1994; Schulz et al., 1995; American Thoracic Society, 1999), of which 14 were included in an earlier meta-

analysis (Lacasse et al., 1996), concluded that endurance training of at least 4 weeks' duration improves quality of life with less fatigue and less dyspnea. A 2003 meta-analysis found that physical training improved maximal exercise capacity and walking distance (Salman et al., 2003). A systematic review (Chavannes et al., 2002) aimed specifically at patients with mild to moderate COPD (FEV<sub>1</sub> > 50% of expected) identified five original studies suitable for evaluation (Clark et al., 1996; Cambach et al., 1997; Grosbois et al., 1999; Clark et al., 2000; Ringbaek et al., 2000) and found that exercise training can improve fitness in this patient group but not the feeling of dyspnea.

The maximal exercise capacity was investigated in 15 trials encompassing 508 patients, 265 of whom received active rehabilitation, while the remaining 243 patients served as controls. In 14 of these trials (255 treated patients; 233 controls) in which the incremental bicycle ergometer test was used as the outcome, the maximal exercise capacity increased by 5.46 W. Functional exercise capacity was investigated in 15 trials (580 patients: 300 actively treated and 280 controls). Limiting the analysis to the 10 trials (235 actively treated, 219 controls) in which a 6 min walking test was used, a 49 m increase was found. Quality of life was investigated in the majority of the trials using a number of different questionnaires that render the data difficult to summarize. Nevertheless, there is good documentation that rehabilitation programs have beneficial effects on the patients' feeling of dyspnea, on health-dependent quality of life and on the patients' sense of control over their condition (Lacasse et al., 1996; Muir et al., 1996; BTS Statement, 2001a). In one trial, it has been shown that it is possible to train patients immediately after admission for acute exacerbation (Behnke et al., 2000). Compared with the control group, patients benefited considerably from 10 days of hospital-based walking exercise followed by 6 months of home-based supervised exercise training where the exercise was incorporated into the daily activities.

Newer trials are also available showing that rehabilitation programs result in fewer admissions and thereby save on resources (Griffiths et al., 2000, 2001). The majority of trials use high-intensity walking exercise. In a single trial in which the effect of a high-intensity, lower-extremity endurance program (treadmill or stationary cycling at 80% of peak oxygen uptake (VO<sub>2max</sub>)) was compared with the effect of a low-intensity, multicomponent callisthenics program, it was found that both programs enhanced fitness, but that patients in the high-intensity, lower-extremity training group showed greater increases in treadmill endurance, whereas those in the low-intensity group showed greater increases in arm endurance. Both programs had beneficial effects on

functional performance, health status and self-rated dyspnea (Normandin et al., 2002). Oxygen therapy in connection with intensive physical training of patients with COPD enhanced the intensity and effect of training in one study (Hawkins et al., 2002), but not in another (Wadell et al., 2001). It is recommended to provide oxygen in connection with the training sessions if the patients are hypoxic or desaturates during training (American Thoracic Society, 1999).

The use of a transportable cassette player to hear music during training yields better results than in patients who do not listen to music during training (Bauldoff et al., 2002). Specific training of the respiratory muscles enhanced respiratory muscle endurance (both inspiratory and expiratory), exercise performance and health-related quality of life (Scherer et al., 2000).

The effect of inspiratory muscle training (IMT) on inspiratory muscle strength and endurance, exercise capacity, dyspnea and quality of life for adults with COPD has been examined in a systematic review. The results indicate that targeted resistive or threshold IMT was associated with significant improvements in some outcomes of inspiratory muscle strength ( $PI_{max}$  (cm H<sub>2</sub>O)) and endurance (Inspiratory Threshold Loading (kPa)), exercise capacity (Borg Scale for Respiratory Effort (modified Borg scale), Work Rate maximum (W)), and dyspnea (Transition Dyspnea Index), whereas IMT without a target or not using threshold training did not improve these variables. The results regarding quality-of-life measures were inconclusive (Geddes et al., 2005).

A pilot study investigated the effects of heavy resistance training in elderly males with COPD. Eighteen home-dwelling male patients were randomized to a training group ( $n = 9$ ) and a control group ( $n = 9$ ). Twelve weeks of heavy resistance training twice a week resulted in significant improvements in muscle size, knee extension strength, leg extension power, functional performance and self-reported health in elderly male COPD patients (Kongsgaard et al., 2004).

### *Type and amount of training*

All patients with COPD, and not least the severe cases, benefit from physical training. The physical training should initially be supervised and should be individually planned and encompass endurance training, walking or cycling at an intensity of 70–85% of peak oxygen consumption for much of the time (BTS Statement, 2001a). Supervised training for 7 weeks yielded better results than a training program lasting 4 weeks (Green et al., 2001).

### *Possible mechanisms*

Physical activity does not improve lung function in patients with COPD, but enhances the cardiorespiratory condition via effects on the musculature and the heart. Patients with COPD are characterized by chronic inflammation, and it is likely that inflammation plays a role in their reduced muscle strength. Tumor necrosis factor (TNF) is found in raised levels in the blood (Eid et al., 2001) and muscle tissue (Palacio et al., 2002) of patients with COPD. The biological effects of TNF on muscle tissue are manifold. TNF affects myocyte differentiation, induces cachexia and thereby reduces muscle strength (Li & Reid, 2001). Physical training appears to affect this process in that working muscles produce the signal molecule interleukin-6 (IL-6), which is released to the circulatory system in large amounts during training. One of the biological functions of muscle-derived IL-6 is to inhibit TNF production in muscles and blood (Pedersen & Hoffman-Goetz, 2000; Pedersen et al., 2001).

### *Prescription*

The patients should walk daily at a speed such that their exertion corresponds to Borg 16–17. The walking distance should be gradually increased. The walking distance is assessed by means of the time the patient is able to walk. The patients attend outpatient supervised walking training twice/week for 7 weeks followed by outpatient checkups every third month, at which walking speed and distance are checked. At the same time, the patients have the possibility to participate in other physical activity in the form of gymnastics or bicycle ergometer training.

The walking training should be preceded by a fitness test, for example a shuttle test aimed at determining walking speed. The patients keep a diary recording dyspnea and duration of walking. The patients must aim to increase their walking distance. The training is lifelong. The Danish Lung Association can help provide material for use in testing COPD patients.

### *Contraindications*

There are no absolute contraindications.

### Coronary heart disease (Fig. 7)

#### *Background*

Coronary heart disease is a common term for heart disease caused by myocardial ischemia due to inadequate regional blood supply relative to myocardial oxygen requirements. The most common cause is atherosclerosis of the coronary blood vessels. Myocardial ischemia lasting more than approximately

Positive effect of training on:	Evidence level			
	Strong evidence A	Moderate evidence B	Limited evidence C	No evidence D
Pathogenesis				
Symptoms specific to the diagnosis				
Physical fitness or strength				
Quality of life				

Fig. 7. Coronary heart disease.

20 min leads to cell death (infarction) unless the collateral blood supply is well developed. Coronary heart disease manifests as chronic stable angina pectoris, acute and chronic heart failure, acute and chronic cardiac arrhythmia, acute unstable angina pectoris, acute myocardial infarct (AMI) and sudden death.

The total population of patients with manifest coronary heart disease in Denmark is estimated to be 150 000–200 000. Each year, approximately 33 000 persons are hospitalized with coronary heart disease or die from the disease before being admitted (primarily AMI or angina pectoris). A further 16 000 persons are treated for coronary heart disease on an outpatient basis. Each year, 12 000 persons are admitted to hospital with AMI, of whom 4000 die (2300 men and 1700 women) (information from the Danish Heart Association website [www.hjerteforeningen.dk](http://www.hjerteforeningen.dk)).

*Evidence for physical training*

The evidence for a beneficial effect of physical training in patients with coronary heart disease is good. Physical training improves survival and is believed to have direct effects on the pathogenesis of the disease.

A 2001 Cochrane Review (Jolliffe et al., 2000) examined the effect of exercise-based rehabilitation of coronary heart disease patients based on 32 randomized-controlled trials (Kentala, 1972; Wilhelmsen et al., 1975; Andersen et al., 1981; Shaw, 1981; Vecchio et al., 1981; Ballantyne et al., 1982; Carson et al., 1982; Sivarajan et al., 1982; Bengtsson, 1983; Stern et al., 1983; Vermeulen et al., 1983; Miller et al., 1984; Bethell & Mullee, 1990; Ornish et al., 1990; Fridlund et al., 1991; Oldridge et al., 1991; The P.R.E.COR group, 1991; Bertie et al., 1992; Lewin et al., 1992; Schuler et al., 1992; Engblom et al., 1992a–c; Heller et al., 1993; Fletcher et al., 1994; Haskell et al., 1994; Holmback et al., 1994; Engblom et al., 1996; Specchia et al., 1996; Wosornu et al., 1996; Carlsson

et al., 1997; Engblom et al., 1997; Krachler et al., 1997; Taylor et al., 1997; Bell, 1998; Carlsson, 1998) encompassing 8440 patients who had previously had myocardial infarction, coronary artery bypass graft or percutaneous transluminal coronary angioplasty or who had angina pectoris or coronary artery disease verified by angiography. The majority of the trials excluded patients with heart failure or comorbidities. The patients were typically randomized at the time of AMI or up to 6 weeks thereafter and were followed for an average of 2.4 years. The meta-analysis made two comparisons: (1) Exercise training+usual standard care was compared with usual standard care; and (2) Exercise training supplemented with psychosocial and/or educational intervention (hereafter termed exercise-based cardiac rehabilitation) was compared with usual standard care. The exercise training was predominantly aerobic, but varied considerably as regards frequency, intensity and duration. The Cochrane Review (Jolliffe et al., 2000) was updated by a new meta-analysis published in 2004 (Taylor et al., 2004) based on 48 randomized-controlled trials and 8940 patients (Kentala, 1972; Wilhelmsen et al., 1975; Kallio et al., 1979; Andersen et al., 1981; Shaw, 1981; Ballantyne et al., 1982; Carson et al., 1982; Sivarajan et al., 1982; Bengtsson, 1983; Stern et al., 1983; Vermeulen et al., 1983; World Health Organization, 1983; Miller et al., 1984; Roviario et al., 1984; Erdman et al., 1986; Agren et al., 1989; Bethell & Mullee, 1990; Ornish et al., 1990; Fridlund et al., 1991; Oldridge et al., 1991; The P.R.E.COR group, 1991; Bertie et al., 1992; Lewin et al., 1992; Schuler et al., 1992; Engblom et al., 1992c; Heller et al., 1993; Fletcher et al., 1994; Haskell et al., 1994; Holmback et al., 1994; Specchia et al., 1996; Wosornu et al., 1996; Carlsson et al., 1997; Krachler et al., 1997; Taylor et al., 1997; Bell, 1998; Carlsson, 1998; Dugmore et al., 1999; Lisspers et al., 1999; Heldal et al., 2000; Manchanda et al., 2000; Stahle et al., 2000; Toobert et al., 2000; Belardinelli et al., 2001; Higgins et al., 2001; Marchionni et al., 2003; Seki et al., 2003; Yu et al., 2003).

*All-cause mortality.* Exercise-based cardiac rehabilitation reduced all-cause mortality by 20% (OR 0.80; 95% CI 0.68–0.93).

*Cardiac mortality.* Exercise-based cardiac rehabilitation reduced cardiac mortality by 26% (OR 0.74; 95% CI 0.61–0.96).

*Other variables.* Exercise-based cardiac rehabilitation reduced total cholesterol, triglyceride level and systolic blood pressure. More patients in the exercise-based cardiac rehabilitation group ceased smoking (OR 0.64; 95% CI 0.50–0.83). There was no effect on non-fatal myocardial infarction.



### *Type and amount of training*

Experience is greatest with aerobic training of at least 12 weeks' duration in a hospital setting (Dinnes et al., 1999; Jolliffe et al., 2000). Compared with no exercise training, home-based exercise training has shown beneficial effects on risk factors, anxiety, quality of life and physical functioning, but it is uncertain whether unsupervised training affects mortality as effectively as supervised training (Dinnes et al., 1999; Jolliffe et al., 2000).

### *Possible mechanisms*

The mechanisms behind the beneficial effects of physical training on the prognosis are undoubtedly attributable to a multitude of factors and encompass exercise-induced increased fibrinolysis, reduced thrombocyte aggregation, improved regulation of blood pressure, optimized lipid profile, improved endothelium-mediated coronary vasodilatation, increased heart rate variability and autonomic tone, beneficial effects on a number of psychosocial factors and generally enhanced monitoring of the patients.

### *Prescription*

A position paper by the European Society of Cardiology concludes that "All patients who have suffered cardiac, and especially coronary, events or who are known to be affected by any asymptomatic cardiac disease should undergo exercise-related risk stratification and be offered a cardiovascular rehabilitation comprehensive program. Low-risk middle-aged male patients who have suffered myocardial infarction should perform moderate-intensity aerobic physical activity of at least 30 min duration on most, and preferably all, days of the week in order to achieve a weekly energy expenditure of about 1000 kcal, which will yield a cardiac mortality reduction of about 20–30%. Even if it appears that there is no biological reason why patients who are older, female or who have undergone myocardial revascularization procedures should not obtain the same benefits from physical activity interventions, there is still no clear scientific evidence to support this" (Giannuzzi et al., 2003).

Graded aerobic training in which the intensity and duration of the exercise sessions are gradually increased is preferable. The exercise training should preferably be supervised and should be carried out in a hospital setting.

Physical training should be initiated relatively rapidly after acute myocardial infarction, optimally within a week following discharge (i.e. 1.5–2 weeks after the infarct). The training program should last at least 12 weeks. Patients with angina pectoris should train to the level just below the ischemic threshold.

The patients should be informed that heart pains and other discomforts should not be "worked away", but that the symptoms are a signal to reduce the tempo or best of all to take a break.

A preceding exercise test aimed at assessing the maximum heart rate and exercise capacity is generally desirable. At the same time, the patient can be investigated for myocardial ischemia, both symptomatic and electrocardiographic.

*In coronary heart disease and after minor AMI.* Example of an exercise training program for patients with coronary heart disease:

- During the first 4 weeks, the sessions start with 10 min of warming up on a bicycle at Borg 10–12.
- Thereafter, the intensity is increased to Borg 12–13 for 10 min followed by 3–5 min at Borg 10.
- This sequence is performed twice the first week, three times the second week and four times the third week. The program entails two training sessions/week the first week and three sessions/week the second and third weeks.
- The training program for weeks 4–8 repeats the program for the third week.
- A fitness test is performed before and after 2 months. If fitness is acceptable, the exercise training is continued as described above, except that the duration of the low-intensity training is reduced. If fitness is still poor, training is carried out in sequences of 5 min at Borg 14–15 followed by 3–5 min at Borg 10. This sequence is performed four times. The program entails three training sessions/week.
- A new fitness test is performed after 1 month with progressively increasing intensity until satisfactory fitness is attained. Thereafter, a fitness test is performed annually. The training can be supplemented with ball throwing or gymnastics, which provides movement training of the whole body.

*After major AMI entailing the risk of chronic heart failure.* One can beneficially use sequential local training of small muscle groups.

Example:

- Each session starts with 10 min of light concomitant movement of the arms and legs.
- Thereafter follows 25 repetitions: first the right arm, then the left arm, then the right leg, then the left leg and finally training of the back and the abdomen. The frequency should be 70 repetitions/min. Elastic bands (e.g. Thera-band) should be used to provide load. The thickness of the elastic bands should be

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chosen such that the training is carried out at Borg 13. The session terminates with 10 min of light concomitant movement of the arms and legs.

- The training program is performed three times/week. In order to enable feedback, a fitness test is performed before training starts, after 2 months and annually.

### Contraindications

The following contraindications are in accordance with the guidelines set in a European Working Group Report (2001b):

- (1) Coronary heart disease (AMI or unstable angina) until the condition has been stable for at least 5 days.
- (2) Dyspnea at rest.
- (3) Pericarditis, myocarditis, endocarditis.
- (4) Symptomatic aortic stenosis.
- (5) Severe hypertension. There is no established, well-documented limit to how high the blood pressure has to be before it entails an enhanced risk. The general recommendation is to refrain from hard physical exercise at a systolic pressure > 180 mmHg or a diastolic pressure > 105 mmHg.
- (6) Fevers.
- (7) Severe non-cardiac diseases.

## Chronic heart failure (Fig. 8)

### Background

Chronic heart failure or cardiac insufficiency is a clinical syndrome defined by the European Society of Cardiology (ESC) as the presence of the following criteria: symptoms (dyspnea, fatigue, ankle swelling) and objective evidence of cardiac dysfunction at rest. Asymptomatic left ventricular dysfunction is often the forerunner for this syndrome. The symptoms

Positive effect of training on:	Evidence			
	Strong evidence A	Moderate evidence B	Limited evidence C	No evidence D
Pathogenesis				
Symptoms specific to the diagnosis				
Physical fitness or strength				
Quality of life				

Fig. 8. Chronic heart failure.

vary from very slightly debilitating to severely debilitating.

Heart failure is subdivided into left heart failure (the most frequent and best studied) and right heart failure, as well as into acute (pulmonary congestion, cardiogenic shock) and chronic heart failure. Heart failure is often caused by ischemic heart disease, but can also be caused by hypertension, valve abnormalities, etc. The number of patients with treatment-demanding chronic heart failure in Denmark is estimated to be approximately 80 000.

Peak oxygen consumption ( $VO_{2max}$ ) is reduced in patients with chronic heart failure (Sullivan et al., 1989b; Cohen-Solal et al., 1990; Working Group Report, 2001b), among other reasons due to reduced cardiac performance and peripheral abnormalities in the musculature (Massie et al., 1988; Sullivan et al., 1990; Working Group Report, 2001b). Patients with chronic heart failure frequently have muscle atrophy, rapid exhaustion and diminished muscle strength (Wilson et al., 1993; Anker et al., 1997; Harrington et al., 1997), and are characterized by defects in the renin-angiotensin system, raised levels of cytokine, including TNF (Bradham et al., 2002), raised noradrenaline level (Jewitt et al., 1969) and insulin resistance (Paolisso et al., 1991). These metabolic conditions can all play a role in the development of muscular atrophy in chronic heart failure (Anker et al., 1997), although no direct relationship has been demonstrated between  $VO_{2max}$  and noradrenaline (Notarius et al., 2002). Patients with chronic heart failure thus have from poor physical condition, poor muscle strength and muscular atrophy. Their characteristic fatigue is probably related to their poor physical functioning. While the consensus in the 1970s advised against physical activity and for bed rest for patients in all stages of chronic heart failure (McDonald et al., 1972), the current consensus is the opposite (Working Group Report, 2001b).

### Evidence for physical training

There is considerable evidence in support of a beneficial effect of physical training in patients with chronic heart failure. Initial uncontrolled studies showed that training enhanced the heart patients' fitness (Letac et al., 1977; Lee et al., 1979; Conn et al., 1982; Sullivan et al., 1988; Sullivan et al., 1989a; Working Group Report, 2001b). Since then, numerous studies have been published. These were subjected to systematic review in a 2002 study (Lloyd-Williams et al., 2002) that encompassed 14 prospective, randomized-controlled trials (Jette et al., 1991; Koch et al., 1992; Gordon et al., 1996; Keteyian et al., 1996; Kiilavuori et al., 1996; Tyni-Lenne et al., 1996; Cider et al., 1997; Johnson et al., 1998; Willenheimer et al., 1998; Belardinelli et al., 1999;

Quittan et al., 1999; Wielenga et al., 1999; Hambrecht et al., 2000; Oka et al., 2000), eight randomized crossover trials (Coats et al., 1992; Davey et al., 1992; Meyer et al., 1996; Tyni-Lenne et al., 1997; Taylor, 1999; Tyni-Lenne et al., 1999; Maiorana et al., 2000; Owen & Croucher, 2000), two non-randomized trials (Belardinelli et al., 1995; Kavanagh et al., 1996) and seven other trials (Conn et al., 1982; Sullivan et al., 1988; Scavini et al., 1992; Shephard et al., 1998; Tyni-Lenne et al., 1998; Delagardelle et al., 1999). All the trials were performed on stable patients with NYHA class II and NYHA class III heart failure, and the majority of the studies excluded patients with comorbidities such as diabetes or chronic obstructive pulmonary disease.

All except four of the 31 trials reported positive effects of physical training, for example as expressed in terms of improved  $\text{VO}_{2\text{max}}$ , resting pulse, systolic blood pressure, ventilation or anaerobic threshold (Lloyd-Williams et al., 2002). The majority of the studies were carried out on patients being treated with ACE inhibitors, diuretics and digitalis, and a small number with  $\beta$ -blockers. They show that the 15–25% increase in  $\text{VO}_{2\text{max}}$  is achieved on top of the effect of the drug treatment. Quality of life was assessed in some of the trials and was shown to improve with training in 11 out of 16 studies. Training renders the patients less tired, makes them experience less dyspnea and better tolerate physical activity. This enables them to manage more of their daily tasks themselves, makes them less depressed and improves their general well-being, i.e. a general improvement in quality of life. The effect of training on psychological parameters is independent of the effect on physiological parameters (Koukouvou et al., 2004).

A 2004 meta-analysis (Piepoli et al., 2004) based on nine randomized-controlled trials encompassing 801 patients with chronic heart failure (395 in exercise training groups and 406 in control groups) revealed that during the course of a 705-day follow-up period, there were 88 (22%) deaths in the training group and 105 (26%) in the control group. Physical training reduced mortality (hazard ratio 0.65; 95% CI 0.46–0.92;  $P = 0.015$ ) as well as the secondary end point of death or admission to hospital (hazard ratio 0.72; 95% CI 0.56–0.93;  $P = 0.01$ ).

#### *Type and amount of training*

**Aerobic training.** Experience with aerobic training in the form of cycling, walking and jogging is good, especially with indoor training on a bicycle ergometer. Interval training on a bicycle ergometer yields good results. For example, interval training with 30 s of activity at 50% of  $\text{VO}_{2\text{max}}$  followed by a 60 s break increases  $\text{VO}_{2\text{max}}$  by 20% over a 3-week

period (Meyer et al., 1996; Working Group Report, 2001b), which corresponds to the effect obtained in other studies with continual training of longer duration (Coats et al., 1992; Belardinelli et al., 1995; Hambrecht et al., 1995; Kavanagh et al., 1996; Keteyian et al., 1996; Belardinelli et al., 1998). Good results have also been reported with training at intensities between 40% and 80% of  $\text{VO}_{2\text{max}}$  (Coats et al., 1992; Belardinelli et al., 1995; Hambrecht et al., 1995; Kavanagh et al., 1996; Keteyian et al., 1996; Belardinelli et al., 1998). The duration of the training sessions ranged from 10 to 60 min with three to seven sessions/week (Coats et al., 1992; Belardinelli et al., 1995; Hambrecht et al., 1995; Kavanagh et al., 1996; Keteyian et al., 1996; Meyer et al., 1996; Working Group Report, 2001b). Improvement in fitness is seen as early as after 3 weeks, although the plateau is usually reached after 16–26 weeks (Kavanagh et al., 1996; Working Group Report, 2001b). A very recent randomized-controlled trial that studied the effect of progressive home-based walking training ( $n = 42$ ) vs normal daily activity ( $n = 37$ ) found a positive effect on the distance walked/day ( $P = 0.001$ ) (Corvera-Tindel et al., 2004).

**Strength conditioning.** Elderly women with chronic heart failure (NYHA class I–III) were randomized to 10 weeks of strength conditioning or control. The training improved not only muscle strength and muscle mass but also endurance (Pu et al., 2001). Another trial of patients with heart failure (NYHA class II–III) found that 5 months of strength conditioning enhanced muscle strength and improved the anaerobic threshold (Cider et al., 1997).

**Local muscle training.** The background for local muscle training is (1) that reversing the peripheral abnormalities in the muscle can protect the heart (Gaffney et al., 1981; Minotti & Massie, 1992) and (2) that sequential dynamic training of small groups of muscles can induce considerable adaptation to training with minimal circulatory stress (Gaffney et al., 1981). In principle, it is an advantage that patients with chronic heart failure can train a single group of muscles at high intensity while placing only a moderate strain on cardiac capacity. As mentioned earlier, the positive effect of training heart patients is largely mediated by peripheral muscle adaptation (Gaffney et al., 1981; Minotti & Massie, 1992). Training benefits from alternately training small groups of muscles instead of training many muscles at one time. A number of trials have been performed to assess the effect of mixed aerobic training and strength conditioning of alternate small groups of muscles (Gordon et al., 1996; Magnusson et al., 1997; Tyni-Lenne et al., 1999, 2001). This entails a form of circuit training but with a larger aerobic component

than normally associated with circuit training. Sequential training of small groups of muscles has been shown to result in improvement not just in local muscle strength and endurance but also in  $\text{VO}_{2\text{max}}$  and quality of life.

### *Possible mechanisms*

The exercise training enhances myocardial function expressed in terms of maximum minute volume (Sullivan et al., 1988; Coats et al., 1992; Demopoulos et al., 1997; Dubach et al., 1997; Working Group Report, 2001b), enhances systemic arterial compliance (Hambrecht et al., 2000; Parnell et al., 2002), enhances stroke volume (Hambrecht et al., 2000), reduces the risk of cardiomegaly (Hambrecht et al., 2000) and induces appropriate changes in the working muscle (Sullivan et al., 1988; Adamopoulos et al., 1993; Hambrecht et al., 1995; Working Group Report, 2001b) and enhances the anaerobic threshold (Sullivan et al., 1988; Sullivan et al., 1989a; Hambrecht et al., 1995; Kiilavuori et al., 1996; Meyer et al., 1996; Working Group Report, 2001b). Training reduces the activity of the sympathetic and renin-angiotensin systems (Coats et al., 1990; Coats et al., 1992; Kiilavuori et al., 1995; Working Group Report, 2001b). Furthermore, training induces skeletal muscle cytochrome C oxidase activity, which is associated with reduced local expression of pro-inflammatory cytokines and inducible nitric oxide synthase (iNOS) and augmented local insulin-like growth factor-I (IGF-I) production (Schulze et al., 2002). Exercise training may thereby help retard the catabolic processes in patients with chronic heart failure and counteract muscle atrophy. Training reduces the plasma level of soluble TNF receptor 1 and 2 (Conraads et al., 2002), TNF and soluble Fas-L (Adamopoulos et al., 2002) and the serum levels of adhesion molecules (Adamopoulos et al., 2001) in patients with chronic heart failure. Physical training inhibits the expression of cytokine in the skeletal muscle (Gielen et al., 2003) and in the blood (LeMaitre et al., 2004).

### *Prescription*

A position paper by the European Society of Cardiology concludes that “All HF patients should attend a rehabilitation program as soon as they are discharged from acute care institutions to assure clinical stability and to prevent hospitalization” (Corra et al., 2005).

Graded aerobic training in which the intensity and duration of the exercise sessions are gradually increased is preferable, or alternatively, interval training or sequential dynamic training/strength conditioning of small muscle groups. The exercise training should preferably be supervised and should

initially be carried out in a hospital setting (Working Group Report, 2001b).

Patients with angina pectoris should train to the level just below the ischemic threshold. The patients should be informed that heart pains and other discomforts should not be “worked away”, but that the symptoms are a signal to reduce their tempo or best of all to take a break.

A preceding exercise test aimed at assessing the maximum heart rate and exercise capacity is generally desirable. At the same time, the patient can be investigated for myocardial ischemia, both symptomatic and electrocardiographic.

### *Example of a graded aerobic training program for patients with chronic heart failure*

- During the first 4 weeks, the sessions start with 10 min of warming up at Borg 12, either walking or cycling.
- Thereafter the intensity is increased to Borg 14 for 10 min followed by 5 min at Borg 10. This sequence is performed twice the first week, three times the second week and four times the third week. The training program entails two training sessions/week the first week and three sessions/week the second and third weeks.
- The training program for weeks 4–8 repeats the program for the third week. The progressive increase can be implemented over longer intervals.
- In order to enable feedback, a fitness test is performed before training starts and after 2 months and 1 year.

### *Example of sequential local training of small muscle groups*

- Each session starts with 10 min of light concomitant movement of the arms and legs.
- Thereafter follow 25 repetitions: first the right arm, then the left arm, then the right leg, then the left leg and finally training of the back and the abdomen. The frequency should be 70 repetitions/minute. Elastic bands (e.g. Thera-band) should be used to provide load. The thickness of the elastic bands should be chosen such that the training is carried out at Borg 13. The session terminates with 10 min of light concomitant movement of the arms and legs.
- The training program is performed three times/week. In order to enable feedback, a fitness test is performed before training starts and after 2 months and 1 year.

*Contraindications*

The following contraindications are in accordance with the guidelines set in a European Working Group report:

- (1) coronary heart disease (AMI or unstable angina) until the condition has been stable for at least 5 days;
- (2) dyspnea at rest;
- (3) pericarditis, myocarditis, endocarditis;
- (4) symptomatic aortic stenosis;
- (5) severe hypertension. There is no established, well-documented limit to how high the blood pressure has to be before it entails an enhanced risk. The general recommendation is to refrain from hard physical exercise at a systolic pressure > 180 mmHg or a diastolic pressure > 105 mmHg;
- (6) fevers; and
- (7) severe non-cardiac diseases.

**Intermittent claudication (Fig. 9)**

*Background*

It is estimated that at least 4% of all Danes over 65 years of age have peripheral arteriosclerosis, and that half of these consequently have intermittent pains (intermittent claudication). In a small proportion of the patients, the peripheral arteriosclerosis progresses to peripheral arterial occlusive disease and results in resting pains and ulceration. The international consensus is that physical training is important in the treatment of patients with intermittent claudication (TASC, 2000). This is in line with the acknowledgement that the disease responds poorly to pharmacotherapy. With increasing severity of intermittent claudication, functionality is reduced. The worsening pains upon walking and the anxiety associated with moving around lead the patient into a sedentary lifestyle and social isolation. This even-

tually leads to the patient becoming unfit and to the development of muscle atrophy and progression of arteriosclerosis. A “vicious circle” thus arises, the most important components of which are deteriorating fitness, pains, anxiety and social isolation. Physical activity disrupts this vicious cycle by directly affecting the disease pathogenesis through improving fitness and muscle strength, changing the pain threshold and probably the experience of pain, preventing anxiety and preventing progression of the disease.

*Evidence for physical training*

There is strong evidence of a beneficial effect of physical training in patients with intermittent claudication. This includes a 2000 Cochrane Review (Leng et al., 2000) based on 10 randomized trials (Larsen & Lassen, 1966; Holm et al., 1973; Dahllof et al., 1974; Lundgren et al., 1989b; Creasy et al., 1990; Hiatt et al., 1990; Mannarino et al., 1991; Ciuffetti et al., 1994; Hiatt et al., 1994), a 1998 systematic review (Brandsma et al., 1998; Robeer et al., 1998) also based on 10 randomized trials (Larsen & Lassen, 1966; Dahllof et al., 1974; Ernst & Matrai, 1987; Kiesewetter et al., 1987; Lundgren et al., 1989a; Creasy et al., 1990; Hiatt et al., 1990; Mannarino et al., 1991; Hiatt et al., 1994; Regensteiner et al., 1996), seven of which were included in the Cochrane Review (Larsen & Lassen, 1966; Dahllof et al., 1974; Lundgren et al., 1989b; Creasy et al., 1990; Hiatt et al., 1990, 1994; Mannarino et al., 1991), and a 1995 meta-analysis based on 21 trials (Gardner & Poehlman, 1995). The three reviews arrive at the same conclusion: Physical exercise increased the walking distance to the onset of pain by 179% or 225 m and the maximum walking distance by 122% or 398 m (Gardner & Poehlman, 1995) or 150% (74–230%) (Leng et al., 2000). In a recently published randomized controlled trial of the effect of exercise training three times weekly for 6 months followed by training twice weekly for a further 12 months (Gardner et al., 2002), marked increases in daily activity, walking distance and pain threshold were found after the first 6 months of exercise training that were maintained during the less intensive training program over the following months. The improvements were significant relative to the control group. Exercise training has a beneficial effect on cardiovascular risk markers (TASC, 2000).

In a controlled trial in which physical exercise was compared with percutaneous transluminal angioplasty (PTA), no significant difference was found after 6 months (Creasy et al., 1990). A review by Chong et al. (2000) comparing the effects of physical exercise (nine trials; 294 patients) and PTA (12 trials; 2071 patients) concluded that while in principle it was impossible to compare the effect of the two

Positive effect of training on:	Evidence level			
	A	B	C	D
Pathogenesis				
Symptoms specific to the diagnosis				
Physical fitness or strength				
Quality of life				

Fig. 9. Intermittent claudication.

treatments in a non-controlled design, the effect of PTA was slightly better than that of exercise, but that PTA entailed a risk of serious side effects.

In another randomized trial comparing (1) physical training alone, (2) surgery and (3) physical training+surgery, it was found that the effect on walking distance was the same in all three groups but that side effects occurred in 18% of the subjects in the two surgery groups (Lundgren et al., 1989b).

The effects of physical training and antiplatelet therapy have been compared in a randomized trial (Mannarino et al., 1991) in which a significantly greater improvement in maximum walking time was detected in the training group (86%) than in the antiplatelet therapy group (38%). A meta-analysis found that physical training programs were considerably cheaper than both surgery and PTA (de Vries et al., 2002).

*Type and amount of training*

By far the majority of studies have solely examined the effect of walking, and information is needed about the effect of other forms of exercise. One study has shown a beneficial effect of polestriding relative to a control group that did not exercise (Langbein et al., 2002). During polestriding, one walks with modified ski poles in both hands. These both provide support and entail that one uses the upper body to get moving, thereby ensuring a greater workload. Little information is available about the importance of walking speed or intensity, but there are strong indications that the effect increases if exercise is continued until symptoms of ischemia appear. Controlled studies point to the importance of the training being supervised (Regensteiner et al., 1996). The effect of training is enhanced by concomitant smoking cessation (Jonason & Ringqvist, 1987).

*Possible mechanisms*

Physical training of patients with cardiac insufficiency enhances local production of the growth factor vascular endothelial growth factor (VEGF) (Gustafsson et al., 2001), which induces the formation of collaterals and hence enhances blood flow. VEGF formation is stimulated by muscle contraction during ischemia. This is probably an important mechanism that also explains the importance of exercising beyond the pain threshold. However, clinical effects have been demonstrated with exercise that does not affect ankle pressure (Tan et al., 2000), and the correlation between ankle pressure and improvement in walking distance is generally poor (Hiatt et al., 1990). Physical activity enhances endothelial function in the lower extremities (Gokce et al., 2002). We believe that the effect of physical exercise is largely attributable to improved fitness

and muscle strength. In addition, it is likely that the patient benefits psychologically from experiencing that the pain threshold can be exceeded, which leads to a change in the perception of pain.

*Prescription*

The physical activity should primarily consist of walking exercise and should be supervised by regular attendance at the therapist. The training can often be carried out at home, however. Training should be performed at least three times/week. The walking should be forced beyond the onset of pain followed by rest until the pain has dissipated, whereafter the walking exercise is resumed. Each exercise session should last at least 30 min, and training should be lifelong and carried out under supervision for the first 6 months. Feedback consists of the patient keeping a diary of walking distance, distance/time to onset of pain and training frequency. The walking distance is tested before starting training, after 3 months and thereafter annually.

With bicycle training, there is the risk that ischemic pain will not occur. It is for this reason that walking training is recommended. If bicycle training is chosen, the patient should be instructed to peddle with the forefoot. Apart from that, the same general training principles apply as for walking.

*Contraindications*

There are no general contraindications.

**Muscle, bone and joint diseases**

**Osteoarthritis (Fig. 10)**

*Background*

Osteoarthritis is the most frequent joint disease and one of the most frequent chronic diseases. Virtually everyone over 60 years of age shows signs of osteoarthritis in at least one joint (Veje et al., 2002). The

Positive effect of training on:	Strong evidence	Moderate evidence	Limited evidence	No evidence
	A	B	C	D
Pathogenesis				
Symptoms specific to the diagnosis				
Physical fitness or strength				
Quality of life				

Fig. 10. Osteoarthritis.

prevalence of radiologically verified osteoarthritis of the hip or knee is 70% among persons aged over 65 years (Wilson et al., 1990; Veje et al., 2002). Loss of articular cartilage is one of the dominant factors in the pathogenesis of osteoarthritis and is accompanied by joint deformation, bone sclerosis, capsule shrinkage, muscle atrophy and varying degrees of synovitis (Veje et al., 2002). The clinical and radiological signs together give the diagnosis. The radiological picture is one of diminution of the cartilage space, which is attributable to loss of articular cartilage. The radiological changes first appear late in the course of the disease. Before these become visible, the patients experience pain when placing pressure on and moving the joints. Over the course of time, the patients develop resting pains and joint swelling. The patient's physical activity is restricted by the pains with the consequence that the patient becomes increasingly unfit with diminishing muscle strength. Osteoarthritis is related to high age (Felson et al., 1987; Miedema, 1994), overweight and weak muscle function (Slemenda et al., 1998), but also occurs among young individuals who have placed inappropriate strain on a joint, often as a result of joint injury. The current international consensus is that all forms of osteoarthritis should be treated with physical training (Hochberg et al., 1995a, b). The primary aim of the physical training is to enhance muscle strength around the affected joints (especially the knee and hip joints).

### *Evidence for physical training*

Physical training is known to be important in osteoarthritis. The evidence includes a 1999 systematic review (van Baar et al., 1999) encompassing 483 patients based on 11 randomized-controlled trials (Chamberlain et al., 1982; Minor et al., 1989; Sylvester, 1989; Jan & Lai, 1991; Kovar et al., 1992; Peterson et al., 1993; Borjesson et al., 1996; Schilke et al., 1996; Ettinger Jr. et al., 1997; Messier et al., 1997; van Baar et al., 1998) selected from among 17 training studies. The systematic review encompassed patients with osteoarthritis of both the knee and hip or just of the knee. However, most of the studies have been performed on knee joints. The training programs differed and included both strength conditioning and aerobic exercise training. The review was unable to compare the effect of the various forms of training, but assessed pain and the ability to function in daily life and found an overall beneficial effect of training on these two parameters. The review did not assess the effect of training on fitness. Since publication of this systematic review, we have identified a number of additional controlled training studies (Schilke et al., 1996; Rogind et al., 1998; Keefe et al., 1999; O'Reilly et al., 1999; Batach et al., 2000;

Deyle et al., 2000; Hartman et al., 2000; Hopman-Rock & Westhoff, 2000; Messier et al., 2000; Petrella & Bartha, 2000; Baker et al., 2001; Penninx et al., 2001; van Baar et al., 2001; Thomas et al., 2002; Topp et al., 2002).

One of these randomized-controlled trials (Thomas et al., 2002) followed 786 patients with knee osteoarthritis (self-reported knee pain) for 2 years. The subjects were randomized to four groups: exercise, monthly telephone contact, exercise+telephone contact or no intervention. The exercises were designed to strengthen the muscles around the knee joint. Elastic bands were used for this purpose. The program was supervised in the home and initially consisted of 30 min of supervision every 2 weeks for the first 2 months. The subjects were encouraged to perform the program with both legs for 20–30 min/day, to increase the number of repetitions and to keep a diary of the results, on which they received feedback every 6 months. Compared with the non-exercise groups, significantly less pain was reported by the pooled exercise groups at 6, 12, 18 and 24 months, while no effect was seen with telephone contact alone.

In a randomized-controlled trial (Penninx et al., 2001) encompassing 250 persons aged over 60 years with knee osteoarthritis and initially free of activities of daily living (ADL) disability, the subjects were randomly assigned to control, aerobic exercise or strength conditioning. Over the 18-month study period, the accumulative ADL score in both exercise groups was 37% lower than in the control group (a low ADL score indicates that the patient is able to manage relatively well in daily living), indicating that exercise is effective in preventing ADL disability in older persons with knee osteoarthritis.

An 8-week progressive knee exercise program has been shown to supplement the effect of non-steroidal anti-inflammatory treatment on pain and function (Petrella & Bartha, 2000). In a small study ( $n = 24$ ) in which patients were randomized to either exercise or exercise+weight loss, improvements in pain, disability and function were found in both groups (Messier et al., 2000).

In addition, there are some studies demonstrating the effects on pain and function of supervised home-based training (Hopman-Rock & Westhoff, 2000) and of combined manual physical therapy and supervised exercise (Deyle et al., 2000). A study encompassing 191 patients showed that a knee-strengthening program reduced pain by 22.5% compared with a 6.2% decrease in the control group (O'Reilly et al., 1999). Twelve weeks of exercise ( $n = 201$ ) reduced knee pain significantly (van Baar et al., 1998), but the effect of exercise disappeared within 3 months in the absence of regular supervision or feedback (van Baar et al., 2001). Physiotherapy

including exercise, massage, taping and mobilization followed by 12 weeks of self management was no more effective than regular contact with a therapist at reducing pain and disability (Bennell et al., 2005).

### *Type and amount of training*

As mentioned above, numerous studies have shown that strength conditioning enhances joint function and general functioning in daily living and reduces pain. However, most information is based on studies performed on knee joints and although generalization to other joints are likely to hold true, such a conclusion is not validated by many experiments. Few studies have evaluated the effect of aerobic training. Professional supervision and feedback and/or psychological support from the patient's spouse enhance compliance and the effect of training in the long run (Keefe et al., 1999). Both dynamic and isometric training seems to have effects on pain and function (Topp et al., 2002). Endurance training is unlikely to have any direct effect on joints affected by osteoarthritis, but the patients should perform endurance training to prevent other diseases.

### *Possible mechanisms*

There are no grounds to believe that training works through a direct effect on the disease pathogenesis. Twelve weeks of training thus had no effect on disease markers (chondroitin subgroups) in synovial fluid (Bautch et al., 2000). Training works by stabilizing the osteoarthritis-affected joint by strength conditioning of the surrounding musculature. In theory, this can halt the progression of the disease as muscle weakness disposes to osteoarthritis (Slemenda et al., 1998). Endurance training enhances the patients general physical functioning and can induce weight loss, thus enabling the patient to manage better.

### *Prescription*

The physical exercise should primarily consist of strength conditioning and coordination training, but where possible should also include endurance training. The training should be supervised by regular attendance at the therapist and can beneficially be performed in groups. The training can also be carried out in the home. Although there is only evidence for an effect of training the affected lower extremity joint(s), we suggest that if possible the training should consist of progressive strength conditioning of all muscle groups, including the affected joint(s), that encompasses training of large muscle groups: muscles around the ankle, knee and hip, underarm/overarm and shoulder and the abdominal and back muscles. The strength-conditioning pro-

gram should be preceded by 10 min of warming up in the form of movement of all joints without placing any pressure on them.

The strength-conditioning program should be adapted to the individual patient, aiming toward 10 exercises that are each repeated twice with 12 repetitions ( $10 \times 2 \times 12$ ). The patient should switch between two exercises, starting with two exercises and a few repetitions and gradually expanding to a full program. In addition, the patient's coordination should be trained.

Patients who are unable or unwilling to attend a training center can be instructed in home exercises with elastic bands or with the body as the load. The training has to be lifelong and supervised the first 3 months, and with regular follow-up and feedback for the remainder of the patient's life. The feedback can consist of the patient keeping a training diary with a record of pains. The therapist can measure the muscle strength at the start of training, after 3 months and thereafter once a year.

If possible, the training should be supplemented with endurance training, e.g. ordinary walking, walking on treadmill, cycling, swimming or water gymnastics 30 min daily, if necessary  $3 \times 10$  min daily.

### *Contraindications*

In cases of acute joint inflammation, the affected joint should be rested until drug treatment has taken effect. If pain worsens after training, a pause should be held, and the training program modified. In the case of young persons with osteoarthritis caused by joint injury, the following should be noted: Sports that place a high workload on joints in the form of both axial compression force and twisting should be avoided. This applies to basketball, football, handball, volleyball and high-intensity running on hard surfaces.

## Rheumatoid arthritis (Fig. 11)

### *Background*

The frequency of rheumatoid arthritis is twice as great in women as in men. Onset of the disease occurs in all age groups, but most frequently when patients are aged 45–65 years. Rheumatoid arthritis is a chronic systematic inflammatory disease that usually presents with symmetric polyarthritis. The disease may also have extra-articular manifestations affecting the heart, lungs and skin. Joint pains are typically caused by inflammation, although in advanced cases they can relate to joint destruction.

The chronic inflammatory condition, physical inactivity and steroid treatment can lead to osteoporosis. Patients with rheumatoid arthritis and restricted



Positive effect of training on:	Evidence level			
	Strong evidence A	Moderate evidence B	Limited evidence C	No evidence D
Pathogenesis				
Symptoms specific to the diagnosis				
Physical fitness or strength				
Quality of life				

Fig. 11. Rheumatoid arthritis.

mobility are described as having considerably reduced muscle strength ranging from 30% to 70% of that of normal persons (Ekblom et al., 1974; Nordesjo et al., 1983; Hsieh et al., 1987; Ekdahl & Broman, 1992; Hakkinen et al., 1995), while endurance is reduced to 50% (Ekdahl & Broman, 1992). The reduced level of physical activity can be related to joint pain, restricted mobility and fatigue, and leads to loss of fitness. In patients who were able to perform a fitness test, fitness was found to be reduced by 20–30% (Ekblom et al., 1974; Beals et al., 1985; Minor et al., 1988; Ekdahl & Broman, 1992).

The physical training aims to improve fitness and muscle strength as well as to provide instruction in appropriate patterns of movement. In addition, a long-term goal is to prevent early death from cardiovascular disease (Wolfe et al., 1994).

*Evidence for physical training*

There is considerable evidence for a beneficial effect of physical training in patients with rheumatoid arthritis, but by far the majority of studies involve functional classes I and II. Only very few studies involve patients in functional classes III and IV. A 1998 Cochrane Review (Van Den Ende et al., 2000b) assessed dynamic training based on six randomized-controlled trials (Harkcom et al., 1985; Baslund et al., 1993; Hansen et al., 1993; Lyngberg et al., 1994; Van Den Ende et al., 1996) selected from among 30 training studies. The same review has subsequently been published as a systematic review (Van Den Ende et al., 2000b). Since the Cochrane Review we have identified a number of additional controlled trials (Komatireddy et al., 1997; Hakkinen et al., 1999, 2001b; Lundgren & Stenstrom, 1999; McMeeken et al., 1999; Westby et al., 2000; Van Den Ende et al., 2000a; Bearne et al., 2002; de Jong et al., 2003; Munneke et al., 2003, 2004; de Jong et al., 2004). There is considerable agreement between the studies. Dynamic physical activity enhances fitness and mus-

cle strength, but has no or only a moderate effect on disease activity and pains. None of the studies report that training enhanced disease activity.

In a randomized-controlled trial (de Jong et al., 2003), 309 patients with rheumatoid arthritis were assigned to a 2-year intensive exercise program or usual care. The intervention group participated in two weekly training sessions lasting 75 min. Each session consisted of endurance training on bicycle, strength conditioning in the form of circuit training and weight-bearing sport in the form of volleyball, football, basketball or badminton. The effects of the training program were assessed every 6 months for 2 years. The intensive exercise program improved functional ability and emotional status and had no negative effects on disease activity. Neither did the training program worsen the radiographic progression apart from a tendency toward slightly more progression in a small group of patients with considerable baseline radiographic damage.

In the above-mentioned trial, the intensive training program was also found to be effective in slowing down loss of bone minerals (de Jong et al., 2004), a finding that is in accordance with an earlier study reporting a modest but positive effect of dynamic training on bone mineral content (Westby et al., 2000). Strength conditioning alone does not appear to affect bone mineral content (Hakkinen et al., 1999, 2001b).

Both general and specific strength conditioning have been shown to have a good effect on muscle strength in patients with both newly diagnosed and long-standing rheumatoid arthritis (Hakkinen et al., 1999; McMeeken et al., 1999; Hakkinen et al., 2001b).

*Type and amount of training*

All patients with rheumatoid arthritis, both those with newly diagnosed and those with long-standing rheumatoid arthritis, benefit from physical training, but evidence is lacking as regards training of patients in functional classes III and IV.

In patients with destruction of the hip, knee or ankle joints, the aerobic training should be non-body-weight-bearing so that the training does not place any load on the joints. Cycling or swimming is thus preferable to running, but the training should be adapted to the individual patient. Some patients can benefit from weight-bearing activities, which perhaps provide greater protection against loss of bone minerals. General strength conditioning of large muscle groups is effective.

*Possible mechanisms*

Fitness and muscle strength is low in patients with rheumatoid arthritis, but this can be improved by

dynamic training and strength conditioning, respectively. Rheumatoid arthritis is an inflammatory disease characterized by raised levels of circulating TNF (Brennan et al., 1992). The biological effects of TNF on muscle tissue are manifold. TNF induces cachexia and thereby reduces muscle strength (Li & Reid, 2001). Physical training appears to induce anti-inflammation and specifically inhibit TNF production (Pedersen et al., 2001; Febbraio & Pedersen, 2002).

#### *Prescription*

The physical training should initially be supervised and should be individually designed and primarily encompass aerobic training of moderate to high intensity. The training can beneficially be carried out in groups and should be combined with cognitive behavioral therapy. The training should be gradually integrated into daily life, possibly with the help of patient associations and gymnastics associations.

The physical training should be adapted to the disease activity and symptoms in the individual patient and should consist of endurance training in the form of non-body-weight-bearing activities such as cycling, swimming or water gymnastics, although some patients can perform weight-bearing activities. The majority of patients can train by means of ordinary walking or polestriding. In patients with severely affected knee joints, cycling can be difficult. Severe rheumatoid arthritis of the neck can make swimming difficult, but may not prevent participation in water gymnastics. The typical patient with rheumatoid arthritis is non-trained, both as regards fitness and strength.

#### *Example of training of a patient with rheumatoid arthritis whose knee joint is not severely affected*

- During the first 4 weeks, the sessions start with 10 min warming up on a bicycle at Borg 10.
- Thereafter the intensity is increased to Borg 15–16 for 10 min followed by 3–5 min at Borg 10. This sequence is performed twice the first week, three times the second week and four times the third week. The program entails two training sessions/week in the first week and three sessions/week in the second and third weeks.
- The training program for weeks 4–8 repeats the program for the third week.
- A fitness test is performed before starting and after 2 months. If fitness is acceptable, training is continued as described above except that the duration of the low-intensity training is reduced. If fitness is still poor, training is carried out in sequences of 5 min at Borg 17–18 followed by 3–5 min at Borg 10. This sequence is performed four times. The program entails three training sessions/week. A new fitness

test is performed after 1 month, and the intensity is gradually increased until fitness is satisfactory. Thereafter, fitness is tested annually.

Strength conditioning of the legs can be performed by carrying out part of the cycling at a high load for 30 s followed by 30 s rest without any load. This sequence is performed 3–5 times. This training can be performed once a week in prolongation of the endurance training. In patients with knee problems, though, experience shows that this form of strength conditioning can worsen joint pain and/or swelling.

The training should also include progressive strength conditioning of all muscle groups, including the affected joint(s). Here too the training must be adapted to the disease activity and symptoms in the individual patient. Training in machines provides great safety.

Patients who are unable or unwilling to attend a training center can be instructed in home exercises with elastic bands or with the body as the load.

The therapist can measure the muscle strength at the start of training, after 3 months and thereafter once a year. The training has to be lifelong and supervised the first 3 months, and with regular follow-up and feedback for the remainder of the patient's life. The feedback can consist of the patient keeping a training diary with a record of pains and with annual measurements of fitness and muscle strength as described above.

#### *Contraindications*

As information about training of patients with severe disease activity is lacking, we presently recommend that a training program should not be initiated until medical treatment has been instigated. Training is contraindicated in cases of severe extra-articular manifestations such as pericarditis and pleuritis. In cases of joint surgery, it is important that the strength conditioning is supervised and that the training is initially performed using a low workload.

#### **Osteoporosis (Fig. 12)**

##### *Background*

Osteoporosis is a disorder in which bone mineral density decreases, thereby enhancing the risk of bone fracture. The age-corrected incidence of osteoporotic fractures is continually increasing in Europe. Within the past 20–30 years, the incidence of spinal fracture has increased three- to fourfold in women and more than fourfold in men (Mosekilde, 2001). The incidence of hip fracture has also increased two- to threefold, with the increase being most pronounced in men (Obrant et al., 1989). Due to the accelerating loss of bone density around menopause, osteoporosis

Positive effect of training on:	Evidence level			
	Strong evidence A	Moderate evidence B	Limited evidence C	No evidence D
Pathogenesis				
Symptoms specific to the diagnosis				
Physical fitness or strength				
Quality of life				

Fig. 12. Osteoporosis.

has been considered a women’s disease. However, this mechanism *cannot* explain: (1) the large age-corrected increase in osteoporotic fractures over the past 30 years (Obrant et al., 1989), (2) the large intra-European differences in the incidence of hip fracture (Kanis, 1993), (3) the large intra-European differences in the hip fracture–gender ratio (Kanis, 1993) and (4) the fact that the fracture incidence is increasing more rapidly in men than in women (Obrant et al., 1989).

The maximum bone mass, which is attained at the age of 20–25 years, is termed the *peak bone mass* and is primarily genetically determined. Intake of calcium and vitamin D is also important for protection against osteoporosis, and dietary supplements of vitamin D and calcium effectively reduce the incidence of fracture (Fairfield & Fletcher, 2002). Other factors of importance for the development of osteoporosis are smoking, early menopause and lack of exercise (Mosekilde, 2001).

A lack of weight-bearing exercise in children prior to puberty is a factor of great importance (McKay et al., 2000). A Dutch longitudinal study in which young people were followed for a 15-year period showed that lumbar and hip bone mineral density at the age of 28 years was significantly related to daily physical activity during adolescence and young adulthood (Kemper et al., 2000).

The “physiological window” within which the bones are affected is wide, and it is reasonable to differentiate between physical inactivity as understood to mean sedentary work/no exercise, and actual immobilization such as in paralysis, strict bed rest or travel in space.

Loss of bone during immobilization is due to an acceleration of the remodelling process caused by an enhanced negative balance/replacement unit (Krolner & Toft, 1983). The clinical consequences of immobilization are considerable. One study thus showed that immobilization due to tibia fracture led to pronounced loss of hip bone on both the

fractured side and on the contralateral side (Van der Wiel et al., 1994). In a follow-up study it was shown that the bone mineral density on the fractured side had still not normalized 5 years later (van der Poest et al., 1999). In addition, a meta-analysis has shown that 3 weeks of bed rest doubles the risk of hip fracture during the following 10 years (Law et al., 1991).

Excessive physical activity can have unintentional negative effects, including on the bones. Girls with exercise-dependent secondary amenorrhea thus lose bone and are (reversibly) sterile with reduced libido (Helge, 2001).

Osteoporosis research, prevention and treatment have previously focused on hormonal factors (especially the cessation of estrogen production around the menopause), but epidemiological, clinical and bone biology studies now indicate that mechanical factors (physical activity) play a prominent role in the health of bones. Generally speaking, the decreasing level of physical activity among the population is probably a major cause of the general increase in the incidence of hip fracture over the past 30 years.

#### Evidence for physical training

Evidence exists that aerobic training can enhance bone mineral density, while combined strength conditioning and balance training reduce the risk of falls and fractures in the elderly.

A 2002 Cochrane Review (Bonaiuti et al., 2002) based on 18 randomized-controlled trials (Chow et al., 1987; Sinaki et al., 1989; Prince et al., 1991; Grove & Londeree, 1992; Lau et al., 1992; Smidt et al., 1992; Hatori et al., 1993; Martin & Notelovitz, 1993; Revel et al., 1993; Nelson et al., 1994; Preisinger et al., 1995; Prince et al., 1995; Pruitt et al., 1995; Bravo et al., 1996; Kerr et al., 1996; Lord et al., 1996; Ebrahim et al., 1997; Mayoux-Benhamou et al., 1997) encompassing 1423 post-menopausal women assessed the effect of aerobic training or strength conditioning on bone mineral density. The study did not differentiate between women with and without osteoporosis. Aerobic training and strength conditioning both improved bone mineral density of the spine, with the weighted mean difference for the combined effect of aerobic training and strength conditioning being 1.79 (95% CI 0.58–3.01). Moderate training in the form of walking improved bone mineral density of both the spine and the hip, while aerobic training only increased bone mineral density of the wrist.

A meta-analysis (Wallace & Cumming, 2000) published in 2000 that identified 35 randomized-controlled trials of aerobic training and strength conditioning, but that also included studies of premenopausal women, concluded that both aerobic

training and strength conditioning had a positive effect on lumbar spinal bone loss in both pre- and post-menopausal women. Aerobic training probably had a positive effect on the neck of the femur, but there were too few trials to enable conclusions to be drawn regarding the effect of strength conditioning on the neck of the femur.

We have also identified a number of other systematic reviews on this topic that will not be mentioned here, either because there is considerable overlap with those already mentioned, or because it is not possible to identify the randomized trials (Ernst, 1998; Kelley, 1998a, b, c; Wolff et al., 1999; Espallargues et al., 2001; Falkenbach, 2001; Kelley et al., 2001b).

In a randomized-controlled trial (de Jong et al., 2003, 2004), 309 patients with rheumatoid arthritis were assigned to a 2-year intensive exercise program. The intervention group participated in two weekly training sessions lasting 75 min. Each session consisted of endurance training on bicycle, strength conditioning in the form of circuit training and weight-bearing sports in the form of volleyball, football, basketball or badminton. The effects of the training program were assessed every 6 months for 2 years.

The intensive exercise program, which included weight-bearing sports activities, inhibited bone mineral loss (de Jong et al., 2004), a finding that is in accordance with an earlier study of rheumatoid arthritis reporting a modest but positive effect of dynamic training on bone mineral content (Westby et al., 2000). Strength conditioning alone does not appear to affect bone mineral content in patients with rheumatoid arthritis (Hakkinen et al., 1999; Hakkinen et al., 2001b). Moreover, a recent meta-analysis found no evidence for an effect of resistance exercise in increasing or maintaining lumbar spine and femoral neck bone mineral density in premenopausal women (Kelley & Kelley, 2004).

In a randomized-controlled trial (Carter et al., 2002) of women aged 65–75 years diagnosed with osteoporosis, 93 women were randomized to a 20-week gymnastics program consisting of two 40 min sessions weekly of balance training and strength conditioning. Training improved both balance and muscle strength, but bone mineral density was not measured at the end of the study. On the other hand, 10 weeks of the same balance training and strength conditioning was not effective (Carter et al., 2001).

In another randomized-controlled trial of postmenopausal women with osteoporosis (Iwamoto et al., 2001), the subjects were randomized to control ( $n = 20$ ), 2 years of training ( $n = 8$ ) or 1 year of training followed by 1 year without training ( $n = 7$ ). The training consisted of daily walking and gymnastics. Bone mineral density improved significantly in

the exercise groups, but reverted to the level in the control group after the year without training.

An important indication for training in elderly persons is the need to improve balance and thereby prevent falls (Skelton & Beyer, 2003). Prospective cohort studies with fractures as the endpoint all show that physical activity protects against fractures (Farmer et al., 1989; Wickham et al., 1989; Paganini-Hill et al., 1991; Cummings et al., 1995; Hoidrup, 1997). A 2001 Cochrane Review (Gillespie et al., 2001) concluded that physical training had a preventative effect on fall-induced fractures.

In a recently published Australian study (Day et al., 2002), 1090 persons aged 70–84 years living at home were assigned to one of eight groups defined by the presence of one or more of the following three interventions: (1) group-based exercise, (2) home hazard management aimed at preventing falls and (3) vision improvement. The training exercises were designed to improve flexibility, leg strength and balance (which improved significantly in the exercise groups). The group-based exercise reduced the fall rate ratio to 0.82 (95% CI 0.70–0.97;  $P < 0.05$ ) relative to no intervention. With all three interventions combined, the corresponding fall rate ratio was 0.67 (95% CI 0.51–0.88;  $P < 0.004$ ).

In a 2002 meta-analysis (Robertson et al., 2002) encompassing 1016 women aged 65–97 years, strength conditioning combined with balance training was found to reduce both falls and fall-related fractures by 35% (incidence rate ratio 0.65 (95% CI 0.57–0.75) and 0.65 (95% CI 0.53–0.81), respectively). The training program was equally effective in men and women and in persons with and without a previous fall, but participants aged 80 and older benefited most from the program. An American meta-analysis arrived at the same conclusions (Province et al., 1995).

#### *Type and amount of training*

It is documented that weight-bearing exercise in very young persons helps prevent osteoporosis, and that aerobic training improves bone mineral density, while less information is available concerning the effect of strength conditioning on bone mineral density. In persons with rheumatoid arthritis, intensive physical training that includes weight-bearing activities improves bone mineral density, while strength conditioning alone does not. In elderly persons, combined strength conditioning and balance training reduces the risk of falls and fractures.

#### *Possible mechanisms*

The beneficial effect of exercise is the same in both sexes, and among other reasons is due to enhancement of bone cross-sectional area and hence to larger

bones. In addition, physical training increases muscle strength and thereby improves balance and reduces the risk of falls.

*Prescription*

The physical training should consist of a combination of aerobic exercises and strength conditioning, e.g. bicycle training, walking, running and mixed gymnastics. In elderly persons, the emphasis should be on strength conditioning and balance training, e.g. Tai Chi. Where possible, the training should initially be supervised and can beneficially be performed in groups. The training can also be integrated into daily life.

*Example of training of non-trained osteoporosis patients*

- During the first 4 weeks the sessions start with 10 min warming up on a bicycle at Borg 10.
- Thereafter the intensity is increased to Borg 15–16 for 10 min followed by 3–5 min at Borg 10. This sequence is performed twice the first week, three times the second week and four times the third week. The program entails two training sessions/week the first week and three sessions/week the second and third weeks.
- The training program for weeks 4–8 repeats the program for the third week.
- A fitness test is performed before and after 2 months. If fitness is acceptable, training is continued as described above except that the duration of the low-intensity training is reduced. If fitness is still poor, training is carried out in sequences of 5 min at Borg 17–18 followed by 3–5 min at Borg 10. This sequence is performed four times. The program entails three training sessions/week. A new fitness test is performed after 1 month.

Strength conditioning should focus on the leg muscles. Specific balance training is also recommended.

*Contraindications*

There are no absolute contraindications. The training for patients with known osteoporosis should encompass activities for which the risk of falling is low.

Fibromyalgia (Fig. 13)

*Background*

The diagnostic criteria for fibromyalgia have been described by the American College of Rheumatology (Wolfe et al., 1990) and later adjusted in a 1996 consensus report (Wolfe, 1996). Fibromyalgia is the

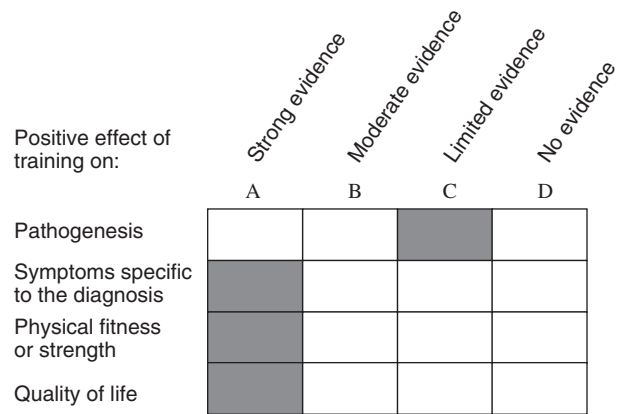


Fig. 13. Fibromyalgia.

designation for a symptom complex or syndrome that occurs in patients with widespread diffuse treatment-resistant, non-inflammatory joint and muscle pains of at least 3 months duration. The diagnosis of fibromyalgia entails: (1) generalized pains of at least 3 months duration in both sides of the body and both over and under the navel and (2) the presence of pain upon palpation of at least 11 out of 18 specified tender points.

Reduced muscle strength and rapid fatigue are common symptoms. Other symptoms are sleep disturbance, concentration difficulties, headache, lowered pain threshold, irritable bowel syndrome and parasthesia. The syndrome usually appears at the age of 30–40 years with a female:male ratio of 7:1. In the USA, the prevalence is 2% (all ages), but increases with age (Wolfe, 1996). The onset of the syndrome after the age of 55 years is rare.

Many patients with fibromyalgia are unfit (Bennett et al., 1989; Burckhardt et al., 1989; Clark et al., 1993; Clark, 1994). It is unknown whether poor fitness and muscle strength are solely a consequence of the fibromyalgia syndrome, or whether they in fact contribute etiologically to the disease. There are many theories as to the cause of the disease, but a coherent pathogenesis has not been agreed upon. Inflammation is not part of the syndrome.

Fibromyalgia is difficult to treat, and no drug treatment is available that has a proven decisive effect (Bagnall et al., 2002). Active physical training in combination with cognitive behavioral therapy is the most promising treatment for this patient group (Rossy et al., 1999).

*Evidence for physical training*

Evidence exists that endurance training has a beneficial effect on fibromyalgia. A meta-analysis (Busch et al., 2002) was published in 2001 based on 16 randomized-controlled trials encompassing 379 persons in exercise intervention groups, 277 persons in

control groups and 68 persons receiving an alternate treatment. Seven of the trials were of high quality (McCain et al., 1988; Mengshoel et al., 1992; Martin et al., 1996; Wigters et al., 1996; Buckelew et al., 1998; Gowans et al., 1999; Hakkinen et al., 2001a): four of the trials examined aerobic training, of which one examined a mixture of aerobic, strength and flexibility training, one examined strength conditioning and two examined exercise training as part of a composite treatment. The four high-quality trials that examined aerobic exercise reported significantly greater improvements in the exercise groups compared with the control groups for fitness (17.1% improvement vs 0.5% improvement) and tender point pain pressure threshold (28.1% increase vs 7% decrease) and reported fewer pains (11.4% decrease in pain vs 1.6% increase). The same conclusion was reached in the trials that did not meet the criteria for a high-quality trial.

The high-quality trials investigated training of 6–20 weeks' duration. Three of the trials included a follow-up (Wigters et al., 1996; Buckelew et al., 1998; Gowans et al., 1999). The trial by Buckelew et al. (1998) included follow-up with monthly monitoring of physical training in the home and found improved physical functioning and less pain after 1 year.

The trial by Wigters et al. (1996) found that the improvements were still apparent  $4\frac{1}{2}$  years after the training program despite the fact that only few of the patients had continued active physical training.

Gowans et al. (1999) conducted a program review of participants 3–6 months after completion of the intervention and reported significant improvements in 6 min walk, fatigue, self-efficacy for controlling pain and other symptoms.

The studies encompassed by the meta-analysis (Busch et al., 2002) differed considerably regarding the question of whether training causes the patients' symptoms to worsen. Considering all 16 trials together, more patients dropped out of the study in the training groups than in the control groups. This was not the case on just considering the high-quality trials, however (Busch et al., 2002). Since publication of the meta-analysis, we have identified a number of additional randomized-controlled trials of exercise training (Hakkinen et al., 2002; Jones et al., 2002; King et al., 2002; Mannerkorpi et al., 2002; Richards & Scott, 2002; Peters et al., 2002; van Santen et al., 2002; Redondo et al., 2004). One of the trials (Richards & Scott, 2002) encompassing 132 patients demonstrated a beneficial effect of 12 weeks of supervised aerobic exercise on pain and general function at the 1-year follow-up.

Another trial (Redondo et al., 2004) comparing 8 weeks of physical training with cognitive behavioral therapy found that functional capacity improved significantly in the training group, whereas only the

physical activity of the vertebral column improved in the cognitive-behavioral therapy group. There were no differences in anxiety, depression and self-efficacy after treatment in either group. After 1 year of follow-up, most of the parameters had returned to baseline values in both groups. However, in the training group, functional capacity remained significantly better.

Supervised training combined with patient education yielded better results than training without supervision and education (King et al., 2002). Compared with low-intensity training, high-intensity training had only a moderately better effect on physical fitness and general well-being after 20 weeks (van Santen et al., 2002). Strength conditioning has been found to enhance flexibility, muscle strength, threshold for tender point pressure and the feeling of well-being relative to a group that only underwent flexibility training (Jones et al., 2002). Pool exercise therapy was found to have beneficial effects on physical function and strength that were still present 6 months later and on pain that was still present both 6 and 24 months later (Mannerkorpi et al., 2002).

#### *Type and amount of training*

The physical training should initially be supervised and should be individually designed and primarily encompass aerobic training of moderate to high intensity. The training can beneficially be carried out in groups and should be combined with cognitive behavioral therapy. The training should gradually be integrated into daily life, possibly with the help of patient associations and gymnastics associations.

The aerobic training should be complemented with strength conditioning. An important principle is to start with low load and intensity and gradually increase them. Unfit patients will often complain of pains when performing body weight-bearing exercise and physical activity entailing eccentric work. By way of educational principle, it is therefore recommended to attempt to prevent the experience of pains during physical training. This is the reason for proposing that the initial training program consists of non-body-weight-bearing exercise devoid of eccentric components. It is important to emphasize, though, that in the long run, there are no contraindications for any form of physical training.

#### *Possible mechanisms*

The training works by breaking a vicious cycle. Pains and reduced muscle strength together with fatigue limit the patient's physical functioning. The training aims to improve fitness, thereby reducing fatigue. The training enhances muscle strength, thereby enabling the patient to better manage daily life. In

addition, it is likely that the patient benefits psychologically from experiencing that the pain threshold can be exceeded, which leads to a change in pain perception and in the pain threshold.

*Prescription*

The physical exercise has to be endurance training, although this may be supplemented with progressive muscle strength conditioning. The load and intensity should initially be low and thereafter gradually increased to the fatigue/exhaustion threshold. After 1–2 months, the training should be performed 2–3 days/week. Each session should last at least 30 min.

In principle, all forms of endurance training can be recommended. However, to avoid pain in connection with the training, it is preferable to use non-body-weight-bearing exercise without eccentric muscle contractions, e.g. cycling, swimming/training in water or rowing. For the same reason, it is recommended not to initially perform exercise entailing sudden, rapid uncontrolled movements, twisting or high loads on joints, e.g. football, handball, high-intensity running and certain forms of gymnastics entailing many twists. It is important to emphasize, though, that the long-term goal should be that the fibromyalgia patient can participate in all forms of physical activity.

*Example of a training program for patients with fibromyalgia*

- During the first 4 weeks, the sessions start with 10 min warming up on a bicycle at Borg 12. Thereafter, the intensity is increased to Borg 15–16 for 3 min followed by 2 min at Borg 12; this sequence is performed twice the first week, three times the second week and four times the third week. The program entails two training sessions/week the first week and three sessions/week the second and third weeks.
- The training program for weeks 4–8 repeats the programme for the third week.
- A fitness test is performed before and after 2 months. If fitness is acceptable, training is continued as described above except that the duration of the low-intensity training is reduced. If fitness is still poor, training is carried out in sequences of 3–4 min at Borg 17–18 followed by 1–2 min at Borg 12. This sequence is performed three or four times. The program entails three training sessions/week. A new fitness test is performed after 1 month.

Strength conditioning of the legs can be performed by carrying out part of the cycling at high load for 30 s followed by 30 s rest without any load. This sequence is performed 3–5 times. This training can be

Positive effect of training on:	Strong evidence	Moderate evidence	Limited evidence	No evidence
	A	B	C	D
Pathogenesis				
Symptoms specific to the diagnosis				
Physical fitness or strength				
Quality of life				

Fig. 14. Chronic fatigue syndrome.

performed once a week in prolongation of the endurance training.

*Contraindications*

None

Chronic fatigue syndrome (Fig. 14)

*Background*

In recent years, the term chronic fatigue syndrome (CFS) has gained acceptance as the designation for a difficult to define state that does not appear to represent a pathological disease entity. In order to promote a more uniform definition of this uncharacteristic state, the Centers for Disease Control proposed a definition in 1988 (Holmes et al., 1988). This requires the presence of two major criteria: new-onset fatigue lasting longer than 6 months with a 50% reduction in activity and the exclusion of other known sources of fatigue. In addition, diagnosis requires the presence of the following minor criteria: (Holmes et al., 1988) at least six of 11 symptoms and at least two of three physical signs or (Sharpe et al., 1991) at least eight of 11 symptoms. The 11 symptoms are: low-grade fever (37.5–38.6 °C), sore throat, painful cervical or axillary lymphadenopathy, generalized muscle weakness, muscle pains, fatigue lasting 24 h or more after moderate exercise, headaches, migratory arthralgia, sleep disturbance, neuropsychological complaints and acute onset. The three physical signs are: long-lasting low-grade fever, non-exudative pharyngitis and cervical or axillary lymphadenopathy. The so-called Oxford criteria differ on some points from the CDC criteria and are mainly applicable in a research context (Sharpe et al., 1991). The diagnosis is primarily an exclusion diagnosis.

The etiology has not been determined, and in particular there is no evidence that the disorder is viral or immunological. The syndrome typically

occurs in young adults, but sometimes also occurs in children. The ratio of the incidence in women and in men is 2:1. The syndrome rarely occurs or is detected in groups with low social status. The symptoms are rarely progressive; on the contrary, there is some tendency toward spontaneous regression. No effective medical treatment is available. Fitness and general muscle strength in patients with CFS are generally comparable with that in inactive persons in the same age group (Sisto et al., 1996; Fulcher & White, 2000).

### *Evidence for physical training*

We have only identified a few randomized-controlled trials of physical training (Fulcher & White, 1997; Wearden et al., 1998; Powell et al., 2001). One of these trials (Wearden et al., 1998) encompassed 136 patients who were randomized to four groups: physical activity and fluoxetine (antidepressant), physical activity and placebo, therapist contact and fluoxetine or therapist contact and placebo. The groups that performed progressive aerobic training were less fatigued and more fit, while the fluoxetine solely affected the depression symptoms.

In another trial (Fulcher & White, 1997), 66 patients were randomized to either graded aerobic exercise or flexibility and relaxation therapy. The graded aerobic exercise consisted of running, swimming or cycling in one daily session lasting a maximum of 30 min, 5 days a week for 12 weeks. The intensity was gradually increased to 60% of peak oxygen consumption ( $VO_{2max}$ ). The aerobic training program had a positive effect on fitness, muscle strength and fatigue, whereas the flexibility and relaxation program had significantly less effect.

In a third study (Powell et al., 2001), 148 patients with CFS were randomized to either a control group that only received standardized medical care, or to one of three intervention groups, each of which received two individual 3 h face-to-face treatment consultations at which symptoms were explained and a graded exercise program designed for the participants. In addition, one of the groups received seven telephone consultations each of 30-min duration over 3 months, and another group received seven 1 h face-to-face treatment consultations over 3 months that had the same function as the telephone consultations. This trial did not assess fitness or muscle strength. The patients' physical functioning in daily life was assessed after 3, 6 and 12 months. A positive effect was seen in all three intervention groups, but no significant differences between the groups that received much vs. little instruction, or between those that received telephone instruction vs personal instruction. Satisfactory physical functioning was achieved in 69% of the patients in the

intervention groups as compared with 6% of the controls. A positive effect was also seen on fatigue, mood, sleep and disability. In principle, the trial did not permit evaluation of whether the improved quality of life was due to the psychological support/contact or the changed physical activity pattern. However, other groups have found that therapy alone does not affect the patient's symptoms (Fulcher & White, 1997).

### *Type and amount of training*

There is some published evidence (Fulcher & White, 1997; Wearden et al., 1998; Powell et al., 2001) for recommending aerobic physical activity that should be started at low intensity and gradually increased to moderate intensity while concomitantly gradually increasing the duration. The training needs to be combined with cognitive behavioral therapy in order to be effective.

### *Possible mechanisms*

The training works by breaking a vicious circle. Fatigue reduces the patient's physical functioning. The training aims to enhance the patient's fitness, thereby reducing the fatigue. The training enhances muscle strength, thereby enabling the patient into better manage daily life. Furthermore, it is likely that the patient achieves a psychological benefit by experiencing that physical activity does not necessarily cause further fatigue.

### *Prescription*

The physical training should primarily consist of cycling or alternatively of walking/running supervised through regular attendance at the therapist and can beneficially be performed as group training. It is recommended that the training be combined with cognitive behavioral therapy.

In addition, the training can be integrated into daily life. It should be started at low intensity and gradually increased to moderate intensity while concomitantly gradually increasing the duration. Each session should last at least 30 min, of which at least 20 min should be at an intensity exceeding 60% of  $VO_{2max}$ .

An example of a training program for patients with chronic fatigue syndrome is shown below. What is essential is naturally to motivate the patient to engage in some form of physical activity.

### *Example of a training program for patients with chronic fatigue syndrome*

- During the first 4 weeks, the sessions start with 10 min warming up at a Borg 10–12, either walking or cycling.



- Thereafter, the intensity is increased to Borg 15–16 for 3min followed by 2min at Borg 10. This sequence is performed twice the first week, three times the second week and four times the third week. The program entails two training sessions/week the first week and three sessions/week the second and third weeks.
- The training program for weeks 4–8 repeats the program for the third week.
- A fitness test is performed before and after 2 months. If fitness is acceptable, training is continued as described above except that the duration of the low-intensity training is reduced. If fitness is still poor, training is carried out in sequences of 3–4 min at Borg 17–18 followed by 1–2 min at Borg 12. This sequence is performed three times. The program entails three training sessions/week. A new fitness test is performed after 1 month.

*Contraindications*

There are no contraindications.

**Other chronic diseases**

Cancer (Fig. 15)

*Background*

In our part of the world, cancer and cardiovascular diseases are the main causes of early death. Cancer is the term for a group of diseases dominated by uncontrolled cell growth resulting in compression, invasion and degradation of adjacent fresh tissue. Malignant cells can be transported by the blood or lymph to peripheral organs and give rise to secondary colonies termed metastases. The underlying common mechanism for all cancer diseases is that the genetic material in a cell changes (mutates). This can be due to environmental factors, e.g. tobacco smoking, radiation, pollution, infections and possibly also inappropriate diet. Mutations can cause

changes in the cell properties that disturb the mechanisms controlling the cell’s lifespan, whereby the cancer cells can live unhindered and uncontrolled.

The symptoms of cancer are innumerable and depend on the type of tumor and its localization. A common feature of many forms of cancer, though, is weight loss, including loss of muscle mass, and fatigue and reduced physical functioning as a result of reduced fitness and muscle atrophy. The general feeling of being unwell, poor appetite, demanding treatment regimens (surgery, chemotherapy, radiotherapy and other treatments or combinations hereof) and difficult circumstances in daily life lead to physical inactivity. Chemotherapy entails an enhanced risk of infections and contributes to physical inactivity and hence to loss of muscle mass and reduced fitness. It has been estimated that as much as one-third of the poor physical condition of cancer patients can be attributed to physical inactivity (Dietz, 1981). Fatigue is a symptom that is not solely associated with patients with active or advanced cancer, but is also found in radically treated patients (Loge et al., 1999). Cancer affects the patient’s quality of life, and attention is now increasingly being accorded to the significance of physical activity for the functioning and quality of life of cancer patients (Thune, 1998; Courneya & Friedenreich, 1999; Courneya et al., 2000; Dimeo, 2001).

*Evidence for physical training*

There is increasing epidemiological evidence that a physically active lifestyle protects against the development of colon cancer and breast cancer (Thune & Furberg, 2001). A prospective observational study based on responses from 2987 female registered nurses diagnosed with stage I, II or III breast cancer found that physical activity after diagnosis of breast cancer may reduce the risk of death from the disease. The greatest benefit was seen in women who performed the equivalent of walking 3–5 h/week at an average pace, with little evidence of a correlation between increased benefit and greater energy expenditure (Holmes et al., 2005). No intervention studies are available concerning the effect of regular exercise training on disease progression and prognosis in breast cancer, however. The aim of physical training in cancer patients is the positive effect on fitness, muscle strength, physical well-being, anxiety, depression and quality of life in the widest sense.

A 2000 review of 38 studies (Thune & Smeland, 2000) encompassed 1451 cancer patients, half of whom had breast cancer (Lindgarde et al., 1982; MacVicar & Winningham, 1986; Winningham & MacVicar, 1988; Mock et al., 1994; Bremer et al., 1997; Dimeo et al., 1997, 1998, 1999; Courneya &

Positive effect of training on:	Strong evidence A	Moderate evidence B	Limited evidence C	No evidence D
Pathogenesis				
Symptoms specific to the diagnosis				
Physical fitness or strength				
Quality of life				

Fig. 15. Cancer.

Friedenreich, 1997a,b, 1999; Pinto et al., 1998; Schulz et al., 1998; Segar et al., 1998; Derman et al., 1999; Keats et al., 1999; Courneya et al., 2000). The majority, but not all, of the studies were intervention studies (Winningham & MacVicar, 1988; Sant et al., 1995; Pinto et al., 1998; Courneya & Friedenreich, 1999; Dimeo et al., 1999; Courneya et al., 2000). Two of the studies were randomized clinical trials (Rohan et al., 1995; Segar et al., 1998). The majority of the patients were participating in curative treatment regimens encompassing radiotherapy, chemotherapy, bone marrow transplants or hormone treatment. The training programs typically encompassed walking and training on a bicycle ergometer at moderate intensity for 20–30 min three to five times a week. Training was initiated both during and after treatment and lasted from a few weeks to 6 months. Cross-section studies, retrospective studies (Bremer et al., 1997; Courneya & Friedenreich, 1997a; Pinto et al., 1998) and intervention studies (Schulz et al., 1998; Segar et al., 1998; Courneya & Friedenreich, 1999; Courneya et al., 2000) showed consistent positive effects of training in patients with breast cancer. Thus, fitness, muscle strength and weight increased, nausea and fatigue decreased and psychological parameters such as self-confidence and satisfaction improved. The same effect has been detected with training in patients with colorectal cancer, malignant blood diseases and solid tumors (Thune & Smeland, 2000; Courneya et al., 2003). A 2001 randomized-controlled trial of training in 123 patients with breast cancer (Segal et al., 2001) also found a positive effect of 6 months of aerobic training on fitness and physical functioning.

#### *Type and amount of training*

The physical training has to be individualized and supervised and include both aerobic training and strength conditioning. Cancer patients who have completed treatment are characteristically tired and physically and possibly also mentally weakened. We recommend aerobic physical activity starting with low intensity and gradually increasing to moderate intensity while concomitantly increasing the duration of the physical activity. The aerobic training is combined with strength conditioning, which is also started at low intensity and in small amounts. The group of cancer patients undergoing treatment is so heterogeneous that we have to restrict ourselves to mentioning that supervised training can be carried out, but that relative or absolute contraindications must be considered.

#### *Possible mechanisms*

Physical activity improves fitness and muscle strength, which alleviates fatigue and enhances phy-

sical functioning. It is possible that physical training enhances the patient's self-confidence and physical well-being.

#### *Prescription*

*Cancer patients who have completed treatment.* These patients will typically be unfit and have poor muscle strength. The following program is recommended:

- During the first 4 weeks, the sessions start with 10 min warming up on bicycle at Borg 10–12.
- Thereafter, the intensity is increased to Borg 15–16 for 3 min followed by 2 min at Borg 12; this sequence is performed twice in the first week, three times in the second week and four times in the third week. The program entails two training sessions/week in the first week and three sessions/week in the second and third weeks.
- The training program for weeks 4–8 repeats the program for the third week.
- A fitness test is performed before and after 2 months. If fitness is acceptable, training is continued as described above except that the duration of the low-intensity training is reduced. If fitness is still poor, training is carried out in sequences of 3–4 min at Borg 17–18 followed by 1–2 min at Borg 12. This sequence is performed three times. The program entails three training sessions/week. A new fitness test is performed after 1 month.

Strength conditioning of the legs can be performed by carrying out part of the cycling at high load for 30 s followed by 30 s rest with no load. This sequence is performed three to five times. This training can be performed once a week in prolongation of the endurance training. In addition, elements of the strength-conditioning program can be incorporated.

*Physical training of cancer patients receiving treatment.* Even hospitalized and bedridden patients can benefit from physical training (Dimeo et al., 1999), but only limited information is available about physical training during ongoing chemotherapy (Dimeo et al., 1999). It is important to underline that this patient group is so heterogeneous that it is meaningless to put forward specific programs. With many cancer patients, especially the elderly, attention should focus on preserving mobility and function.

#### *Contraindications*

Patients undergoing chemotherapy or radiotherapy with a leukocyte concentration below  $0.5 \times 10^9/L$ , hemoglobin below 6 mmol/L, thrombocyte concentration below  $20 \times 10^9/L$  and temperature above

Positive effect of training on:	Strong evidence	Moderate evidence	Limited evidence	No evidence
	A	B	C	D
Pathogenesis				
Symptoms specific to the diagnosis				
Physical fitness or strength				
Quality of life				

Fig. 16. Depression.

38 °C should not engage in physical training. Patients with bone metastases should not perform strength conditioning at high load. In cases of infection, a pause in training is recommended until the patient has been asymptomatic for a day whereafter training can be slowly resumed.

Depression (Fig. 16)

Background

Around 500 000 Danes are affected by severe depression during the course of their lifetime. The prevalence is 6%. An even greater number experience milder forms of depression. Women are affected twice as frequently as men. Some depressed persons feel unhappy and sad, while others have difficulty in feeling anything at all; a cardinal symptom is fatigue. Depressed persons are often plagued by feelings of guilt and self-reproach about being inadequate or about things that they have done wrong in the past. Some suffer from sleep disturbance. Others are plagued by painful inner uneasiness, restlessness and anxiety, which makes them unable to relax. Appetite is often reduced in depression. In some cases, the opposite is seen – markedly increased appetite, especially for carbohydrate-rich foods.

The DSM-IV criteria for diagnosis of depression are as follows: five (or more) of the following symptoms, including at least one of symptoms (1) and (2), have been present during the same 2-week period and represent a change from previous functioning: (1) depressed mood, nearly every day during most of the day, (2) marked diminished interest or pleasure in almost all activities, (3) significant weight loss (when not dieting), weight gain, or a change in appetite, (4) insomnia or hypersomnia (excess sleep), (5) psychomotor agitation or psychomotor retardation, (6) fatigue or loss of energy, (7) feelings of worthlessness or inappropriate guilt, (8) impaired ability to concentrate or indecisiveness and (9)

recurrent thoughts of death, recurrent suicidal ideation.

Evidence for physical training

There is some evidence for a beneficial effect of physical training as a supplement to medical treatment in mild and moderate depression. A 2001 meta-analysis (Lawlor & Hopker, 2001) encompassed 14 trials (Greist et al., 1979; McCann & Holmes, 1984; Reuter et al., 1981, 1984; Klein et al., 1985; Martinsen et al., 1985; Epstein, 1986; Doyne et al., 1987; Fremont & Wilcoxon Craighead, 1987; Mutric, 1988; Veale & Le Fevre, 1988; McNeil et al., 1991; Veale et al., 1992; Singh et al., 1997; Blumenthal et al., 1999). Compared with no treatment, exercise significantly reduced symptoms of depression (Beck Depression Inventory) (weighted mean difference - 7.3; 95% CI - 10.0 to - 4.6). The effect of exercise was similar to that of cognitive therapy (Lawlor & Hopker, 2001). The authors of the meta-analysis concluded that the effectiveness of exercise in reducing symptoms of depression could not be determined due to the methodological weakness of the trials. This conclusion has been partially contradicted, however (Brosse et al., 2002).

In a comprehensive study encompassing 156 persons over 50 years of age with severe depression, the patients were randomized to 4 months of aerobic physical exercise alone, 4 months of antidepressant treatment (sertraline) or 4 months of combination treatment in the form of both sertraline and physical exercise (Blumenthal et al., 1999). The onset of effect was more rapid with the drug treatment, but after 4 months there was no difference between the three groups as regards symptoms of depression. Upon reinvestigation of the patients 6 months after completion of treatment (Babyak et al., 2000), it was found that the degree of depression and relapse rate were considerably lower in the exercise-alone group. Exercising on the patients' own initiative during the 6-month follow-up period was associated with a reduced probability of depression diagnosis at the end of that period (OR 0.49; P = 0.0009). The latter naturally does not exclude the possibility that the least depressive patients had the greatest desire to exercise.

A recent study investigated the effect of different exercise regimens performed in a supervised laboratory setting in adults (n = 80) aged 20–45 years diagnosed with mild to moderate major depressive disorder (Dunn et al., 2005). Participants were randomized to one of four aerobic exercise treatment groups that varied total energy expenditure (7.0 kcal/kg/week or 17.5 kcal/kg/week) and frequency (3 days/week or 5 days/week) or to exercise placebo control (3 days/week flexibility exercise). The

17.5 kcal/kg/week dose is consistent with public health recommendations for physical activity. The study demonstrated that aerobic exercise at this dose is an effective treatment for major depressive disorder of mild to moderate severity. The effect of the lower dose was only comparable to placebo.

In concert with studies comparing the effects of various forms of exercise in depression (Martinsen, 1988; Martinsen et al., 1989; Sexton et al., 1989; Bosscher, 1993), the meta-analysis did not reveal any difference between the effects of aerobic and non-aerobic exercise. There is a lack of studies that evaluate the possible dose response in the effect on depressive symptoms (Dunn et al., 2001). A comprehensive randomized-controlled trial is examining the efficacy of five different exercise regimens varying in intensity and amount. The protocol has been published (Dunn et al., 2002), but the results are not yet available. Since publication of the meta-analysis, we have not identified any further randomized-controlled trials of exercise in depression.

*Type and amount of training*

The physical training should be individualized and supervised and encompass both aerobic training and strength conditioning. The training can beneficially be performed in small groups. We recommend aerobic exercise, starting with low intensity and gradually increasing to moderate intensity while concomitantly increasing the duration of the exercise. The aerobic exercise is combined with strength conditioning, which is also started at low intensity and strain. Due to the paucity of evidence, we recommend that training should be used as a supplement to medical treatment. With mild depression, physical activity alone can be attempted. However, it is important that the patient is followed closely by a physician.

*Possible mechanisms*

The beneficial effect on depression is assumed to be multifactorial (Salmon, 2001). In the Western world, it is considered healthy to be physically active, and depressed persons who exercise can expect both positive feedback from their milieu and social contact (Scott, 1960). As exercising is considered a normal pastime, this can make people who exercise feel normal. Moreover, if one performs high-intensity physical exercise it is difficult to concomitantly think/speculate too much, and physical exercise can be used to take one's mind off sad thoughts. Depressive persons often suffer from fatigue and feelings that things are insurmountable, which can lead to physical inactivity and loss of fitness and hence of enhanced fatigue. Physical activity enhances fitness and muscle strength and hence physical well-being. In addition, there are a number of theories that

hormonal changes during physical activity can affect mood. This applies for example to the  $\beta$ -endorphin level and monoamine concentrations (Mynors-Wallis et al., 2000). Some depressed persons have anxiety with feelings of inner uneasiness. During physical activity, the pulse increases, and one sweats. To experience these physiological changes in connection with normal physical activity could be expected to give depressed/anxious persons the important experience that it is not dangerous to have a high pulse, to sweat, etc.

*Prescription*

Supervised, progressive aerobic training or strength conditioning, where possible daily. The aerobic training can be walking/running, cycling or swimming. Initially, the training is at Borg 12–13 for 10–20 min and then gradually increased to Borg 15–16 for a total of 30 min.

The patient's fitness and muscle strength are tested prior to and after 3 months of training. If strength and fitness are satisfactory, the training program is continued. If the result is unsatisfactory, the intensity/strain is increased.

*Contraindications*

None.

**Asthma (Fig. 17)**

*Background*

Asthma is a chronic inflammatory disorder of the airways characterized by episodes of reversible reduction of lung function and airway hyper-responsiveness to a number of stimuli (National Institute of Health, 1995). Allergy is a major cause of asthma symptoms, especially in children, while many adults have asthma without the involvement of an allergic component. Environmental factors, including

Positive effect of training on:	Evidence level			
	A Strong evidence	B Moderate evidence	C Limited evidence	D No evidence
Pathogenesis				
Symptoms specific to the diagnosis				
Physical fitness or strength				
Quality of life				

*Fig. 17.* Asthma.

tobacco smoke and air pollution, contribute to the development of asthma; 6–8% of Danes have asthma.

Physical training poses a particular problem for asthmatics. On the one hand, physical activity can provoke bronchoconstriction in the majority of asthmatics (Carlsen & Carlsen, 2002). On the other, regular physical activity is important in the rehabilitation of asthma and in patient education (Orenstein, 1995). Asthmatic patients need instruction in how they can prevent exercise-induced symptoms so that they, like other people, can benefit from the positive effects of exercise on other diseases. With children, in particular, it is important that they are instructed in how physical activity can be adapted to asthma as physical activity is important for their motor and social development.

Exercise-induced asthma can be prevented by thorough warm-up as well as by the use of a number of antiasthmatics, e.g. short-acting or long-acting  $\beta$ -agonists, leukotriene antagonists or chromones. Moreover, some of the exercise-induced symptoms can be alleviated by adapting the prophylactic treatment so as to bring the asthma and hence airway responsiveness under control. Regular treatment with asthma medicine, first and foremost inhaled steroids, is decisive for the possibilities for physical training. Finally, it is important to be aware of triggers such as airway infections or triggers in the surroundings where physical activity is carried out, e.g. pollen, mold fungus, cold, air pollution, tobacco smoke, etc. Physical fitness has been found to be poor among asthmatics in some studies (Clark & Cochrane, 1988; Garfinkel et al., 1992; Malkia & Impivaara, 1998), but not in others (Santuz et al., 1997). Irrespective of how physically fit the patient is, guidance and medicine are important to enable all asthmatics to be physically active without being afraid of the symptoms.

### *Evidence for physical training*

The positive effect of physical training in patients with asthma is documented, for example in a 1999 Cochrane Review (Ram et al., 2000a,b) based on eight randomized-controlled trials (Sly et al., 1972; Swann & Hanson, 1983; Fitch et al., 1986; Cochrane & Clark, 1990; Varray et al., 1991; Girodo et al., 1992; Ahmaidi et al., 1993; Varray et al., 1995) selected from among 18 training trials.

The Cochrane Review encompasses trials of asthmatics ( $n = 226$ ) aged at least 8 years who carried out aerobic training of at least 20–30 min duration two to three times a week for at least 4 weeks. The majority of the trials included children, and none of the trials included persons aged over 40 years. No effect was found on lung function assessed as PEFr (two

trials), FEV<sub>1</sub> (three trials), FVC (two trials) or VE<sub>max</sub> (three trials). Training had no effect on the number of days with wheezing. However, physical training increased physical functioning (five trials). Fitness assessed as peak oxygen uptake (VO<sub>2max</sub>) thus increased by 5.6 mL/kg/min (95% CI 3.94–7.19,  $P < 0.00001$ ), while work capacity (one trial) increased by 28 W (95% CI 22.56–33.43,  $P < 0.00001$ ).

A non-controlled trial showed that it is possible for adult asthmatics to participate in a high-intensity training program (Emtner et al., 1996). The patients trained in an indoor swimming pool at 80–90% of their VO<sub>2max</sub> for 45 min sessions, initially once a week and thereafter twice a week for 10 weeks. Physical fitness improved, and there were fewer cases of exercise-induced asthma attacks, less anxiety in connection with exercise and less feeling of dyspnea. At the 3-year follow-up examination, 68% of the patients were still physically active, training 1–2 times a week (Emtner et al., 1998).

### *Type and amount of training*

The physical training program has to be designed individually and should primarily consist of aerobic training of moderate to high intensity, for example running, cycling, ball games or swimming.

### *Possible mechanisms*

Physical activity does not improve lung function in patients with asthma, but increases the cardiorespiratory condition via effects on the muscles and the heart. A common hypothesis (Ram et al., 2000a) is that physical training in asthmatics helps reduce ventilation during work and thereby reduces the risk of provoking an asthma attack during exercise.

### *Prescription*

Anti-inflammatory therapy, particularly with local steroids, is the single most important treatment for airway allergic diseases (Carlsen, 2004). Ten to 20 min prior to training, both fit and unfit patients should be treated with inhaled  $\beta$ -2 agonist, 1–2 puffs (Tan & Spector, 2002), and should then warm up with low-intensity exercises for 15 min.

Completely unfit patients are recommended an aerobic exercise program that starts at low intensity and gradually increases to moderate intensity while concomitantly gradually increasing the duration. After 1–2 months the training should be carried out at least 3 days a week.

### *Example of a training program for unfit asthmatics*

- All training is preceded by the administration of inhaled  $\beta$ -2 agonist, one to two puffs taken 20 min

prior to 15 min of walking or light cycling at Borg 10.

- Thereafter the intensity is increased to Borg 15–16 for 10 min followed by 3–5 min at Borg 10; this sequence is repeated two times in the first week, three times in the second week and four times in the third week. The program entails two training sessions/week in the first week and three sessions/week in the second and third weeks.
- The training program for weeks 4–8 repeats the program for the third week.
- A fitness test is performed before and after 2 months. If fitness is acceptable, training is continued as described above except that the duration of the low-intensity training is reduced. If fitness is still poor, training is carried out in sequences of 5 min at Borg 17–18 followed by 3–5 min at Borg 10; this sequence is repeated four times. The program entails three training sessions/week. A new fitness test is performed after 1 month.

*Contraindications*

In cases of acute exacerbation, a pause in training is recommended. In cases of infection, a pause in training is recommended until the patient has been asymptomatic for a day, whereafter training can be slowly resumed.

Type 1 diabetes (Fig. 18)

*Background*

Type 1 diabetes is an autoimmune disease that has its onset in childhood or adulthood. The disease is caused by the deterioration of the pancreatic  $\beta$  cells, which leads to the cessation of insulin production. The etiology is not yet known, but environmental factors (e.g. viruses, chemicals), genetic disposition and autoimmune reactions are involved. In Denmark, the incidence is approximately 15/100 000/

year, 10–15% higher in men than in women. In approximately half of all cases, the onset is after the age of 30 years. Of the persons born in any one year, approximately 1% will develop type 1 diabetes during their lifetime.

*Evidence for physical training*

Patients with type 1 diabetes are at great risk of developing cardiovascular disease (Krolewski, 1987), and physical activity protects against this (Moy et al., 1993). It is therefore important that patients with type 1 diabetes exercise regularly. Insulin requirements decrease with physical activity, thus entailing that the patient have to reduce the insulin dose when planning physical training (Rabasa-Lhoret et al., 2001), or consume carbohydrate in connection with the training (Soo et al., 1996). Patients with type 1 diabetes therefore need instruction in how to avoid hypoglycemia such that they, like other people, can benefit from the positive effects of exercise on other diseases.

Very few studies have investigated the specific effects of training in patients with type 1 diabetes, but in general there is no major difference in glycemic control between physically active and inactive patients with type 1 diabetes (Wasserman & Zinman, 1994; Veves et al., 1997), and physical exercise does not lead to any improvement (Wallberg-Henriksson et al., 1984; Yki-Jarvinen et al., 1984; Wallberg-Henriksson et al., 1986; Laaksonen et al., 2000). On the other hand, as in healthy persons, physical training leads to increased insulin sensitivity in patients with type 1 diabetes (Yki-Jarvinen et al., 1984), which is associated with a minor (approximately 5%) reduction in exogenous insulin requirement (Wallberg-Henriksson et al., 1984). Some (Johnstone et al., 1993; McNally et al., 1994; Makimattila et al., 1996; Skyrme-Jones et al., 2000), but not all (Calver et al., 1992; Elliott et al., 1993; Makimattila et al., 1997; Pinkney et al., 1999) patients with type 1 diabetes have endothelial dysfunction. Little is known about the effect of physical training on this parameter, which is reportedly both improved (Fuchsjager-Mayrl et al., 2002) and unchanged (Veves et al., 1997) after physical training.

Physical training possibly also has a positive effect on the lipid profile in patients with type 1 diabetes. In controlled trials, training has been shown to lower LDL cholesterol and triglyceride concentrations (Laaksonen et al., 2000) and raise the HDL cholesterol concentration (Laaksonen et al., 2000) and HDL cholesterol/total cholesterol ratio (Yki-Jarvinen et al., 1984; Laaksonen et al., 2000). This aspect has not been comprehensively investigated, though, and a gender difference may also exist (Wallberg-Henriksson et al., 1986). In uncontrolled or cross-section studies, an association has been found between physical training

Positive effect of training on:	Evidence level			
	A	B	C	D
Pathogenesis				
Symptoms specific to the diagnosis				
Physical fitness or strength				
Quality of life				

Fig. 18. Type 2 diabetes.

and increased HDL2 cholesterol and decreased serum triglyceride and LDL cholesterol (Gunnarsson et al., 1987; Lehmann et al., 1997). A randomized-controlled trial (Laaksonen et al., 2000) investigated the effect of 30–60 min of moderate intensity running three to five times a week for 12–16 weeks in young men with type 1 diabetes ( $n = 28+28$ ). The aerobic exercise improved fitness and work capacity as well as the lipid profile. A controlled trial showed that 4 months of aerobic physical training increased fitness by 27% ( $P = 0.04$ ), reduced insulin requirement ( $P < 0.05$ ) (Wiesinger et al., 2001) and improved endothelial function (Fuchsjäger-Mayrl et al., 2002) in patients with type 1 diabetes ( $n = 18+8$ ).

### *Type and amount of training*

Experience is greatest with aerobic training. In principle, though, patients with type 1 diabetes can participate in all forms of sports provided the contraindications/precautions are complied with. The training should be regular and should be planned taking into account insulin treatment and adjustment and regulation of diet.

### *Possible mechanisms*

Physical training enhances muscle contraction-induced glucose uptake in the muscle. The lipoproteins in the blood seem to play an important role in the development of atherosclerosis, including in patients with type 1 diabetes (Winocour et al., 1992). Physical training has beneficial effects on the plasma lipoprotein profile, both in patients with (Laaksonen et al., 2000) and without (Kraus et al., 2002) diabetes.

### *Prescription*

It is very important that the patient is carefully informed/instructed. The patient has to be instructed regarding precautions so that hypoglycemia can be prevented. The precautions include blood glucose monitoring, dietary modification and adjustment of the insulin dose. The advice given below is in line with Danish Endocrine Society recommendations and Danish Diabetes Association guidelines ([www.diabetesforeningen.dk](http://www.diabetesforeningen.dk)).

In order to prevent hypoglycemia, 10–20 g carbohydrate should be consumed 30 min prior to exercise provided the blood glucose is satisfactory. During prolonged physical activity, a 10–20 g carbohydrate snack (fruit, juice or a soft drink) should be consumed for each 30 min of exercise.

When beginning a specific training program, patients should measure their blood glucose frequently during and after the training session in order to learn their individual response to a given amount of exercise of a given duration. If hypoglycemia never-

theless still occurs, the insulin dose will have to be reduced. The insulin should be injected in a region that is not active during the training (Koivisto & Felig, 1978), and the performance of exercise immediately after the administration of regular insulin or a rapidly acting analogue cannot be recommended (Tuominen et al., 1995). The necessity for and extent of carbohydrate consumption and insulin reduction can differ depending on the type of sport being performed: specific guidelines are available for nearly all types of sport (Colberg, 2001).

Whenever possible, the training should be carried out at the same time of day and with approximately the same intensity each time. Fluid intake before and during exercise is important, especially during prolonged exercise in warm weather. Special attention should be accorded to the feet of exercising diabetes patients. Thus, if neuropathy is present, special footwear should be recommended before starting an exercise program.

The recommendations have to be individualized and should take into account late diabetic complications, but both endurance training and strength conditioning can be recommended, either combined or separately. The goal is at least 30 min of moderate intensity exercise (Borg 12–13 with short periods at Borg 15–16) daily or 3–4 h/week in the form of brisk walking, cycling, jogging, swimming, rowing, golf, etc. Attention should be paid to the presence of autonomic neuropathy, where the Borg scale is particularly well suited for assessing the intensity of the exercise, in contrast to the heart rate.

Strength conditioning should include many repetitions. The training program should also include 5–10 min warming up, 5–10 min cooling down and the intake of carbohydrate.

### *Contraindications/precautions*

Generally speaking, the danger associated with not exercising is greater than that associated with exercising, although special precautions apply.

Exercise should be postponed if blood glucose is  $> 14$  mmol/L together with ketonuria and  $> 17$  mmol/L without ketonuria, in both cases before it is corrected. The same applies if blood glucose is  $< 7$  mmol/L.

In patients with hypertension and active proliferative retinopathy, high-intensity training or training involving Valsalva-like maneuvers should be avoided. Strength conditioning should be carried out only using light weights and in short series.

Patients with neuropathy and incipient foot ulcers should refrain from activities entailing the bearing of the patient's own body weight. Repeated strain on neuropathic feet can lead to ulceration and fractures. Treadmills, long walks/jogs and step exercises are

advised against, while non-body-weight-bearing exercises such as cycling, swimming and rowing are recommended.

One should be aware that patients with autonomic neuropathy can have severe ischemia without ischemic symptoms (silent ischemia). These patients typically have resting tachycardia, orthostatism and poor thermoregulation. They are at risk of sudden cardiac death. Referral to a cardiologist, exercise ECG or myocardial scintigraphy should be considered. The patients should be instructed to avoid exercising in cold/warm temperatures and to ensure adequate hydration when exercising.

## Acknowledgments

This article is based upon a translation by David I Barry of a chapter of our book *Fysisk aktivitet – håndbog om forebyggelse og behandling* published by the National Board of Health, Copenhagen in 2003 and updated in October 2004 (ISBN printed: 87-91232-77-5; electronic: 87-91232-78-3; available at www.sst.dk/publikationer). We thank David I Barry for help in ensuring correct interpretation of and reference to original source material. The Centre of Inflammation and Metabolism is supported by a grant from the Danish National Research Foundation (# 02-512-55). The Copenhagen Muscle Research Centre is supported by grants from The Copenhagen Hospital Corporation, The University of Copenhagen, The Faculties of Science and of Health Sciences at this University.

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