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Exercise as medicine – evidence for prescribing exercise as therapy in 26 different chronic diseases

B. K. Pedersen[1], **B. Saltin**[2]

[1]The Centre of Inflammation and Metabolism and The Center for Physical Activity Research, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark, [2]The Copenhagen Muscle Research Centre, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark
Corresponding author: Bente Klarlund Pedersen, Rigshospitalet 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

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This review provides the reader with the up-to-date evidence-based basis for prescribing exercise as medicine in the treatment of 26 different diseases: psychiatric diseases (depression, anxiety, stress, schizophrenia); neurological diseases (dementia, Parkinson's disease, multiple sclerosis); metabolic diseases (obesity, hyperlipidemia, metabolic syndrome, polycystic ovarian syndrome, type 2 diabetes, type 1 diabetes); cardiovascular diseases (hypertension, coronary heart disease, heart failure, cerebral apoplexy, and claudication intermittent); pulmonary diseases (chronic obstructive pulmonary disease, asthma, cystic fibrosis); musculo-skeletal disorders (osteoarthritis, osteoporosis, back pain, rheumatoid arthritis); and cancer. The effect of exercise therapy on disease pathogenesis and symptoms are given and the possible mechanisms of action are discussed. We have interpreted the scientific literature and for each disease, we provide the reader with our best advice regarding the optimal type and dose for prescription of exercise.

Introduction

Here we present an update of a previously published review "Evidence for prescribing exercise as therapy in chronic disease" from 2006 (Pedersen & Saltin, 2006). Physical activity represents a cornerstone in the primary prevention of at least 35 chronic conditions (Booth et al., 2012). However, over the past two decades, considerable knowledge has accumulated concerning the significance of exercise as the first-line treatment of several chronic diseases. Of note, today exercise has a role as medicine in diseases that do not primarily manifest as disorders of the locomotive apparatus. When we selected diagnoses to be included in this review, we took into account both the frequency of the diseases and the relative need for exercise therapy. Twenty-six diseases covering various aspects of the medical curriculum are included. These are psychiatric diseases (depression, anxiety, stress, schizophrenia); neurological diseases (dementia, Parkinson's disease, multiple sclerosis); metabolic diseases (adiposity, hyperlipidemia, metabolic syndrome, polycystic ovarian syndrome, type 2 diabetes, type 1 diabetes); cardiovascular diseases (hypertension, coronary heart disease, heart failure, cerebral apoplexy, and intermittent claudication); pulmonary diseases (chronic obstructive pulmonary disease, asthma, cystic fibrosis); musculo-skeletal disorders (osteoarthritis, osteoporosis, back pain, rheumatoid arthritis); and cancer. We provide the reader with the evidence-based basis for prescribing exercise as medicine for all of these diseases. We than briefly discuss possible mechanisms of action. Finally, regarding type and dose of exercise we suggest specific recommendations, which are based on evidence, experience and common sense.

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 meta-analyses and thereafter identified additional controlled trials. We then selected studies in which the intervention was aerobic or strength exercise and have given priority to randomized controlled trials (RCTs).

Psychiatric diseases

Depression

Background

Depression is a common and important cause of morbidity and mortality worldwide. Depression is commonly treated with antidepressants and/or psychological therapy, but some people may prefer alternative approaches such as exercise. Cross-sectional studies show an inverse association between fitness and depression symptoms (Thirlaway & Benton, 1992; Galper et al., 2006; Tolmunen et al., 2006). One study found that regular physical activity was associated with a lower incidence of depression (Paffenbarger et al., 1994). Another prospective epidemiological study indicates that being physically fit prevents depression (Sui et al., 2009). Most recently a prospective study was published suggesting that low fitness is more strongly associated with the onset of elevated depressive symptoms than is fatness (Becofsky et al., 2015). These studies are, however, unable to indicate whether there is a causal relationship between physical activity and depression.

Evidence-based physical training

There is some, but modest evidence of a positive effect of physical training on depression symptoms (Josefsson et al., 2014). A 2013 Cochrane Review (Cooney et al., 2013), which was an update of a 2009 review (Mead et al., 2009), comprised 39 trials (2326 participants) that met the inclusion criteria, of which 37 provided data for meta-analyses. There were, however, multiple sources of bias in many of the trials; randomization was adequately concealed in 14 studies, 15 used intention-to-treat analyses and 12 used blinded outcome assessors. For the 35 trials (1356 participants) comparing exercise with no treatment or a control intervention, the pooled standardized mean difference (SMD) for the primary outcome of depression at the end of treatment was −0.62 [95% confidence interval (CI): −0.81 to −0.42], indicating a moderate clinical effect. When the authors included only the six trials

(464 participants) with adequate allocation concealment, intention-to-treat analysis and blinded outcome assessment, the pooled SMD for this outcome was not statistically significant (−0.18, 95% CI: −0.47 to 0.11). Pooled data from the eight trials (377 participants) providing long-term follow-up data on mood found a small effect in favor of exercise (SMD: −0.33, 95% CI: −0.63 to −0.03). Seven trials compared exercise with psychological therapy (189 participants), and found no significant difference (SMD: −.03, 95% CI: −0.32 to 0.26). Four trials (n = 300) compared exercise with pharmacological treatment and found no significant difference (SMD: −0.11, 95% CI: −0.34, 0.12). One trial (n = 18) reported that exercise was more effective than bright light therapy (SMD: −6.40, 95% CI: −10.20 to −2.60). In the individual studies showing a significant effect on depression symptoms, the amount of exercise and/or intensity was greater than in the studies showing negative results.

A comprehensive study comprising 156 subjects over the age of 50 with severe depression randomized the patients to 4 months of aerobic exercise, 4 months of treatment with antidepressants (sertraline), and 4 months of treatment with both sertraline and physical training (Blumenthal et al., 1999). The exercise groups received supervised training of a relatively high intensity three times a week. Each session began with 10 min of warm-up, 30 min of cycling or jogging, and 5 min of cool down. Participants were assigned individual training ranges equivalent to 70% to 85% of heart rate reserve calculated from the maximum heart rate achieved during the treadmill test. The intensity was checked three times during each training session. The medical treatment had a quicker initial effect, but after 4 months, there was no difference between the three groups for symptoms of depression (Blumenthal et al., 1999). The patients were examined again after 10 months (Babyak et al., 2000). This check-up showed that there were significantly lower levels of depression symptoms and fewer incidences of relapse in the exercise groups. When all of the patients were analyzed together using multivariate analysis, there was a reduced risk of depression symptoms if the patients were physically active, regardless of group (odds ratio = 0.49, P = 0.0009). This last fact does not exclude that the least depressed individuals had the strongest desire to exercise.

Experience derives largely from the field of aerobic exercise. A 2009 Cochrane Review (Mead et al., 2009), however, was unable to point to a particular type of training as the most effective, similar to studies that directly compared various types of exercise (Martinsen, 1988; Martinsen et al., 1989; Sexton et al., 1989; Bosscher, 1993). The 2013 Cochrane Review (Cooney et al., 2013) concluded that the tendency was that more sessions have a larger effect on mood than a smaller number of sessions, and that resistance and mixed training were more effective than aerobic training. It appears, however, that it is not possible to determine the optimum type, frequency, and duration of exercise, whether it should be performed supervised or unsupervised, indoors or outdoors, or in a group or alone.

A meta-analysis from 2015 found some evidence that exercise may be effective in treating depression during pregnancy but the conclusion is based on only six low-moderate quality trials (Daley et al., 2015). Another meta-analysis from 2014 found strong evidence for an effect of exercise on depression in patients with heart failure (Tu et al., 2014).

Possible mechanisms

The positive effect on depression is believed to be multifactorial (Salmon, 2001). In the Western world, physical exercise is considered part of a healthy lifestyle and the depressed individuals who exercise regularly can expect positive feedback from their environment and social contact (Scott, 1960). Exercise is a normal activity that can lead to a positive cycle, i.e., the person engaging in physical exercise feels normal. Physical activity at a relatively high intensity makes it difficult to simultaneously think/worry excessively, and physical activity can be used as a distraction from sad thoughts.

Depressed people often suffer from fatigue and the feeling that life is insurmountable, which can lead to physical inactivity, a loss of fitness, and thus increased fatigue. Physical activity increases aerobic capacity and muscle strength, and thus physical well-being.

There are also various theories that hormonal changes occurring during physical activity can have an effect on mood. This applies, for example, to the amount of beta-endorphins and monoamine concentrations (Mynors-Wallis et al., 2000). Some depressed people suffer from anxiety with a feeling of inner turmoil. During physical activity, the heart rate increases and perspiration occurs. Experiencing these physiological changes in the context of normal physical activity may give the depressed individual the significant insight that a high pulse and sweating are not dangerous.

Exercise stimulates growth of new nerve cells and release of proteins known to improve health and survival of nerve cells. It is indeed possible that physical activity has a direct positive effect on the hippocampus. People with depression have reduced hippocampal volume (Campbell et al., 2004), and treatment with antidepressants allows the formation of new cells in the hippocampus (Manji et al., 2000). When rats exercise, their hippocampus grows (Bjornebekk et al., 2005). In humans, regular physical activity for 3 months has been shown to lead to an increase in hippocampal volume and improved short-term memory (Pajonk et al., 2010). Brain-derived neutrophic factor (BDNF) is a growth factor for the hippocampus. People with dementia may have low levels of BDNF in the brain and in the blood (Pedersen, 2011). However, elevated levels of BDNF have been found in rapid cycling bipolar disorder patients (Munkholm et al., 2014). Every time physical activity occurs, the BDNF level increases in the brain, blood, and muscles (Pedersen, 2011) and it is possible that BDNF represents a mechanism by which physical activity can influence symptoms of depression (Matthews et al., 2009; Pedersen et al., 2009; Huang et al., 2014).

Type of training

Due to the modest evidence, specific recommendations cannot be made regarding the type of exercise. It is important to create a framework in which patients with mental illness can exercise in keeping with general recommendations. The trend is, however, that more sessions have a larger effect on depression score than a smaller number of sessions. Furthermore, resistance and mixed training may be more effective than aerobic training.

Contraindications

No general contraindications.

Anxiety

Background

Anxiety disorders are the most common mental health problem globally (Campbell Burton et al., 2013). An estimated 5% of the adult population is currently suffering from morbid anxiety. In the course of a year, approximately 7% of the population will experience some form of anxiety disorder, while 15% will experience having an anxiety disorder during their lifetime. Women experience anxiety twice as often as men, with the exception of obsessive compulsive disorder (OCD) and fear of illness (hypochondria), where the frequency is the same for both sexes.

In some instances, anxiety is functionally appropriate and even advantageous when it prompts protective health behavior, and a certain amount would be considered a normal reaction to experiencing a life-threatening events (Campbell Burton et al., 2013). However, anxiety disorders or anxiety 'caseness' (i.e., substantially elevated levels of anxiety symptoms as identified by a rating scale) are associated with reduced quality of life (Donnellan et al., 2010) and risk of disabling health conditions and may even augment risk of death (Martens et al., 2010; Campbell Burton et al., 2013).

The main overall anxiety orders are phobias (agoraphobia, social phobia, and specific phobia), panic disorder, and generalized anxiety disorder. There are also special forms of anxiety such as OCD and post-traumatic stress disorder. Anxiety also appears as a symptom in many different physical and mental illnesses.

The exact causes of anxiety are unknown, but it is often a case of a combination of biological vulnerability and stress during childhood or later in life. The severity of the anxiety may vary over time and spontaneous improvement can occur. Without treatment, many people experience long-term or chronic disablement. Epidemiological studies indicate that regular physical activity helps to prevent symptoms of anxiety, but there are no studies that shed light on whether a causal relationship exists (Pasco et al., 2011).

Evidence-based physical training

There is some, but limited knowledge about the effects of physical activity as a treatment for anxiety (Bartley et al., 2013; Wegner et al., 2014). In several randomized controlled trials involving subjects with a normal or increased level of anxiety who do not meet the criteria for psychiatric diagnosis, it has been shown that physical activity can reduce symptoms of anxiety and tension. It is uncertain, however, whether it has a long-lasting effect (Raglin, 1997; Conn, 2010; Bartley et al., 2013).

Classical studies from the 1970s examine individuals who experienced anxiety attacks when they had to ride the bus. When the subjects got on the bus, they were gripped by anxiety, had a high pulse, were sweating, and felt they were unable to breathe. The patients were asked to run for the bus so they had a high pulse and were breathless when they got on it. Consequently, their physical symptoms were at their maximum level and did not worsen when they got on the bus. The patients attributed their high heart rate, tendency to perspire, and breathlessness to running for the bus and their fear declined (Orwin, 1973, 1974).

A meta-analysis from 2010 comprising 40 studies concludes that physical training reduces symptoms of anxiety in people with chronic illnesses, including cardiovascular disease, fibromyalgia, multiple sclerosis, mental disorders, cancer, and chronic obstructive pulmonary disease (Herring et al., 2010).

Possible mechanisms

The positive effect on anxiety disorders is thought to be multifactorial. Some suggest that physical activity is a form of distraction that diverts the patient's anxiety symptoms. In support of this theory, it is argued that the same effect can be achieved by resting in a soundproof room (Bahrke & Morgan, 1978). As described for depression, physical activity is considered part of a healthy lifestyle and individuals with mental illness who are physically active can expect positive feedback from their environment and social contact (Scott, 1960) mood. People with anxiety experience inner turmoil. During physical activity, the heart rate increases and perspiration occurs. Experiencing these physiological changes in the context of normal physical activity may give the anxious individual the significant insight that a high pulse and sweating are not dangerous.

Type of training

The physical training program must be individualized and supervision is beneficial. Experience derives largely from the field of aerobic exercise. Training is best done in small groups. It is recommended to start with low-intensity aerobic physical activity and steadily increase to moderate intensity, with a gradual increase in duration (Herring et al., 2010). Patients with anxiety may be taking beta blockers and will therefore not experience an increased heart rate, but can instead be monitored using the Borg Scale. Supervised progressive aerobic exercise is advantageous. Examples of aerobic exercise include walking/running, cycling, and swimming. The physical activity should be monitored so that the patient gradually reaches a Borg Scale of 15–16. Initially, the training should be 12–13 on the Borg Scale for 10–20 min with a gradual increase to 15–16 for 30 min in total.

Contraindications

No general contraindications.

Stress

Background

Stress is a common occurrence in everyday life and repeated or traumatic stress can be a precipitating factor for illnesses of the central nervous system, as well as peripheral organ systems. Stress alone is not a disease, but long-term stress can lead to illness. Thus, severe or long-term psychological stress can not only induce depression, a leading illness worldwide, but can also cause psychosomatic diseases such as asthma and rheumatoid arthritis (Iwata et al., 2013).

It is difficult to measure stress directly. There are, however, a number of physiological changes in the body that occur when it is exposed to stress. Typically, it is possible to measure elevated levels of cytokines and stress hormones, such as cortisol and catecholamines, which can then serve as stress markers. High levels of catecholamines can lead to an increase in blood pressure, while high levels of cortisol in chronic stress may contribute to changes in glucose and fat metabolism, as well as in the coagulation system (Iwata et al., 2013).

People who feel stressed often have undesirable lifestyles in terms of tobacco smoke, alcohol consumption, diet, and exercise. This lifestyle is probably a major direct reason why an increased risk of, e.g., cardiovascular disease, is found in people suffering from stress (Theorell et al., 2006).

Evidence-based physical training

There is some, though modest evidence that physical training can have a positive effect on psychological stress symptoms. Physically fit individuals exhibit fewer pronounced signs of the physiological activation associated with psychosocial stress (Peronnet et al., 1981; Georgiades et al., 2000; Rimmele et al., 2007).

An American study (Galper et al., 2006) examines the relationship between level of physical fitness and mental well-being. The 5451 adult subjects (aged 20–88) in the study completed a treadmill test to determine their fitness level and filled out a questionnaire asking them to indicate their participation in leisure and sports activities over the preceding 3 months. The subjects' mental well-being was evaluated based on questionnaires asking about the presence of symptoms of depression. The subjects were divided into three groups, depending on their level of fitness as measured by the treadmill test. The subjects were then divided into an additional four groups based on self-reported participation in regular exercise activities (inactive, insufficiently active, sufficiently active, and very active). The study showed the subjects who were more physically fit and more physically active experienced fewer symptoms of depression. Furthermore, an association was found between physical fitness and overall mental well-being.

One intervention study (Norris et al., 1992) examines the effect of physical training on stress in adolescents (13- to 17-year olds). Sixty subjects were randomized into four groups. Over a period of 10 weeks, three of the groups completed training programs comprising, respectively, high-intensity aerobic exercise (70–75% of maximum pulse), moderately intense aerobic exercise (50–60% of maximum pulse), and stretching and flexibility training, while the last group did not exercise and thus served as the control group. Before and after the training program, the subjects completed questionnaires to determine self-reported stress levels (perceived stress scale), anxiety, and depression. They also did a step test to determine their level of fitness based on heart rate values. The group that did high-intensity cardio achieved a lower resting heart rate and improved diastolic blood pressure compared to the other groups. With regard to the self-reported stress level, the questionnaire results showed that the group that did high-intensity exercise had the greatest reduction in stress and anxiety symptoms. The findings from the study indicate that a relatively short period of training can have beneficial psychological effects in adolescents, including reducing stress if the exercise is of high intensity.

Another study showed, however, that moderately intense exercise can also reduce stress indicators (Rogers et al., 1996). After 12 weeks of exercise, the subjects in the moderate-intensity exercise group [40–50% of maximum oxygen uptake (VO_{2max})] had a lower resting blood pressure and a lower blood pressure in response to a stress compared to the group that did high-intensity exercise (70–80% of VO_{2max}).

The type of exercise also appears to determine whether it has a positive effect on stress (Norris et al., 1990). One study randomized healthy English police officers to either 10 weeks of aerobic training (n = 28) or 10 weeks of strength training (n = 24), while a group of 25 male police officers served as the control group. After the training period, the subjects in the aerobic exercise group had significantly less work-related stress than both the strength training and control group. There was, on the other hand, no difference in work-related stress between the strength training and control groups after the training period.

A systematic Review from 2014 (Wang et al., 2014) suggests that qigong exercise immediately relieve anxiety among healthy adults, compared to lecture attendance and structured movements only.

In summary, there is thus some evidence to suggest that regular exercise and being physically fit can reduce stress levels. The degree of perceived stress is less apparent the higher one's level of physical fitness is. There are divergent research findings in terms of whether to exercise at a high or moderate intensity to avoid stress, but aerobic exercise seems to have a better effect than strength training.

Possible mechanisms

Some studies suggest that physical activity acts as a form of distraction that diverts the patient's psychological stress (Scott, 1960).

Type of training

The physical training program needs to be individualized and should be supervised. The training must involve aerobic exercise that begins at a low intensity and gradually increases to moderate intensity, just as the duration of the physical activity should steadily increase. There is no evidence that exercising at a specific intensity is more beneficial than another. The aerobic training can involve walking/running, cycling, or swimming.

Contraindications

No general contraindications.

Schizophrenia

Background

Schizophrenia is the name for a group of mental disorders characterized by abnormal thoughts and emotions. Typical symptoms of schizophrenia are hallucinations, delusions, and thought disorder. Other symptoms include social withdrawal, lack of energy, impoverished language, lack of emotion and cognitive symptoms, such as problems with verbal learning, visual learning, social cognition, speed of information processing, and problems with forming and finding words. Life time risk is below 1% worldwide and schizophrenia affects 24 million people around the world (Rastad et al., 2014). Symptoms tend to decline between the ages of 45 and 50, but the disorder is often severely disabling and only very few schizophrenia patients are in employment. Approximately 25% of patients recover completely, 50% recover socially (i.e., receive medical treatment but function socially), and the last 25% remain at a low functioning level and need support in their daily lives.

The general consensus is that schizophrenia is caused by a combination of several different factors – including biological, psychological, and social. Dopamine is believed to play a role in the pathogenesis of schizophrenia. The dopamine hypothesis assumes that schizophrenia develops due to excessive levels of dopamine or oversensitivity to dopamine in the prefrontal cortex. Antipsychotic medicine works by blocking much of the dopaminergic activity in the brain. Many incidences of schizophrenia are largely hereditary, but the disorder does not seem to have a direct genetic cause (Glenthoj & Hemmingsen, 1997).

There is a significant prevalence of excess mortality among schizophrenia patients compared to the general population, even discounting suicide. This excess mortality is linked, among other things, to an increased incidence of type 2 diabetes and cardiovascular disease (Laursen & Nordentoft, 2011; Schoepf et al., 2012).

It has consistently been shown that lower physical activity participation is correlated with the presence of negative symptoms and cardio-metabolic comorbidity. Also, side effects of antipsychotic medication, lack of knowledge on cardiovascular disease risk factors, no belief in the health benefits, a lower self-efficacy, other unhealthy lifestyle habits, and social isolation are correlated with lower low physical activity (Vancampfort et al., 2012a).

Evidence-based physical training

A meta-analysis from 2015 (Firth et al., 2015) identified 20 eligible studies. Exercise interventions have no significant effect on body mass index (BMI), but can improve physical fitness and other cardiometabolic risk factors. Psychiatric symptoms were significantly reduced by interventions using around 90 min of moderate-to-vigorous exercise per week. This amount of exercise was also reported to improve functioning, co-morbid disorders, and cognition.

A systematic review from 2012 included 10 randomized controlled trials; six of these studies addressed the use of aerobic and strength exercises. In two of these studies, yoga techniques also were investigated. Four studies addressed the use of progressive muscle relaxation. There is evidence that aerobic and strength exercises and yoga reduce psychiatric symptoms, state anxiety, and psychological distress and improve health-related quality of life, that aerobic exercise improves short-term memory, that progressive muscle relaxation reduces state anxiety and psychological distress, and that physical training therapy in general offers added value in the multidisciplinary care of people with schizophrenia (Vancampfort et al., 2012b). Routine physical activity/exercise appears to decrease the severity of negative symptoms (Beebe et al., 2005; Acil et al., 2008; Gorczynski & Faulkner, 2010), reduce stress and anxiety (Fleshner, 2005), improve concentration and attention (Chaddock et al., 2010), and reduce depression severity (Laske et al., 2010) in schizophrenia.

Older studies indicate that physical activity reduces auditory hallucinations (Chamove, 1986; Lukoff et al., 1986). Other studies show that physically active patients experience auditory hallucinations as less distressing (Falloon & Talbot, 1981; Holmes et al., 1994; Shergill et al., 1998).

People with schizophrenia are often overweight because their medication stimulates their appetite and at the same time increases social withdrawal and a physically inactive lifestyle. A healthy diet and physical activity are found to affect patients' weight and simple health parameters such as triglycerides, total cholesterol, plasma insulin, and plasma glucose in the same way as they are said to affect the weight of people who do not suffer from mental illness (Wu et al., 2007, 2008).

People with schizophrenia often have accompanying symptoms, such as anxiety and stress, and physical activity can help alleviate these symptoms. In some cases, physical activity can provide an infrastructure and an environment that support social interactions and thus help the patients to establish networks, counteracting the tendency toward social withdrawal. Patients with schizophrenia are found to have a lower hippocampus volume compared to healthy people, a finding that may be significant for the pathogenesis of the chronic psychotic symptoms (Harrison, 2004; Steen et al., 2006). A 2010 study shows that aerobic exercise over a 3-month period led to an increase in the size of the hippocampus and an improvement in the short-term memory of people with schizophrenia (Pajonk et al., 2010).

Possible mechanisms

Some studies indicate that physical activity acts as a type of distraction, diverting the patient's attention away from the hallucinations so they are perceived as less troublesome. In the Western world, physical exercise is considered part of a healthy lifestyle and people suffering from a mental disorder who exercise can expect positive feedback from their environment and social contacts (Scott, 1960). Exercising is a normal activity that can lead to a positive cycle: the person engaging in physical exercise feels normal. Relatively high-intensity exercise makes it difficult to think/worry excessively and physical activity can be used as a diversion from hallucinations, thoughts, and situations that can lead to anxiety. Patients with schizophrenia tend to have a poor body image (Sell, 1994). The feeling of well-being that is often experienced after physical activity can contribute positively to the experience of the body. Moreover, physical exercise often leads to a stimulation of sensory input from the body.

The effect of training on the hippocampus is presumably brought about by (BDNF), which is a growth factor for the hippocampus. Intensive physical training increases BDNF levels in the brain and increase hippocampal volume in patients with schizophrenia (Pedersen et al., 2009).

Type of training

It is important for the training to take into account the individual situation of the person in terms of physical environment, a recognizable structure and level of social participation. Sustained motivation and support often also play a key role in participation (Brown et al., 1999; Faulkner et al., 2006). The physical training program needs to be individualized and supervision is beneficial.

Experience derives largely from the field of aerobic exercise. Training is best done in small groups. It is recommended to start with low-intensity aerobic exercise and gradually increase to moderate intensity, with a gradual increase in duration.

Adults with schizophrenia who wish to lose weight should aim to be physically active at least 1 h a day. Many patients would certainly also benefit from strength training, although only limited experience is available with this type of training.

Contraindications

No general contraindications.

Neurological diseases

Dementia

Background

Dementia is an impairment of the brain's cognitive function beyond what would normally be expected regarding impairment due to old age. There are more than 200 different diseases that may cause dementia, of which the most common is neurodegenerative diseases, such as Alzheimer's disease, which causes over half of all cases of dementia. Vascular dementia is also an important type of dementia and is caused by atherosclerosis in the brain's blood vessels. Dementia is not a natural consequence of aging. It is always due to illness or injury in the brain tissue, although old age is the strongest risk factor for developing dementia. The majority of older people retain their cognitive functions and do not become demented. However, as a result of increasing life expectancy, the number of elderly will rise in the future and the amount of people with dementia is likely to follow this trend. While only 3% of people between the ages of 65–74 have dementia, 47% of people over the age of 85 have some form of dementia (Budson & Solomon, 2011).

A 2010 meta-analysis (Aarsland et al., 2010) concludes that physical activity prevents vascular dementia. The analysis, which includes 24 studies, finds a significant association between physical activity and a reduced risk of 0.62 (95% CI: 0.42–0.92) for developing vascular dementia. Other studies show that regular physical activity prevents Alzheimer's disease (Yoshitake et al., 1995; Laurin et al., 2001; Verghese et al., 2003; Abbott et al., 2004; Podewils et al., 2005; Rovio et al., 2005; Rovio et al., 2007; Ravaglia et al., 2008; Andel et al., 2008; Larson et al., 2006; Akbaraly et al., 2009; Scarmeas et al., 2009; Elwood et al., 2013).

One meta-analysis (Williams et al., 2010) shows that the hazard ratio for developing Alzheimer's disease is 0.718 (0.525–0.982), which corresponds to physical activity, especially of high intensity, being associated with an approximately 28% reduced risk. These studies are supported by a twin study showing that persistent vigorous leisure-time physical activity protects from dementia, and that the effect appears to remain after taking into account childhood environment (Iso-Markku et al., 2015). Another twin study showed that low physical fitness (Nyberg et al., 2014) is a risk factor for early-onset dementia.

Most studies also suggest that physical activity prevents cognitive impairment, but the results are not robust and there is a need for more research applying standardized methods for measuring the level of physical activity in daily life (Ho et al., 2001; Laurin et al., 2001; Schuit et al., 2001; Yaffe et al., 2001; Verghese et al., 2006; Devore et al., 2009; Yaffe et al., 2009; Lytle et al., 2004; Williams et al., 2010).

Evidence-based physical training

Despite the strong evidence that physical exercise may lower the risk of dementia, there are relatively few studies allowing to conclude on the effects of exercise in patients with a diagnosis of dementia. According to a Cochrane review 2013, there is promising evidence that exercise programs can have a significant impact in improving ability to perform activity of daily living (ADL) and possibly in improving cognition in people with dementia, although some caution is advised in interpreting these findings (Forbes et al., 2015).

Sixteen trials with 937 participants met the inclusion criteria. The included trials were highly heterogeneous in terms of subtype and severity of participants' dementia, and type, duration, and frequency of exercise. Only two trials included participants living at home. The meta-analysis suggested that exercise programs might have a significant impact on improving cognitive functioning and found a significant effect of exercise programs on the ability of people with dementia to perform ADLs. It was further found that the burden experienced by informal caregivers providing care in the home may be reduced when they supervise the participation of the family member with dementia in an exercise program.

One study (Kemoun et al., 2010) included 31 elderly subjects with dementia randomized to a training group or a control group. The training program comprised 15 weeks of 1 h of physical activity three times a week. After 15 weeks, the training group had improved their cognitive function, while the control group experienced a decline in cognitive function. The training group improved their gate function, but the opposite was true in the control group. Similar to the previous study, other studies find that simple interventions in the form of a few hours of physical activity per week have a positive effect on physical function in elderly people with dementia (Rolland et al., 2007; Steinberg et al., 2009).

Most older persons with dementia living in nursing homes spend their days without engaging in much physical activity. A systematic review therefore looked at the influence that the environment has on their level of physical activity. Three hundred and twenty-six studies were selected as potentially relevant; of these, 24 met all the inclusion criteria. Positive results on the residents' levels of physical activity were found for music, a homelike environment and functional modifications (Anderiesen et al., 2014).

Studies have also been undertaken examining whether physical activity affects the cognitive function of elderly people without dementia. Lautenschlager et al. (2008) included 170 elderly subjects who experienced subjective memory impairment without dementia. The participants were randomized to either a control group or a training group, which did a 24-week home-based program with 3 × 50 min workouts a week. The training had a significant, albeit modest, positive effect on the participant‘s cognitive function. The effect was still present 1 year after cessation of exercise (Lautenschlager et al., 2008).

Baker et al. (2010) included 33 middle-aged and older people with mild cognitive impairment who were randomized to either a control group that did stretching and balance exercises or to a training group that did intensive aerobic training 45–60 min a day, 4 days a week for up to 6 months. There was a significant positive effect on the participants' cognitive function measured with the help of a neurological test battery. The effect was twice as strong for women as for men (Baker et al., 2010).

Erickson et al. (2011) included 120 elderly subjects who were randomized to either a control group that did stretching and muscle training or to a training group that walked three times a week for 40 min for a year at a brisk pace. The physical training had a significantly positive effect on the volume of the hippocampus and a non-significant effect on the participants' spatial memory (Erickson et al., 2011).

Overall, there is some evidence that physical activity prevents dementia but only modest evidence for an effect of physical activity on cognitive function in people who have already developed dementia. Physical training has a positive effect on physical function, for example, the gait function of people with dementia.

Possible mechanisms

The epidemiology suggests that vascular and metabolic risk factors are the major players in cognitive impairment and dementia, including Alzheimer‘s disease (Fillit et al., 2008; Li et al., 2014). Theoretically, physical activity can prevent dementia due to an effect on the hippocampus. The effect of exercise on the hippocampus is probably mediated by BDNF, which is a growth factor in the hippocampus. Acute physical exercise increases BDNF levels in the brain (Pedersen et al., 2009). Environmental enrichment and voluntary exercise have consistently been shown to increase adult hippocampal neurogenesis and improve spatial learning ability (Olson et al., 2006).

People with dementia have low levels of BDNF (Kim et al., 2011). A randomized controlled trial with 120 older adults showed that aerobic exercise training increases the size of the anterior hippocampus, leading to improvements in spatial memory. Exercise training increased hippocampal volume by 2%, effectively reversing age-related loss in volume. Furthermore, increased hippocampal volume is associated with greater serum levels of BDNF. Hippocampal volume declined in the control group, but higher pre-intervention fitness partially attenuated the decline, suggesting that fitness protects against volume loss (Erickson et al., 2011).

Following exercise training, relative hippocampal volume increased significantly in patients (12%) and healthy subjects (16%), with no change in the non-exercise group of patients. Changes in hippocampal volume in the exercise group were correlated with improvements in aerobic fitness measured by change in maximum oxygen consumption ($r = 0.71$; $P = 0.003$). Furthermore, improvement in test scores for short-term memory in the combined exercise and non-exercise schizophrenia group was correlated with change in hippocampal volume (Pajonk et al., 2010). Other studies confirm that cardiorespiratory fitness (CRF) may have a positive impact on brain volume (Scheewe et al., 2013). Inflammation contributes to the pathogenesis of Alzheimer's disease (Pedersen, 2009). The fact that regular physical exercise induces anti-inflammatory effects (Petersen & Pedersen, 2005) may contribute to explain the positive effects of exercise in the treatment of dementia.

Type of training

Training needs to be individualized and supervised, as well as designed to maintain gait, balance, and functional ability.

Contraindications

No general contraindications.

Parkinson's disease

Background

Parkinson's disease is the second most common neurodegenerative disease after Alzheimer's disease and affects approximately seven million people globally. Parkinson's disease is more common in the elderly and prevalence rises from 1% in those over 60 years of age to 4% of the population over 80. The mean age of onset is around 60 years, although 5–10% of cases, classified as young onset, begin between the ages of 20 and 50 (de Lau & Breteler, 2006).

At disease onset, symptoms often affect the upper and/or lower limbs on one side of the body, but generally spread to the rest of the body as the disease progresses. Typical symptoms are tremors, rigidity, and slow movement as well as problems with fine motor skills. Later symptoms a stooped posture, a slow, shuffling gait with stiff arms, and problems of balance. Speech can become monotonous and toneless and patients may develop problems with swallowing. Symptoms affecting the autonomic nervous system generally take the form of constipation, incontinence, and in some cases erectile dysfunction and orthostatic hypotension. Patients also experience insomnia and depression at an advanced stage of the disease, with some patients experiencing memory problems and a lack of concentration and initiative. Approximately 20% develop a slow progressive dementia.

Evidence-based physical training

There is evidence pointing to the positive impact of physical training (Ahlskog, 2011; Alonso-Frech et al., 2011; Earhart & Falvo, 2013; Frazzitta et al., 2013; Konerth & Childers, 2013). A 2010 Cochrane Review (Mehrholz et al., 2010) assessed the significance of treadmill training. The analysis included eight trials involving 203 participants. Treadmill training was found to increase walking speed, stride, and walking distance. The conclusions of the analysis echoed those of a systematic review from 2008 (Goodwin et al., 2008). These analyses add to a 2001 meta-analysis (de Goede et al., 2001) involving a wide range of therapy, all-round physical training, sensory training, and mobility training. The duration of the physical exercise was 3–21 weeks with a total of 9–157.5 h of training. Overall, it was established that the training regime had a significant impact on walking speed.

A prospective crossover study investigated the effects of 4 weeks of treadmill training with partial body weight support and general physiotherapy (n = 10). The study found that the aerobic exercise, unlike the unspecific physiotherapy, improved the patients' ability to manage their daily lives (ADL) and their muscle function (Miyai et al., 2000). In a later study, patients were randomized for the same form of training or physiotherapy (Miyai et al., 2002) (n = 24) and were monitored for 6 months. The training had a sustainable effect, especially on gait function.

In one study, 33 patients were randomized to walking training over 4 weeks or to conventional physiotherapy. The walking training had a positive effect on gait function (Yang et al., 2010). Randomizing for 10 weeks' training with or without supervision by the physiotherapist showed that the supervised training had a greater effect than the training program carried out by the patients independently at home (Dereli & Yaliman, 2010).

Another study compared group boxing training to traditional group exercise on function and quality of life in persons with Parkinson's disease. A convenience sample of adults with Parkinson's disease (n = 31) were randomly assigned to boxing training or traditional exercise for 24–36 sessions, each lasting 90 min, over 12 weeks. Boxing training included: stretching, boxing (e.g., lateral foot work, punching bags), resistance exercises, and aerobic training. Traditional exercise included: stretching, resistance exercises, aerobic training, and balance activities. The traditional exercise group demonstrated greater gains in balance confidence than the boxing group. Only the boxing group demonstrated significant improvements in gait velocity and endurance over time. Both groups demonstrated significant improvements with the balance, mobility, and quality of life (Combs et al., 2013).

A 16-month randomized controlled exercise intervention investigated three exercise approaches: flexibility/balance/function exercise (FBF), supervised aerobic exercise (AE), and home-based exercise (control). The participants were 121 individuals with early- or mid-stage Parkinson's disease. The FBF program (individualized spinal and extremity flexibility exercises followed by group balance/functional training) was supervised by a physical therapist. The AE program (using a treadmill, bike, or elliptical trainer) was supervised by an exercise trainer. Supervision was provided 3 days/week for 4 months, and then monthly (16 months total). The control group participants exercised at home using the National Parkinson Foundation Fitness Counts program, with one supervised, clinic-based group session/month. Of the 121 participants, 86.8%, 82.6%, and 79.3% completed 4, 10, and 16 months, respectively, of the intervention. Findings demonstrated overall functional benefits at 4 months in the FBF group and improved walking economy (up to 16 months) in the AE group. Thus, both FBF and AE programs may be important for people with early- and mid-stage Parkinson's disease (Schenkman et al., 2012).

The latter study showed that supervised training may have long-term effects in Parkinson's disease. A pilot study explored the feasibility, acceptability, and preliminary evidence of the effectiveness of a virtual exercise coach to promote daily walking in community-dwelling persons with Parkinson's disease. Twenty patients participated in this phase 1, single-group, non-randomized clinical trial. The subjects were instructed to interact with the virtual exercise coach for 5 min, wear a pedometer, and walk daily for 1 month. At the study completion, there was 100% retention rate. Interaction history revealed that the participants logged in for a mean (SD) of 25.4 days of the recommended 30 days. The mean adherence to daily walking was 85%. Both gait speed and the 6-min walk test significantly improved (Ellis et al., 2013).

Possible mechanisms

Parkinson's patients have a changed frequency modulation of motor units when initiating a muscle contraction (Petajan & Jarcho, 1975). Through medication in the form of L-DOPA, the motor units can be recruited more easily (Petajan & Jarcho, 1975) and energy is utilized more efficiently during physical activity (LeWitt et al., 1994). In rodent models of Parkinson disease, which rely on administration of neurotoxins (6-OHDA or MPTP) to induce parkinsonian symptoms, exercise attenuates the degree of injury to midbrain dopaminergic neurons, and restores basal ganglia function through adaptive mechanisms of dopamine and glutamate neurotransmission. However, these findings have yet to be translated to the human disease (Speelman et al., 2011).

Type of training

Training should be tailored to the individual and depends on the stage of the disease. Patients should ideally undergo an exercise program that involves fitness and strength training as well as balance and coordination training. Auditory rhythm stimulation may be tried with a view to stimulating increased walking speed.

A program of aerobic training on a treadmill with the necessary support is recommended, starting at an intensity with which the patient can cope and gradually increasing the duration of training to 10 min and subsequently gradually increasing intensity. Patients should be encouraged to try balance and muscle strength training.

Contraindications

No general contraindications.

Multiple sclerosis

Background

Multiple sclerosis is a chronic disease normally resulting in gradual, progressive disability. The number of people with multiple sclerosis is 2–2.5 million (approximately 30 per 100 000) globally, with rates varying widely in different regions. The disease occurs more often in women than in men and it usually develops between the ages of 20–40. It is characterized by recurring neurological deficits (attacks) in different parts of the nervous system caused by local demyelination processes (plaques). Over time, the symptoms spread to different parts of the body. Individual attacks can manifest themselves in highly different ways, but common symptoms are paresis, disturbed sensation, ataxia, loss of autonomic functions, weakness, and fatigue. The symptomatology of each patient is different, depending on the location of the plaques, which makes evidence-based studies difficult to carry out.

Evidence-based physical training

A systematic review from 2013 included 54 studies and found strong evidence that exercise performed two times/week at a moderate intensity increases aerobic capacity and muscular strength. The authors concluded that among those with mild to moderate disability from multiple sclerosis, there is sufficient evidence that exercise training is effective for improving both aerobic capacity and muscular strength and that exercise may improve mobility, fatigue, and health-related quality of life (Latimer-Cheung et al., 2013).

It has been suggested that physical exercise might have the potential to have an impact on multiple sclerosis pathology and thereby slow down the disease process in patients with multiple sclerosis. However, it was recently concluded that although some evidence supports the possibility of a disease-modifying potential of exercise (or physical activity) in MS patients, future studies using better methodologies are needed to confirm this (Dalgas & Stenager, 2012; Amatya et al., 2013).

A systematic review from 2012 evaluated the effect of resistance training (Kjolhede et al., 2012). Sixteen studies were included. The authors found strong evidence regarding the beneficial effect of progressive resistance training on muscle strength. Regarding functional capacity, balance, and self-reported measures (fatigue, quality of life, and mood) evidence is less strong, but the tendency is overall positive. Indications of an effect on underlying mechanisms such as muscle morphological changes, neural adaptations and cytokines also exist, but the studies investigating these aspects are few and inconclusive (Kjolhede et al., 2012). A 2009 meta-analysis (Snook & Motl, 2009), which includes 22 studies involving nearly 600 people with multiple sclerosis, assesses the effect of physical training on walking ability. The physical training involved physiotherapy both with and without equipment and different forms of physical training on land and in water. Walking ability was found to improvement by 19% and this increased to 32% if the training was supervised. The meta-analysis found that the physical training described above has an overall positive effect on patients' quality of life (Motl & Gosney, 2008).

A 2007 Cochrane Review evaluates the impact of multi-disciplinary interventions (Khan et al., 2007). The main conclusion of the study, and that of a 2005 Cochrane Review, is that further research is needed on the effects of structured physical training for this patient group (Rietberg et al., 2005).

A randomized controlled study assessed the effects of progressive strength training and identified a clear impact on strength and function after 12 weeks (Dalgas et al., 2009), as well as an improvement in depression score, fatigue symptoms, and quality of life (Dalgas et al., 2010).

The importance of aerobic exercise was assessed in a randomized controlled trial involving 54 patients with multiple sclerosis (Petajan et al., 1996), which was randomized to a control group or training program consisting of 3 × 40 min of combined arm and leg bicycle ergometry over 15 weeks. The training group increased maximum oxygen uptake (VO_{2max}), improved leg and arm muscle strength, improved bladder function, and showed fewer depression and fatigue symptoms. There was also an improvement in lipid profile.

Another randomized control trial (Rodgers et al., 1999) involving 18 patients with multiple sclerosis found that 6 months of physical training increased mobility but had only a moderate effect on walking ability. Two randomized controlled trials showed that it was possible to increase inspiratory and expiratory muscle strength and thus cough force after 3 months of training for the respiratory muscles (Smeltzer et al., 1996; Gosselink et al., 2000).

A 2001 meta-analysis involving 23 studies shows that ergotherapy/physiotherapy increases muscle strength, mobility, and physical well-being, and improves the ability to carry out daily functions such as getting dressed and taking care of personal hygiene (Baker & Tickle-Degnen, 2001).

A meta-analysis from 2014 concludes that the available evidence indicates that exercise training can yield a small, yet statistically significant and reliable reduction in depressive symptoms for people with multiple sclerosis (Ensari et al., 2014).

Possible mechanisms

Deficits lead to paresis, which leads to restricted motor function. This in turn limits the possibilities for physical activity, leading to deterioration in physical fitness. Low muscle strength and poor physical condition can contribute to the experience of fatigue while muscle fatigue is not related to any change in metabolic conditions in patients with multiple sclerosis (Kent-Braun et al., 1994). The aim of the training program is to recover muscle strength, coordination, and fitness.

Type of training

The training program needs to be individualized and depends on the stage of the disease. Initially the program should be supervised, with a combination of fitness and muscle training recommended in early stages and in the case of patients with light to moderate deficits. Ergotherapy is important at all stages of the disease. Many patients experience a worsening of symptoms during training; however, this is a temporary phenomenon and thus does not imply any "danger", which is why the patient should be encouraged to continue with the program (Smith et al., 2006). As a number of patients suffer from temperature sensitivity, it is important to make sure they do not become chilled during training.

Contraindications

No general contraindications. A recent systematic review concluded that cardiopulmonary exercise testing is safe (van den Akker et al., 2015).

Metabolic diseases

Obesity

Background

Several studies show a *U*-shaped association between BMI and mortality, which means that both low and high BMI are associated with increased risk of premature death. The risk associated with low BMI is associated with decreased lean body mass and not reduced fat mass (Heitmann & Frederiksen, 2009). A review from 2014 (Barry et al., 2014) attempted to quantify the joint association of CRF and weight status on mortality from all causes using meta-analytical methodology. Ten articles were included in the final analysis and pooled hazard ratios were assessed for each comparison group (i.e., normal weight-unfit, overweight-unfit and -fit, and obese-unfit and -fit) using a random-effects model. Compared to normal weight-fit individuals, unfit individuals had twice the risk of mortality regardless of BMI. It appears that overweight and obese-fit individuals have similar mortality risks as normal weight-fit individuals.

Evidence-based physical training

The importance of physical activity for weight loss assessed by body weight or BMI is controversial, but physical training leads to a reduction in fat mass and abdominal obesity, in addition to counteracting loss of muscle mass during dieting. Strong evidence exists that physical activity is important for preventing weight gain in general, as well as for maintaining body weight after weight loss.

Weight loss through physical training

A Cochrane Review from 2006 (Shaw et al., 2006) comprising 3476 overweight or obese individuals studied 41 randomized controlled trials and concluded that physical activity alone induced significant weight loss, while physical activity combined with a restricted diet and dietary counseling was more effective. High-intensity physical activity was more effective than moderate activity. The authors defined physical training as "any form of physical exercise that is repeated regularly for a certain period of time". A prerequisite was that the physical training had to be quantifiable. The physical training intervention mainly consisted of walking, using an exercise bike, jogging, and weight training. In most of the studies, the intensity of the training was greater than 60% of the maximum oxygen uptake/heart rate. The participants exercised most frequently for 40–50 min per session, 3–5 times a week. All of the studies showed that physical exercise induced a slight reduction in body weight and BMI. The combination of exercise and diet resulted in an average greater weight loss (difference: 1.0 kg, 95% CI: 0.7–1.3 kg, n = 2157) and a greater decrease in BMI (difference: 0.4 kg/m^2, 95% CI: 0.1–0.7 kg/m^2, n = 452) than diet alone. Without diet, high-intensity physical training (~60% of the maximum oxygen uptake/pulse) led to greater weight loss (difference: 1.5 kg, 95% CI: 0.7–2.3 kg, n = 317) than low-intensity physical training.

The Cochrane Review showed that physical training for overweight and obese adults had positive effects on both body weight and risk factors for cardiovascular disease. Physical training combined with a restricted diet/dietary counseling reduces body weight slightly but significantly more than a restricted diet/dietary counseling only. Studies with physical training without dietary change showed that high-intensity physical training reduced body weight more than low-intensity physical training. These results are consistent with other meta-analyses (Wu et al., 2009; Johns et al., 2014).

Maintaining body weight through physical exercise

A 2001 meta-analysis (Anderson et al., 2001) comprised six non-randomized studies (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) containing information about the importance of physical activity for maintaining body weight after weight loss. The group of physically active subjects initially lost 21 kg, while the group of physically inactive subjects lost 22 kg. After 2.7 years, the weight loss in the physically active group was 15 and 7 kg for the physically inactive group.

A Danish follow-up study (Svendsen et al., 1994) included 118 overweight post-menopausal women who had completed a randomized weight loss intervention in which they were allocated to 12 weeks of diet alone, diet plus physical training or to the control group. The 12 weeks of training had no long-term effect, but a significant effect on body weight and fat mass, if the women continued to exercise on their own.

Observational studies generally indicate that physical activity has a positive effect on maintenance of weight loss after a diet (Rissanen et al., 1991; Williamson et al., 1993; Haapanen et al., 1997; Barefoot et al., 1998; Donnelly et al., 2004). Individuals who increase their level of physical activity after a diet maintain their weight better in some studies (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), while other studies cannot demonstrate an effect from physical activity (Bild et al., 1996; Crawford et al., 1999). Non-randomized weight loss studies with a prospective follow-up find that individuals with a high level of physical activity gain less weight than individuals 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; McGuire et al., 1999). One study found no such correlation (Sarlio-Lahteenkorva et al., 2000).

Studies in which participants were randomized to physical training or to a control group (Perri et al., 1988; Leermakers et al., 1999; Fogelholm et al., 2000) (n = 672) assessed the effect of physical activity on maintaining body weight. The patients who exercised had a weight gain of 4.8 kg, while the control group gained 6.0 kg. A number of studies (Perri et al., 1986; Sikand et al., 1988; King et al., 1989a; Pavlou et al., 1989; van Dale et al., 1990; Wadden et al., 1998) assessed patients (n = 475) who were randomized to a weight reduction program with or without physical training. After 1–2 years, the exercise group had gained 4.8 kg on average, while the control group had gained 6.6 kg. Similar results were confirmed in a 1997 meta-analysis (Miller et al., 1997), which showed that among 493 moderately overweight individuals, there was an average weight loss of 11 kg after 15 weeks of a restricted diet/counseling or restricted diet/counseling plus training.

After 1 year, the restricted diet/counseling group had maintained a weight loss of 6.6 kg, while the restricted diet/dietary counseling plus exercise group had maintained its weight loss of 8.6 kg.

A literature review of 26 articles assessed the independent effects of normal weight vs obesity: fit vs unfit and physically active vs physically inactive. The risk of all-cause mortality and cardiovascular death was lower in individuals with high BMI who were physically fit compared to individuals with normal BMI and a lower level of physical fitness. The literature review, however, could not confirm results from other studies that showed that a high level of physical activity gave the same protection as being physically fit. Individuals with a high BMI and a high level of physical activity had a greater risk of developing type 2 diabetes and cardiovascular disease than those with a normal BMI and low level of physical activity.

There are many possible explanations as to why physical fitness and not a high level of physical activity protect against the serious health consequences of overweight and obesity. Information on physical activity in most studies is based on self-reported information, which is subject to considerable inaccuracy, while fitness is an objective measure. Another possible explanation is that primarily physical activity of high intensity leads to improved fitness and thereby protection against diseases associated with obesity (Fogelholm, 2010).

Obesity is often associated with hypertension, hypercholesterolemia, hypertriglyceridemia, and insulin resistance. The effect of physical training on these risk markers is described separately on pages 14, 16 and 26. Obesity is also frequently associated with erectile dysfunction, which physical training can contribute to prevent (Derby et al., 2000; Esposito et al., 2004).

Possible mechanisms

Physical training increases energy expenditure and induces lipolysis, whereupon the fat mass is reduced, if the energy expended is not compensated for with an increase in caloric intake.

Type of training

For weight loss, a large volume of moderately intense aerobic exercise is recommended, preferably in combination with strength training. Because physical fitness has an independent impact on preventing diseases associated with obesity, it is recommended that moderate physical activity be combined with activities that build fitness in the form of high-intensity physical activity. The goal is at least 60 min of moderately intense physical activity daily. Many overweight and obese patients have, however, concomitant hypertension or symptomatic ischemic cardiovascular disease. As a result, recommendations must be individualized.

Contraindications

There are no general contraindications; however, training should take into account any competing diseases. With ischemic heart disease, brief rigorously intensive workouts should be refrained from. With hypertension, strength training should be performed with light weights and low contraction velocity.

Hyperlipidemia

Background

Hyperlipidemia is a group of disorders of lipoprotein metabolism entailing elevated blood levels of certain forms of cholesterol and triglyceride. Primary hyperlipidemia 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. There is consensus that physical activity protects against the development of cardiovascular diseases (National Heart, Lung and Blood Institute, 1998; Brown et al., 2001) and it has been suggested that one of many mechanisms could be a positive effect of exercise on the lipid profile of the blood (Prong, 1003; National Institutes of Health Consensus Development Panel, 1993). Epidemiological studies indicate that physical activity prevents hyperlipidemia (Thelle et al., 1976; Forde et al., 1986).

Evidence-based physical training

Today, evidence shows that a large volume of physical training, independent of weight loss, has a beneficial effect on the lipid profile of the blood. A number of review articles summarize this knowledge (Prong, 1003; Tran et al., 1983; Tran & Weltman, 1985; Lokey & Tran, 1989; Leon, 1991; Durstine & Haskell, 1994; Stefanick & Wood, 1994; U.S. Department of Health and Human Services, 1996; Crouse et al., 1997; Stefanick et al., 1998; Leon, 1999; Leon & Sanchez, 2001; Armstrong & Simons-Morton, 1994; Farrell et al., 2012; Mann et al., 2014).

A 2007 meta-analysis studied the effect of training on high-density lipoprotein (HDL) cholesterol. The analysis included 25 randomized controlled trials. The training comprised walking, cycling or swimming (Kodama et al., 2007). Training had a significant but moderate effect on HDL cholesterol. The minimum amount of physical activity needed to cause an effect was 120 min of physical activity weekly or an energy expenditure equivalent to 3780 kJ. The duration of the physical activity was more important than its intensity. Each time the duration of the physical activity was increased by 10 min, the HDL cholesterol level increased on average by 1.4 mg/dL (0.036 mmol/L).

The average effect of physical activity on HDL is clinically relevant, albeit somewhat smaller than the effect achieved when using drugs that lower lipid levels (Knopp, 1999). It is estimated that each time HDL increases 0.025 mmol/L, the cardiovascular risk goes down by 2% for men and by at least 3% for women (Pasternak et al., 1990; Nicklas et al., 1997). Training induced a mean increase of 0.036 mmol/L in the level of HDL. For the subgroup of individuals with a BMI of less than 28 and a total cholesterol level over 5.7 mmol/L, it was found that exercise induced an increase of 0.054 mmol/L in the level of HDL (Kraus et al., 2002). For the latter group, physical training was thus able to reduce the cardiovascular risk by about 4% for men and by 6% for women.

A review article from 2014 (Mann et al., 2014) includes 13 published investigations and two review articles and conclude that both aerobic, resistance exercise and the combination of aerobic and resistance training have impact on cholesterol levels and blood lipids.

A randomized clinical controlled trial evaluated the effect of training volume and intensity in a study comprising 111 physically inactive overweight men with mild to moderate hyperlipidemia (Kraus et al., 2002). The subjects were randomized to a control group or 8 months of high-volume/high-intensity physical training [32 km/week at 65–80% maximum oxygen uptake (VO_{2max})]; low volume/high intensity (19 km/week at 65–80% of VO_{2max}) or low volume/low intensity (19 km/week at 40–55% of VO_{2max}). This study distinguishes itself by evaluating an extensive lipid profile in which the size of the lipid–protein particles is also included. Subjects were asked to maintain their weight and individuals with excessive weight loss were excluded. Despite this, there was a small but significant amount of weight loss in the training groups. All of the training groups achieved a positive effect on their lipid profile compared to the control group, but there was no significant difference in the effect of training in the two groups with a low volume of exercise, although the high-intensity group achieved a greater improvement in fitness. There is a significantly better effect from a high volume of physical training on virtually all lipid parameters, although the two groups with high-intensity training achieved the same improvement in fitness level. There was no effect on the total cholesterol level. High-volume/high-intensity training reduced the level of low-density lipoprotein (LDL), intermediate-density lipoprotein (IDL), and small LDL particles and increased the size of the LDL particles and the level of HDL. All of the groups had a positive effect on the level of triglyceride, VLD triglyceride, and the size of VLDL. Thus, the volume of training had clear effects, but the intensity of the training had less impact.

A 2010 meta-analysis compared 13 randomized controlled trials that examined the effect of resistance training on parameters related to metabolic syndrome. Resistance training showed a significant effect on obesity, HbA1c, and systolic blood pressure, but no effect on total cholesterol, HDL cholesterol, or LDL cholesterol (Strasser et al., 2010).

A 2012 systematic review (Hayashino et al., 2012) assessed the effect of supervised exercise interventions on lipid profiles and blood pressure control in patients with type 2 diabetes. Forty-two RCTs (2808 subjects) met inclusion criteria and were included in the meta-analysis. It was concluded that supervised exercise is effective in improving blood pressure control, lowering LDL-C, and elevating HDL-C levels in people with diabetes.

Possible mechanisms

Training increases the ability of muscles to better burn fat instead of glycogen. This is achieved by activation of a number of enzymes in the skeletal muscle necessary for lipid turnover (Saltin & Helge, 2000).

Type of training

There is solid evidence that physical training should be of a large volume, assessed as the distance covered, or energy expended. There is evidence for an effect of both aerobic training and resistance training. If light to moderately intense physical activity is preferred, then it is necessary to train twice as long compared to doing high-intensity physical activity.

Many patients with hyperlipidemia have hypertension or symptomatic ischemic heart disease. Recommendations should thus be largely tailored to the individual. Treatment should follow the general recommendations for physical activity for adults, but it is recommended that the volume be increased, for example, to 60 min of moderately intense physical activity daily most days of the week. Alternatively, it is possible to increase the intensity and halve the time or to alternate. According to the previously mentioned dose–response study (Kraus et al., 2002), it is advantageous to walk or run at least 20 km a week, preferably 30, in order to control one's cholesterol level with physical activity.

Contraindications

There are no general contraindications; however, measures will depend on the co-morbidity. With hypertension, strength training should be performed with light weights and low contraction velocity.

Metabolic syndrome

Background

Metabolic syndrome is also known as insulin resistance syndrome, as one of the traits of the disorder is reduced insulin activity. There are several definitions for metabolic syndrome but it encompasses abdominal obesity, insulin resistance, hypertension, and hyperlipidemia.

The International Diabetes Federation (Ford, 2005) defines metabolic syndrome as follows:

Abdominal obesity, i.e., waist circumference ≥94 cm for men and ≥80 cm for women, plus at least two of the following four risk factors:

Plasma concentration of triglycerides	≥1.7 mmol/L
Plasma concentration of HDL cholesterol	<1.0 mmol/L for men and <1.2 mmol/L for women
Blood pressure	Systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg or receiving antihypersensitive therapy
Plasma concentration of glucose (fasting)	≥5.6 mmol/L or type 2 diabetes

Metabolic syndrome rarely occurs in people with normal weight but it can occur and there is a higher incidence among members of the Pakistani and Turkish ethnic minorities than members of the general population with the same BMI. Metabolic syndrome is a precursor of type 2 diabetes and large-scale epidemiological studies show that physical activity can prevent the onset of metabolic syndrome (Cho et al., 2009; Ilanne-Parikka et al., 2010).

Evidence-based physical exercise

Physical exercise and insulin resistance/prevention of type 2 diabetes. A 2008 Cochrane Review (Orozco et al., 2008) assessed the effect of a combination of diet and physical exercise as prophylaxis against type 2 diabetes. Physical exercise varied from a recommended increase in daily physical activity to supervised physical training of varying intensity and up to several times a week. Most programs included walking, running, or cycling at different intensities. The diets were low calorie with reduced fat and high fiber.

The participants in the analysis had a pathological glucose tolerance and/or metabolic syndrome. The analysis included eight trials with 2241 participants in one group, who were prescribed physical activity and placed on a diet as described above, and 2509 control persons. The studies ran over a period of 1 and 6 years. Exercise and diet significantly lowered the risk of type 2 diabetes (RR: 0.63, 95% CI: 0.49–0.79). A significant impact on body weight, BMI, waist-to-hip ratio, and waist circumference was also identified, as was a moderate impact on blood lipids. The intervention had a marked effect on both systolic and diastolic blood pressure (Orozco et al., 2008).

The isolated effect of exercise alone as prevention against diabetes in patients with pathological glucose tolerance is sparsely documented but there is solid evidence pointing to the effect of combined physical exercise and diet. A Chinese study divided 577 people with pathological glucose tolerance into four groups: diet, exercise, diet + exercise and control, and monitored them over 6 years (Pan et al., 1997). The risk of diabetes fell 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 were given a health check-up. Those with pathological glucose tolerance were divided into two groups: (a) exercise + diet ($n = 288$) and (b) no intervention ($n = 135$) (Eriksson & Lindgarde, 1998) and were monitored over 12 years. The mortality rate was the same in the intervention group as among the healthy control group (6.5% vs 6.2%) and lower than in the group with pathological glucose tolerance, which did not exercise (6.5% vs 14%). Thus, among all the participants with pathological glucose tolerance there was a predictive effect of intervention but not a predictive effect of BMI, blood pressure, smoking, cholesterol, or glucose level.

Two randomized controlled trials included people with pathological glucose tolerance and found that changes in lifestyle protected against development of type 2 diabetes. A Finnish study randomized 522 overweight middle-aged men and women with pathological glucose tolerance to physical exercise and diet or control (Tuomilehto et al., 2001) and monitored them over 3.2 years. The lifestyle intervention consisted of individual counseling on reduction of calorie intake, reduction of fat intake, and an increase in fiber-rich foods and daily physical activity. The risk of type 2 diabetes fell by 58% in the intervention group. The greatest effect was recorded with the patients who underwent the most extensive lifestyle changes (Lindstrom et al., 2003a; Lindstrom et al., 2003b).

An American study randomized 3234 people with pathological glucose tolerance to either treatment with metformin or a lifestyle program involving moderate physical activity in the form of at least 150 min of brisk walking a week and a reduced-calorie diet or no intervention. The subjects were monitored over 2.8 years (Knowler et al., 2002). The lifestyle intervention group had a 58% lower risk of contracting type 2 diabetes. Thus, the reduction matched the findings in the Finnish study (Tuomilehto et al., 2001), while the metformin treatment only reduced the risk of diabetes by 31%. As can be seen, it is not formally possible to assess the isolated effect of exercise with respect to diet in three of the studies mentioned (Eriksson & Lindgarde, 1998; Tuomilehto et al., 2001; Knowler et al., 2002), but the intervention group experienced only a moderate weight loss.

In the Finnish study, 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). The intervention group thus experienced a drop in BMI from around 31 to around 30 in the Finnish study (Tuomilehto et al., 2001) and from 34 to 33 in the American study (Knowler et al., 2002).

Physical exercise and abdominal obesity. Visceral fat constitutes an independent risk factor for developing heart disease. A cross-sectional study showed that overweight men with a high level of fitness have a significantly lower visceral fat than overweight men with a poor level of fitness (O'Donovan et al., 2009).

A group of young, healthy, normal weight men who normally walked 10 000 paces every day reduced their paces to 1500 per day over a period of 2 weeks. They experienced a significant rise in volume of visceral fat (7%) despite a total average weight loss of 1.2 kg (Olsen et al., 2008).

Irrespective of other fat deposits, abdominal obesity is a major risk factor for hyperlipidemia (Nguyen-Duy et al., 2003; Janiszewski et al., 2008), lower glucose tolerance (Janssen et al., 2002), insulin resistance (Ross et al., 2002), systemic inflammation (Forouhi et al., 2001), hypertension (Hayashi et al., 2004), type 2 diabetes (Boyko et al., 2000), and all-cause mortality (Kuk et al., 2006). There is a link between regular physical activity, with or without weight loss, and reduction in visceral fat volume (Ross & Janssen, 2001; Irwin et al., 2003; Giannopoulou et al., 2005; Janiszewski & Ross, 2007).

Increasing physical activity to 60 min/day over 3 months has been found to reduce visceral fat volume by about 30% (Ross et al., 2000; Ross et al., 2004). It should be emphasized, however, that changes in visceral fat volume as a response to physical exercise vary considerably and that it is not possible to identify a clear correlation between amount of physical exercise and reduction in visceral fat (Green et al., 2004; Ross et al., 2004; Ohkawara et al., 2007).

In relation to reduction of visceral fat tissue deposits, however, no specific method exists (surgery, diet, physical activity, etc.) for achieving this. Intervention-induced reduction of visceral fat tissue deposits relates to reduction of the total volume of fat tissue and the initial ratio of volume of visceral fat tissue to volume of total fat, regardless of how the reduction in fat tissue is achieved (Hallgreen & Hall, 2008).

Studies have shown that an increase in daily physical activity leads to a significant reduction in quantity of visceral fat and/or abdominal circumference, despite no or minimal alteration in total body weight. Thus, studies on people with type 2 diabetes show that 2–3 months of regular moderate-intensity aerobic training leads to a significant reduction in quantity of visceral fat (−27% to −45%) (Mourier et al., 1997; Boudou et al., 2003; Lee et al., 2005). There is a corresponding finding for healthy, normal weight pre-menopausal women (Thomas et al., 2000), healthy, middle-aged men (Shojaee-Moradie et al., 2007), and HIV-positive men with lipodystrophy (Lindegaard et al., 2008).

Middle-aged, normal weight or overweight men, and overweight women can expect to see a reduction in visceral fat volume (−10 to −19%) after 3 months of regular physical activity. These results also apply to older, overweight individuals (60–80 years) (Davidson et al., 2009). As a result of exercise, either strength or stamina training for 80 min a week, test subjects did not accumulate visceral fat after dieting and losing weight, while the control group that did not exercise increased their volume of visceral fact by 38% (Hunter et al., 2010).

The effect of physical exercise on hypertension and hyperlipidemia are described on pages 14 and 26.

Possible mechanisms

The mechanisms behind the effect of physical exercise on blood lipids, hypertension, and insulin resistance (type 2 diabetes) are described on pages 14, 16, 19 and 26.

Type of training

Resistance and aerobic exercises can both be recommended as effective treatments for people with the metabolic syndrome. A meta-analysis included 12 trials (n = 626) and concluded that although differences in some diabetic control and physical fitness measures between resistance exercise and aerobic exercise groups reached statistical significance, there is no evidence that they are of clinical importance (Yang et al., 2014).

There is also no evidence that resistance exercise differs from aerobic exercise in impact on cardiovascular risk markers or safety. Using one or the other type of exercise for type 2 diabetes may be less important than doing some form of physical activity. Future long-term studies focusing on patient-relevant outcomes are warranted.

There is solid evidence that physical exercise should ideally be in large amounts. If light to moderately intense physical activity is preferred, then it is necessary to train twice as long compared to doing high-intensity physical activity. Many patients with metabolic syndrome have hypertension or symptomatic coronary heart disease. Recommendations should thus be largely tailored to the individual. Treatment should follow the general recommendations for physical activity for adults, but it is recommended that the volume be increased, for example, to 60 min of moderately intense physical activity per day. Alternatively, it is possible to increase the intensity and halve the time or to alternate. There has been an increase in technology-based interventions and a recent review provides a systematic and descriptive assessment of the effectiveness of technology to promote physical activity in people with Type 2 diabetes, which could also be applied for people with the metabolic syndrome (Connelly et al., 2013).

For the latter review, technology included mobile phones and text messages, websites and computer-learning-based technology, and excluded telephone calls. In total, 15 articles were eligible for review: web-based (9), mobile phone (3), CD-ROM (2), and computer based (1). All studies found an increase in physical activity but only nine were significant. Thus, in general technology-based interventions to promote physical activity were found to be effective.

Contraindications

There are no general contraindications; however, training should take into account any competing diseases. People with coronary heart disease should refrain from high-intensity workouts (Borg Scale 15–16). People with hypertension should perform strength training only with light weights and low contraction velocity.

Polycystic ovarian syndrome

Background

Polycystic ovary (PCO) is a term used when ovaries have numerous cysts, i.e., blisters, on their surface. PCO is diagnosed using ultrasound scanning. Most women are diagnosed with the condition in connection with examination for irregular menstruation or infertility (Creatsas & Deligeoroglou, 2007; Hart, 2007; Yii et al., 2009). PCO occurs in approximately 20% of all women of child-bearing age. Another term is polycystic ovary syndrome (PCOS), which occurs in 15% of women. The term PCOS indicates that women diagnosed with PCO can also have several other signs of hormone disorders.

PCOS is diagnosed in women who fulfill at least two of the following criteria: (a) PCO established after ultrasound scan; (b) irregular or no ovulation; and/or (c) increased body hair or increased levels of testosterone in the blood. Other causes of these symptoms must be ruled out, as several other hormone disorders can produce the same symptoms as PCOS. One of the most common symptoms of PCOS is an irregular menstrual cycle with long intervals between menstruation and no menstruation. This can be an indication of an ovulation disorder. Women with PCOS often tend to be overweight with an increased waist-to-hip ratio, and a large number of them are severely overweight. Many also have excess body hair, for example facial hair. Others have acne and a tendency to have thin hair or hair loss. Increased levels of testosterone are another frequent symptom.

The various symptoms in connection with PCOS manifest themselves very differently in each individual. Some women with PCOS have very light symptoms while others are more affected. PCOS can be present for a number of years without clinical symptoms before it becomes apparent, often in connection with an increase in weight and physical inactivity. The symptoms can also change over the years. Initial symptoms can already occur at the age of 14.

For many years, research on PCOS has focused on fertility and on investigating how women with PCOS can have a normal pregnancy. Families of women with PCOS, however, often have a high incidence of type 2 diabetes. Women with PCOS often have insulin resistance, higher cholesterol in the blood, abdominal obesity, and early signs of atherosclerosis. As the definition of PCOS has changed throughout the years, it is difficult to clearly and conclusively interpret earlier and present-day research in the field, but the evidence points to women with PCOS having a higher risk of developing clinical cardiovascular disease (Srikanthan et al., 2006; Lorenz & Wild, 2007; Lunde & Tanbo, 2007; Guzick, 2008; Mak & Dokras, 2009) and type 2 diabetes (Kelestimur et al., 2006; Talbott et al., 2007). Of note, young women with PCOS engaged in physical activities less than controls. Also, women with PCOS were less likely to be aware of the positive effects of exercise on their health (Eleftheriadou et al., 2012).

Evidence-based physical exercise

There is some evidence that physical exercise can have an impact. There is a 2011 systematic review that consists of eight manuscripts, five randomized controlled trials and three cohort studies. All studies involved moderate physical exercise (aerobic or strength training) over a period of 12–24 weeks. Training was found to have a positive effect on ovulation, insulin resistance, and weight loss. It was, however, not possible to identify a specific form of training program that produced the optimum effect (Harrison et al., 2011). This conclusion is supported by other systematic reviews (Hoeger, 2008; Thomson et al., 2011). Training in connection with a hypocaloric diet leads to better body composition than diet alone (Thomson et al., 2008) and exercise training enhances flow-mediated dilation, an adaptation associated with reduced cardiovascular disease risk. Of note, this effect occurred independent of changes in body composition (Sprung et al., 2013).

Possible mechanisms

Training prevents insulin resistance, hyperlipidemia, and hypertension, which are symptoms that can be seen as components of PCOS. It is not known whether physical training inhibits the production of ovarian cysts. People with PCOS, however, often have increased circulating plasma levels of tumor necrosis factor (TNF)-alpha (Jakubowska et al., 2008), which has been found in laboratory experiments to stimulate the production of ovarian cysts. Physical exercise inhibits TNF production, presumably via the production of interleukin-6 (IL-6) by the muscles. Thus, it is possible in theory for training to obstruct the new production of ovarian cysts (Pedersen & Febbraio, 2008).

Type of training

Training should follow general recommendations. If the patient wishes to lose weight, a minimum of 60 min of physical activity a day is recommended. As people with PCOS are assumed to have a considerably higher risk of developing type 2 diabetes and cardiovascular disease, women with PCOS should be encouraged to engage in physical exercise in excess of the generally recommended level.

Contraindications

There are no general contraindications.

Type 2 diabetes

Background

The global prevalence of diabetes is predicted to increase from 171 million individuals (2.8%) in 2000 to 336 million (4.4%) in 2030 (Wild et al., 2004). Type 2 diabetes is a metabolic disease characterized by hyperglycemia and abnormalities in glucose, fat, and protein metabolism (Beck-Nielsen et al., 2000; Campbell, 2009). The disease is due to insulin resistance in the striated muscle tissue and a beta cell defect that inhibits the increase in insulin secretion to compensate for insulin resistance. In almost all cases, type 2 diabetes is present for several years before being diagnosed and over half of all newly diagnosed diabetes patients exhibit signs of late diabetic complications, in particular diabetic macroangiopathy in the form of ischemic heart disease, stroke, and lower limb ischemia, but microvascular complications such as nephropathy, retinopathy, and especially diabetic maculopathy, are also common. 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, there is a high incidence of other risk factors: for example, 80% of patients are overweight, 60–80% have hypertension, and 40–50% have hyperlipidemia (Kannel & McGee, 1979; Goldbourt et al., 1993; Stamler et al., 1993). The excess mortality rate in patients with type 2 diabetes is 60% (Kannel & McGee, 1979; Goldbourt et al., 1993; Stamler et al., 1993). Multifactorial intensive intervention can prevent late diabetic complications (Gaede et al., 2003).

Evidence-based physical exercise

Impact on metabolic control. The positive gains from physical exercise for patients with type 2 diabetes are very well documented and there is an international consensus that physical exercise is one of the three cornerstones in the treatment of diabetes, along with diet and medication (Joslin et al., 1959; Albright et al., 2000; American Diabetes Association, 2002).

Several reviews (Sigal et al., 2004; Zanuso et al., 2010) and meta-analyses (Boule et al., 2001; Snowling & Hopkins, 2006; Thomas et al., 2006; Umpierre et al., 2011) report that increased physical exercise produce a significant improvement in glucose control in people with type 2 diabetes, yielding an average improvement in hemoglobin A1c (HbA1c) of between −0.4% and −0.6%.

A 2006 Cochrane Review, which includes 14 randomized controlled trials with a total of 377 patients with type 2 diabetes, compares the independent effect of training with no training (Thomas et al., 2006). The training interventions were 8–10 months in length and consisted of progressive aerobic training, strength training or a combination of the two, with typically three training sessions per week. Compared to the control group, the training interventions showed a significant improvement in glycemic control in the form of a reduction in HbA1c (glycated hemoglobin) of 0.6% (−0.6% HbA1c), 95% CI: −0.9 to 0.3; $P < 0.05$). By comparison, intensive glycemic control using metformin showed a reduction in HbAc1 of 0.6%, and a risk reduction of 32% for diabetes-related complications and of 42% for diabetes-related mortality (UK Prospective Diabetes Study (UKPDS) Group, 1998).

Despite the clear effect of exercise training on metabolic control, there was no significant effect on body weight. The reason for this is presumably that the exercise group reduced fat mass but increased muscle mass. One of the studies in the meta-analysis reported an increase in fat-free mass of 6.3 kg (95% CI: 0.0–12.6), measured by dual energy X-ray absorptiometry (DXA) scanning, and a reduction in visceral fat volume, measured in by magnetic resonance imaging (MRI) scanning, of -45.5 cm^2 (95% CI: -63.8 to 27.3). No adverse effects of physical exercise were reported.

Physical exercise significantly reduced insulin response as an expression of increased insulin sensitivity and triglyceride levels. This Cochrane Review found no significant difference with regard to quality of life, plasma cholesterol, or blood pressure (Thomas et al., 2006). The findings from the Cochrane Review (Thomas et al., 2006) agree with the conclusions from a 2001 meta-analysis, which also evaluated the impact of a minimum 8-week training program on glycemic control (Boule et al., 2001). Training was found to have no effect on body weight (Boule et al., 2001). There are several possible explanations for this: the training period was relatively short, the patients over-compensated for their loss of energy by eating more, or patients lost fat but their volume of fat-free mass increased. There is reason to assume that the final explanation is the most significant one. It is well-known that physically inactive people who start to exercise increase their fat-free mass (Brooks et al., 1995; Fox & Keteyian, 1998). Only one of the studies included in the meta-analysis assessed abdominal obesity using MRI scanning (Mourier et al., 1997). The aerobic training program (55 min three times a week over 10 weeks) resulted in a reduction of abdominal subcutaneous fat, measured using MRI scanning (227.3–186.7 cm^2, $P < 0.05$) and visceral fat (156.1–80.4 cm^2, $P < 0.05$). The same study did not identify any effect from exercise on body weight.

A 2007 meta-analysis assessed the effect of self-management interventions with a view to increasing physical activity levels in patients with type 2 diabetes. The analysis involved 103 trials with 10 455 subjects. Self-management training was found to have a significant effect of 0.45% on HbA1c.

Interventions that included several different lifestyle recommendations such as diet and physical activity had less effect than interventions that included physical exercise only. Basic levels of HbA1c and BMI were not related to metabolic effect. The overall conclusion is that self-management interventions that include physical activity increase metabolic control (Conn et al., 2007).

A 2009 systematic review included nine studies with 372 patients with type 2 diabetes. Progressive resistance training vs no training induced a statistically significant reduction in HbA1c of 0.3%. There was no difference between resistance training and aerobic training as far as the effect on changes in HbA1c was concerned. Progressive resistance training resulted in large improvements in strength compared to aerobic training or no training. No significant effect on body composition was found (Irvine & Taylor, 2009).

A meta-analysis from 2013 found that exercise lowers postprandial glucose but not fasting glucose in type 2 diabetes (MacLeod et al., 2013). A 2007 meta-analysis evaluated the effect of aerobic physical training for a minimum of 8 weeks on lipids and lipoproteins in patients with type 2 diabetes. The analysis included seven trials with 220 men and women, of which 112 were in a training group and 108 in a control group. A statistically significant reduction of approximately 5% in LDL cholesterol was found but there was no significant effect with regard to triglycerides, HDL cholesterol, or total cholesterol (Kelley & Kelley, 2007).

A 2011 meta-analysis concluded that structured exercise training that consists of aerobic exercise, resistance training, or both combined is associated with HbA1c reduction in patients with type 2 diabetes. Structured exercise training of more than 150 min/week is associated with greater HbA1c declines than that of 150 min or less per week. Physical activity advice is associated with lower HbA1c, but only when combined with dietary advice (Umpierre et al., 2011).

A systematic review and meta-analysis from 2014 compared resistance exercise and aerobic exercise and concluded that there was no evidence that resistance exercise differs from aerobic exercise in impact on glucose control, cardiovascular risk markers or safety. Using one or the other type of exercise for type 2 diabetes may be less important than doing some form of physical activity (Yang et al., 2014).

Measures of fasting glucose and HbA1c do not accurately represent glycemic control because they do not reflect what occurs after meals and throughout the day in the free-living condition (Kearney & Thyfault, 2015). An accumulating body of evidence now suggests that postprandial glucose fluctuations are more tightly correlated with microvascular and macrovascular morbidities and cardiovascular mortality than HbA1c or fasting glucose, stagnant measure of glycemia. It is therefore important that unlike medications, which generally have a poor effect at improving postprandial glucose, exercise has been proven effective in reducing postprandial glycemic excursions in as little as a few days (MacLeod et al., 2013; Kearney & Thyfault, 2015).

Effect on fitness and muscle strength

Poor fitness is an independent prognostic marker for death in patients with type 2 diabetes (Kohl et al., 1992; Wei et al., 2000; Myers et al., 2002). A meta-analysis (Boule et al., 2003) assesses the effect of a minimum of 8 weeks of physical training on maximum oxygen uptake (VO_{2max}). The analysis involved 266 patients with type 2 diabetes. Average training quantity was 3.4 sessions/week, each lasting 49 min; intensity was 50–75% of maximum pulse; the length of the interventions was in average 20 weeks. Altogether, there was an 11.8% increase in VO_{2max} in the training group vs a drop of 1% in the control group.

Older patients with type 2 diabetes ($n = 31$) were randomized to a 24-month resistance training program. Average increase in muscle strength was 31% in the exercise group, while no effect on muscle strength was identified in the control group (Brandon et al., 2003). Patients with type 2 diabetes can thus adapt to training with regard to both fitness and muscle strength.

There was a more striking impact on fitness when the physical exercise was supervised, was done in groups and took place over a long period. There was no correlation between level of fitness improvement and HbA1c, age, BMI, or sex (Nielsen et al., 2006).

Effect on mortality

The Look AHEAD study included 16 centers in the United States, and randomly assigned 5145 overweight or obese patients with type 2 diabetes to participate in an intensive lifestyle intervention that promoted weight loss through decreased caloric intake and increased physical activity (intervention group) or to receive diabetes support and education (control group). The trial was stopped early on the basis of a futility analysis when the median follow-up was 9.6 years as the intervention did not reduce the rate of cardiovascular events in overweight or obese adults with type 2 diabetes. It is noteworthy that although weight loss was greater in the intervention group than in the control group, there was only an initial improvement in fitness and only when related to weight loss. The exercise training was not supervised and it appears that the intervention actually had very little effect on physical fitness (Wing et al., 2013).

Motivation

Patients with type 2 diabetes can be motivated to change their physical activity habits after consultation with health practitioners (Kirk et al., 2003). Seventy physically inactive patients with type 2 diabetes received standard information about the health benefits of regular physical exercise. They were subsequently randomized to either no consultation or 30 min of individual consultation with information/instruction about physical activity based on a trans-theoretical model (Marcus & Simkin, 1994). The intervention group increased their level of moderate physical exercise, assessed with accelerometer measurements ($P < 0.001$), and achieved a significant decrease in systolic blood pressure ($P < 0.05$) and HbA1c ($P < 0.05$).

First Step Program (FSP) was developed in partnership with a number of diabetes organizations (Yamanouchi et al., 1995; Tudor-Locke et al., 2000; Tudor-Locke et al., 2001; Tudor-Locke et al., 2002) and aims to increase patients' understanding of the importance of walking on a daily basis. A pedometer is used to monitor daily activity and as feedback and encouragement to increase the number of steps in daily life. FSP was used as an intervention measure 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. The subjects in the FSP group increased their number of steps to 3000 steps/day ($P < 0.0001$).

As an increase in insulin sensitivity as a result of physical exercise (Bogardus et al., 1984; Trovati et al., 1984; Krotkiewski et al., 1985; Dela et al., 1995; Yamanouchi et al., 1995; Mourier et al., 1997) leads to an increase in glucose uptake in insulin-sensitive tissues with a lower consumption of insulin, the aforementioned effect on glycemic level can be expected. Thus, clinical experience also shows that an increase in insulin sensitivity due to weight loss and/or physical training should be accompanied by a reduction in any anti-diabetic medication or insulin therapy. A decrease in hyperinsulinemia – if present – has also been identified with (Bogardus et al., 1984; Barnard et al., 1992; Yamanouchi et al., 1995; Halle et al., 1999) and without (Trovati et al., 1984; Vanninen et al., 1992; Di et al., 1993; Dela et al., 1995) dietary intervention. Numerous studies, however, have found unchanged insulin levels after training (Ruderman et al., 1979; Reitman et al., 1984; Schneider et al., 1984; Krotkiewski et al., 1985; Ronnemaa et al., 1986; Allenberg et al., 1988; Wing et al., 1988; Hornsby et al., 1990; Vanninen et al., 1992; Lehmann et al., 1995; Mourier et al., 1997; Eriksson et al., 1998; Walker et al., 1999; Lehmann et al., 2001; Dunstan et al., 1997), but never an increase. A decrease in hyperinsulinemia is desirable, as it is a risk factor for atherosclerosis and hypertension.

Physical training has a number of other well-documented effects, which are important for patients with type 2 diabetes (Stewart, 2002). As mentioned above, hypertension occurs in 60–80% of patients with type 2 diabetes. The positive effect of training on hypertension is well documented in non-diabetics (Stewart, 2001; Whelton et al., 2002). A meta-analysis including 54 randomized trials found that aerobic training was associated with a reduction in systolic blood pressure of 3.8 mmHg on average independent of weight loss. A subgroup analysis showed a decrease in blood pressure of 4.9 mmHg in hypersensitive patients. Another meta-analysis involving 47 trials (Kelley et al., 2001) found a decrease in systolic blood pressure of 6 mmHg in hypersensitive patients as opposed to 2 mmHg in normotensive individuals. Patients with type 2 diabetes tend to have diastolic dysfunction in the left ventricle (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 increased levels of, for example, C-reactive protein (Pradhan et al., 2001). The latter is a negative prognostic value with regard to competing diseases and early mortality (Duncan & Schmidt, 2001; Abramson et al., 2002). Physical training increases the diastolic filling of the left ventricle (Kelemen et al., 1990; Levy et al., 1993), increases the endothelial vasodilatory function (Higashi et al., 1999a, b) and induces anti-inflammatory effects (Febbraio & Pedersen, 2002).

Possible mechanisms

There is extensive literature on the effect of physical training on type 2 diabetes; however, the mechanisms are only briefly outlined here. Physical training increases insulin sensitivity in the trained muscle and muscle contraction-induced glucose uptake in the muscle. Mechanisms include increased postreceptor insulin signaling (Dela et al., 1993), increased glucose transporter (GLUT4) mRNA and protein (Dela et al., 1994), increased glucose synthesis activity (Ebeling et al., 1993) and heksokinase (Coggan et al., 1993), lower release and higher clearance of free fatty acids (Ivy et al., 1999), and increased transport of glucose to the muscles due to an enlarged muscle capillary network and blood flow (Saltin et al., 1977; Mandroukas et al., 1984; Coggan et al., 1993). Resistance training increased insulin-mediated glucose uptake, GLUT4 content and insulin signaling in skeletal muscles in patients with type 2 diabetes (Holten et al., 2004). Physical activity increases blood flow and thus so-called sheer stress on the vessel wall, which is assumed to be a stimulus for endothelial nitrogen oxide, which induces smooth muscle cell relaxation and vasodilation (McAllister et al., 1995). The anti-hypertensive effect is assumed to be mediated via a less sympathy-induced vasoconstriction in a fit condition (Alam et al., 2004).

Type of training

Aerobic training and resistance training are both beneficial; however, a combination of the two is perhaps the optimal form of exercise for people with type 2 diabetes (Church et al., 2010). Evidence also suggests that high-intensity exercise improves glycemic control more than low-intensity exercise.

A 2003 meta-analysis assessed the effect of a minimum of 8 weeks of physical exercise (Boule et al., 2003) and found a link between relatively high-intensity physical training and a decrease in HbA1c ($r = -0.91$, $P = 0.002$), while no significant link between quantity of physical activity and a decrease in HbA1c ($r = -0.46$, $P = 0.26$) was established. These correlations partly contradict an intervention trial, which showed that regular physical training increased insulin sensitivity in physically inactive people who did not have diabetes – an effect which was greater for those who spent a good deal of their time being physically active – but that the intensity of the activity was not significant (Houmard et al., 2004). Recent studies of interval training programs have shown remarkable results on glycemic control (Tjonna et al., 2008; Little et al., 2011; Higgins et al., 2014; Shaban et al., 2014).

In this context, it has been shown that interval-walking training more favorably improves glycemic control in T2DM subjects when compared to energy expenditure-matched continuous-walking training (Karstoft et al., 2013, 2014). Scheduled daily exercise is ideal with regard to insulin therapy and adjustment and regulating diet.

Most patients with type 2 diabetes can engage in physical activity without following any particular instructions or rules. It is important, however, for patients being treated with sulphonylurea, postprandial regulators, or insulin to receive guidance in order to avoid hypoglycemia. Precautions include monitoring blood sugar, adjusting diet, and adjusting medication.

Insulin should be injected in a part of the body that is not active during training (Koivisto & Felig, 1978) and it is not advisable to engage in physical activity immediately after using regular insulin or a short-acting insulin analog (Tuominen et al., 1995). Many patients with type 2 diabetes have chronic complications in the musculo-skeletal system (e.g., painful arthroses) and ischemic heart disease. Due to neuropathy, special attention should be paid to the exercising patient's feet ± neuropathy and footwear. Recommendations should be individual as far as possible, but both fitness and strength training can be recommended, either in combination or singly.

A combination of aerobic training and resistance training is recommended. Increasing the intensity of the aerobic physical activity is an effective measure;

however, specific guidelines would require several studies to examine the significance of quantity and intensity. Strength training should consist of many repetitions.

Contraindications

Overall, avoiding physical activity carries greater risks than engaging in physical activity; however, special precautions are necessary.

Physical activity should be postponed in the case of a blood sugar level >17 until it has been corrected. The same applies to low blood sugar <7 mmol/L if the patient is receiving insulin therapy.

In the case of hypertension and active proliferative retinopathy, it is recommended that high-intensity training or training involving Valsalva maneuvers be avoided. Strength training should be done with light weights and at low contraction velocity.

In the case of neuropathy and the risk of foot ulcers, body-bearing activities should be avoided. Repeated strain on neuropathic feet can lead to ulcers and fracture. Treadmill exercises, long walks/runs, and step exercises are not recommended, while non-body-bearing exercise is recommendable, such as cycling, swimming, and rowing.

One should be aware that patients with autonomic neuropathy may have severe ischemia without symptoms (silent ischemia). These patients typically suffer from resting tachycardia, orthostatism, and poor thermoregulation. There is a danger of sudden cardiac death. It may be advisable to consult a cardiologist and carry out an exercise ECG or a myocardial scintigraphy. Patients should be instructed to avoid physical activity in cold or hot temperatures and to ensure adequate hydration during physical activity.

Type 1 diabetes

Background

Type 1 diabetes is an autoimmune disease that occurs in children or adults. The disease is caused by the destruction of beta cells in the pancreas, which stops production of insulin. The etiology is still unknown, but environmental factors (e.g., viruses and chemicals), genetic disposition and autoimmune reactions all play a part.

Evidence-based physical exercise

Patients with type 1 diabetes have a high risk of developing cardiovascular disease (Krolevski, 1987), and physical activity offers good prevention (Moy et al., 1993). It is therefore important for patients with type 1 diabetes to be physically active on a regular basis. Insulin requirement decreases during physical activity, which is why patients must reduce their insulin dose if they plan to do physical training (Rabasa-Lhoret et al., 2001) and/or ingest carbohydrates in connection with training (Soo et al., 1996). Patients with type 1 diabetes thus need guidance on how to avoid hypoglycemia so that they, like others, can benefit from the positive effects of physical activity against other diseases.

A systematic review from 2014 analyzed physical activity interventions in children and young people with Type 1 diabetes mellitus. A total of 26 articles (10 randomized and 16 non-randomized studies), published in the period 1964–2012, were reviewed. Meta-analyses showed potential benefits of physical activity on HbA1c, BMI, triglycerides, and cholesterol (Quirk et al., 2014).

There are relatively few studies that shed light on the specific impact of training in patients with type 1 diabetes, but in general little or no difference in glycemic control can be identified in patients with type 1 diabetes who are physically active compared to those who are inactive (Wasserman & Zinman, 1994; Veves et al., 1997). Some studies find no improvement in HbA1c with physical training (Wallberg-Henriksson et al., 1984, 1986; Yki-Jarvinen et al., 1984; Laaksonen et al., 2000; Kennedy et al., 2013), whereas other find that the most physically active patients have the lowest HbA1c (Cuenca-Garcia et al., 2012; Carral et al., 2013; Beraki et al., 2014).

A large study included 4655 patients and found an inverse dose–response association was found between physical activity level and HbA1c (Beraki et al., 2014). Another study showed that intense physical activity was associated with better metabolic control in patients with type 1 diabetes.

An observational, cross-sectional study included 130 adult patients with type 1 diabetes. The study found no differences in HbA1c levels in relation to time dedicated to moderate physical activities. However, patients who dedicated more than 150 min/week to intense physical activity had lower levels of HbA1c (HbA1c: $7.2 \pm 1.0\%$ vs $7.8 \pm 1.1\%$ vs $8.0 \pm 1.0\%$ in more than 149 min, between 0 and 149 min or 0 min of intense physical activity per week, respectively) (Carral et al., 2013).

On the other hand patients with type 1 diabetes – like non-diabetics – improve insulin sensitivity (Yki-Jarvinen et al., 1984), which is associated with a lower (ca. 5%) reduction in the exogenous insulin requirements (Wallberg-Henriksson et al., 1984). Endothelial dysfunction is a trait of some (Johnstone et al., 1993; McNally et al., 1994; Makimattila et al., 1996; Skyrme-Jones et al., 2000), though not all (Calver et al., 1992; Elliott et al., 1993; Smits et al., 1993; Makimattila et al., 1997; Pinkney et al., 1999), patients with type 1 diabetes, and the effect of physical training on this parameter is only sparsely illuminated. Endothelial function has been found to be both improved (Fuchsjager-Mayrl et al., 2002; Seeger et al., 2011) and unchanged (Veves et al., 1997) after physical training.

Physical training possibly has a positive impact on the lipid profile, also in patients with type 1 diabetes. Controlled studies show that training reduces the level of LDL cholesterol and triglycerides in the blood (Laaksonen et al., 2000) and increases the level of HDL cholesterol (Laaksonen et al., 2000) and HDL cholesterol/total cholesterol ratio (Yki-Jarvinen et al., 1984; Laaksonen et al., 2000). The ratio, however, has not been thoroughly investigated and there might also be a difference between the sexes (Wallberg-Henriksson et al., 1986). In uncontrolled or cross-sectional trials a link has been found between training and an increase in HDL2 cholesterol and a decrease in serum triglyceride and LDL cholesterol (Gunnarsson et al., 1987; Lehmann et al., 1997).

A randomized controlled trial examined the effect of 30–60 min of running at a moderate intensity 3–5 times a week over 12–16 weeks. The study included young men with type 1 diabetes ($n = 28$ and the control group $n = 28$). Aerobic training increased fitness, exercise capacity, and improved lipid profile (Laaksonen et al., 2000). A controlled study showed that 4 months of aerobic training increased fitness by 27% ($P = 0.04$), reduced insulin requirement ($P < 0.05$) (Wiesinger et al., 2001), and improved endothelial function (Fuchsjager-Mayrl et al., 2002) in patients with type 1 diabetes.

Possible mechanisms

Physical training increases glucose uptake in the muscle, which is induced by muscle contraction. The lipoproteins in the blood appear to be significant in the development of atherosclerosis, also in patients with type 1 diabetes (Winocour et al., 1992). Physical training affects the lipid composition of the blood in a desirable way (Kraus et al., 2002).

Type of training

Most experience has been drawn from aerobic training, but in principle, patients with type1 diabetes can take part in all forms of sport, if contraindications/precautions are observed. There are some indications that high-intense exercise has a more profound effect on glycemic control compared to moderate exercise. Training needs to be regular and planned in line with insulin treatment and adjustment and dietary regulation.

The risk of hypoglycemia is lower with interval training than with moderate-intensity continuous training, as training at high intensity stimulates glucose production in the liver more than moderate-intensity training (Guelfi et al., 2007b).

It is very important for patients to be carefully informed and educated. They must be instructed on steps for avoiding hypoglycemia, which include monitoring blood sugar, adjusting diet, and adjusting insulin (Briscoe et al., 2007; Guelfi et al., 2007a).

When starting on a specific training program, patients should frequently measure their blood sugar level during and after training and thus learn what their individual response is to a given strain over a given duration. Patients must be instructed on how insulin and consumption of carbohydrates are adjusted according to the physical activity. Ideally, training should always be at the same time of day and of more or less the same intensity. It is important to drink before and during the physical activity, especially when the training is over a long period and in hot weather. Patients should be particularly aware of their feet ± neuropathy and footwear.

The recommendations have to be tailored to the individual and take into account late diabetic complications, but both aerobic fitness and strength training are advisable, either a combination of the two or on their own. The goal should be at least 30 min of moderate-intensity exercise daily.

Contraindications/precautions

Overall, avoiding physical activity carries greater risks than being active; however, special precautions are necessary.

Physical activity should be postponed in the case of a blood sugar level >14 mmol/L and ketonuria, and blood sugar level >17 mmol/L without ketonuria, until this has been corrected. The same applies to low blood sugar <7 mmol/L.

In the case of hypertension and active proliferative retinopathy, it is recommended that high-intensity training or training involving Valsalva maneuvers be avoided. Resistance training should be done with light weights and in short series.

In the case of neuropathy and the risk of foot ulcers, body-bearing exercise should be avoided. Repeated strain on neuropathic feet can lead to ulcers and fracture. Jogging/walking treadmill, long walks/runs, and step exercises are not recommended, while non-body-bearing physical exercise is recommendable, such as cycling, swimming, and rowing.

One should be aware that patients with autonomic neuropathy may have severe ischemia without symptoms (silent ischemia). These patients typically suffer from resting tachycardia, orthostatism, and poor thermoregulation. There is a danger of sudden cardiac death. It may be advisable to consult a cardiologist and carry out an exercise ECG or a myocardial scintigraphy. Patients should be instructed to avoid physical activity in cold or hot temperatures and to ensure adequate hydration during physical activity.

Cardiovascular diseases

Cerebral apoplexy

Background

Cerebral apoplexy (stroke, cerebrovascular accident, apoplexy) is defined by WHO as a rapid onset disorder of brain function with symptoms lasting more than 24 h or leading to death, and where the probable cause is vascular. The reasons are infarction due to cardiac embolism, intracerebral hemorrhage, or subarachnoid hemorrhage after ruptured aneurysm. The average age is 75 years, but 20% of the patients are less than 65 years of age. Depending on localization of the brain damage, different parts of the brain functions are affected, but the majority of stroke patients have unilateral paresis of the upper and lower extremities, while about one-third also have aphasia. Moreover, most of the patients need hospitalization and will require rehabilitation (Hisham & Bayraktutan, 2013).

Most stroke patients are affected cognitively and emotionally after their attack. Approximately one-third of them experience post-stroke depression (Paolucci et al., 2006). These effects coupled with low physical function make it difficult to comply with recommendations for physical activity. Patients with stroke generally have low levels of physical activity (Rand et al., 2009).

Physical inactivity is a risk factor for atherosclerosis and hypertension, which explains why physical inactivity in epidemiological studies is a prognostic factor for apoplexy (Wannamethee & Shaper, 1992; Lindenstrom et al., 1993; Ellekjaer et al., 2000; Lee et al., 2003; Wendel-Vos et al., 2004; Hu et al., 2007; Krarup et al., 2007; Krarup et al., 2008; Sui et al., 2007; Boysen & Krarup, 2009). Stroke patients who have a relatively high level of physical activity have been found to have comparatively fewer severe stroke episodes and better recovery of function after 2 years (Krarup et al., 2008).

Evidence-based physical training

There is evidence that aerobic exercise in patients with stroke has a positive effect on walking speed and function. Furthermore, there is support for an effect on mortality.

A meta-analysis from 2014 included 38 randomized controlled trials. There was high evidence that in the subacute stage of stroke, specific walking training resulted in improved walking speed and distance compared with traditional walking training of the same intensity. In the chronic stage, walking training resulted in increased walking speed and walking distance compared with no/placebo treatment, and increased walking speed compared with overall physiotherapy. On average, 24 training sessions for 7 weeks were needed (Peurala et al., 2014).

A meta-analysis from 2013 of randomized trials included nine studies of treadmill training comprising 977 participants and found evidence that, for people with stroke who can walk, treadmill training without body weight support results in faster walking speed and greater distance than no intervention/non-walking intervention and the benefit is maintained beyond the training period (Polese et al., 2013).

Another study from 2013 included meta-analyses of randomized controlled trials with mortality outcomes comparing the effectiveness of exercise and drug interventions with each other or with control (placebo or usual care). In total, they included 16 (four exercise and 12 drug) meta-analyses. Three trials concerned exercise interventions among patients with stroke (n = 227) compared with 10 trials of anticoagulants (n = 22 786), 14 of antiplatelets (n = 43 041), and three directly comparing anticoagulants with antiplatelets (n = 11 567). Physical activity interventions were more effective than drug treatment among patients with stroke (odds ratios, exercise vs anticoagulants: 0.09, 95% credible intervals: 0.01–0.70 and exercise vs antiplatelets: 0.10, 0.01–0.62) (Naci & Ioannidis, 2013).

As physical activity helps to prevent risk factors for stroke, i.e., hypertension, atherosclerosis, and type 2 diabetes, it is likely that physical training of stroke patients can prevent new episodes of stroke, but there is no evidence to support this.

A Cochrane Review from 2013 included 45 trials, involving 2188 participants, which comprised cardiorespiratory (22 trials, 995 participants), resistance (eight trials, 275 participants), and mixed training interventions (15 trials, 918 participants). It was concluded that there is sufficient evidence to incorporate cardiorespiratory and mixed training, involving walking, within post-stroke rehabilitation programs to improve the speed and tolerance of walking; improvement in balance may also occur. Presently, there is however insufficient evidence to support the use of resistance training (Saunders et al., 2013).

However, individuals with hemiparesis are often older and have a low level of activity, and it must be assumed that this group can achieve the same advantages from strength training as individuals without neurological deficits. In other words, physically active people with hemiparesis will have lower mortality, more active years, reduced risk of metabolic syndrome, and increased bone density (Carda et al., 2009; Ryan et al., 2011).

Possible mechanisms

Patients with apoplexy have poor physical function and a low level of (age-adjusted) fitness (Hoskins, 1975; King et al., 1989b), which means that they have less energy to carry out rehabilitation. Their poor level of fitness is presumably also related to the smaller number of motor units that can be recruited during dynamic muscle contractions (Ragnarsson, 1988), to the altered composition of fibers resulting from prolonged physical inactivity and to reduced oxidative capacity in the paretic muscle (Landin et al., 1977). The absolute energy expenditure per submaximum workload in the hemiplegic patient is greater than what is seen in normal individuals of the same age and weight (Brinkmann & Hoskins, 1979). The increased energy expenditure is related to inefficient patterns of movement and spasticity (Olgiati et al., 1988). Aerobic exercise breaks this vicious cycle by improving aerobic capacity and reducing energy exertion. This increases the patient's overall physical capabilities and the ability to carry out rehabilitation.

Type of training

Physical therapy methods will not be reviewed here (Broderick et al., 1999; Socialstyrelsen, 2000). The training program should be individualized but focus on walking and cardiorespiratory training.

Contraindications

There are no contraindications, but specific measures incorporating partial body weight support may be necessary.

Hypertension

Background

Hypertension is a significant risk factor for stroke, acute myocardial infarction, heart failure, and sudden death. The borderline between low and normal blood pressure is fuzzy, as the incidence of these cardiovascular diseases already rises from a relatively low blood pressure level. A meta-analysis involving 61 prospective studies (1 million people) showed a linear relationship between decrease in the risk of cardiovascular mortality and decrease in blood pressure to a systolic blood pressure of below 115 mmHg and a diastolic blood pressure of below 75 mmHg (Lewington et al., 2002). A decrease of 20 mmHg in systolic blood pressure or 10 mmHg in diastolic blood pressure halves the risk of cardiovascular mortality. Thus, for example, a person with systolic blood pressure of 120 mmHg has half the risk of cardiovascular mortality as a person with systolic blood pressure of 140 mmHg (Lewington et al., 2002). Hypertension is defined as systolic blood pressure >140 and diastolic blood pressure >90 mmHg. According to this definition, about 20% of the population have high blood pressure or require blood pressure-lowering medication (Burt et al., 1995). However, the borderlines between optimal and normal blood pressure and between mild, moderate, and severe hypertension are arbitrary (Burt et al., 1995). Large-scale epidemiological studies indicate that regular physical exercise and/or fitness prevents hypertension or lowers blood pressure (Fagard, 2005; Fagard & Cornelissen, 2005).

Evidence-based physical training

Effect on resting blood pressure (normotensive and hypertensive). Several meta-analyses have concluded that physical exercise has a positive effect on blood pressure in both normotensive and hypertensive cases (Stewart, 2001; Whelton et al., 2002; Pescatello et al., 2004; Fagard & Cornelissen, 2007; Cornelissen & Smart, 2013; Cornelissen et al., 2013; Garcia-Hermoso et al., 2013; Huang et al., 2013; Carlson et al., 2014).

A meta-analysis included randomized controlled trials lasting ≥4 weeks investigating the effects of exercise on blood pressure in healthy adults (age ≥18 years) (Cornelissen & Smart, 2013).

The study included 93 trials, involving 105 endurance, 29 dynamic resistance, 14 combined, and 5 isometric resistance groups, totaling 5223 participants (3401 exercise and 1822 control). Systolic BP (SBP) was reduced after endurance (−3.5 mmHg [confidence limits −4.6 to −2.3]), dynamic resistance (−1.8 mmHg [−3.7 to −0.011]), and isometric resistance (−10.9 mmHg [−14.5 to −7.4]) but not after combined training. Reductions in diastolic BP (DBP) were observed after endurance (−2.5 mmHg [−3.2 to −1.7]), dynamic resistance (−3.2 mmHg [−4.5 to −2.0]), isometric resistance (−6.2 mmHg [−10.3 to −2.0]), and combined (−2.2 mmHg [−3.9 to −0.48]) training. BP reductions after endurance training were greater ($P < 0.0001$) in 26 study groups of hypertensive subjects (−8.3 [−10.7 to −6.0]/−5.2 [−6.8 to −3.4] mmHg) than in 50 groups of pre-hypertensive subjects (−2.1 [−3.3 to −0.83]/−1.7 [−2.7 to −0.68]) and 29 groups of subjects with normal BP levels (−0.75 [−2.2 to +0.69]/−1.1 [−2.2 to −0.068]). BP reductions after dynamic resistance training were largest for pre-hypertensive participants (−4.0 [−7.4 to −0.5]/−3.8 [−5.7 to −1.9] mmHg) compared with patients with hypertension or normal BP. It was concluded that endurance, dynamic resistance, and isometric resistance training lower SBP and DBP, whereas combined training lowers only DBP. Data from a small number of isometric resistance training studies suggest this form of training has the potential for the largest reductions in SBP.

A meta-analysis from 2010 focused specifically on the effect of isometric exercise, which has not traditionally been recommended as an alternative to dynamic exercise (Owen et al., 2010). Five trials were identified including a total of 122 subjects. Isometric exercise for <1 h/week reduced systolic blood pressure by 10.4 mmHg and diastolic blood pressure by 6.7 mmHg. Also this study found that isometric exercise induces changes in blood pressure that are similar to that of endurance or dynamic resistance training and similar to those achieved with a single pharmacological agent. Interestingly, a smaller study suggested that even handgrip exercise had effect on blood pressure-lowering effects (Kelley & Kelley, 2010).

Another meta-analysis from 2013 included aerobic exercise training studies among previously sedentary older adults (Huang et al., 2013). Twenty-three studies, representing a total of 1226 older subjects, were included in the final analysis. Robust statistically significant effects were found when older exercisers were compared with the control group, representing a 3.9% reduction in SBP and a 4.5% reduction in DBP.

A meta-analysis was carried out in 2007 (Fagard & Cornelissen, 2007) involving randomized controlled trials in which the training consisted of either endurance or resistance training. The meta-analysis was based on 72 trials and 105 study groups. Physical training was found to induce a significant reduction in resting blood pressure and systolic/diastolic blood pressure, measured during outpatient visits, of 3.0/2.4 mmHg ($P < 0.001$) and 3.3/3.5 mmHg ($P < 0.01$), respectively. The reduction in blood pressure was more pronounced for the 30 hypersensitive trial groups, in which an effect of −6.9/−4.9 was achieved, while the normotensive group achieved an effect of −1.9/−1.6 ($P < 0.001$). Training had a positive effect on a number of clinical and paraclinical variables, namely systemic vascular resistance, plasma noradrenalin, plasma renin activity, body weight, abdominal girth, fat percentage, HOMA, and HDL cholesterol.

An expert panel of the American College of Sports Medicine (ACSM) (Pescatello et al., 2004) extrapolated data from a total of 16 studies involving patients with hypertension (systolic blood pressure >140 mmHg; diastolic blood pressure >90 mmHg) and found the effect of physical training in people with hypertension to be a decrease in blood pressure of 7.4 mmHg (systolic) and 5.8 mmHg (diastolic). A general finding was that the blood pressure-lowering effect of physical training was most pronounced in the patients with the highest blood pressure.

A meta-analysis from 2011 identified studies that had examined the effect of strength training on blood pressure and other cardiovascular risk factors in adults (Cornelissen et al., 2011).

The study included 28 randomized, controlled trials, involving 33 study groups and 1012 participants. Overall, resistance training induced a significant blood pressure reduction in 28 normotensive or prehypertensive study groups [−3.9 (−6.4; −1.2)/−3.9 (−5.6; −2.2) mmHg], whereas the reduction [−4.1 (−0.63; +1.4)/−1.5 (−3.4; +0.40) mmHg] was not significant for the five hypertensive study groups. When study groups were divided according to the mode of training, isometric handgrip training in three groups resulted in a larger decrease in blood pressure [−13.5 (−16.5; −10.5)/−6.1(−8.3; −3.9) mmHg] than dynamic resistance training in 30 groups [−2.8 (−4.3; −1.3)/−2.7 (−3.8; −1.7) mmHg]. This meta-analysis supports the blood pressure-lowering potential of dynamic resistance training and point at an interesting effect of isometric handgrip training. The latter study adds to previous meta-analysis (Kelley & Kelley, 2000; Cornelissen & Fagard, 2005).

Blood pressure was measured daily (24 h) in 11 studies (Pescatello et al., 2004) and showed the same effect from training as the studies mentioned above.

Acute effect of physical activity. Physical activity induced a decrease in blood pressure after it was carried out. This decrease in blood pressure typically lasted for 4–10 h, but was measured up to 22 h later. The average decrease was 15 mmHg and 4 mmHg for systolic and diastolic blood pressure, respectively (Pescatello et al., 2004). This means that people with hypertension can achieve normotensive values many hours of the day, which should be seen as having considerable clinical significance (Pescatello et al., 2004).

Overall, it is well documented that training for hypersensitive people induces a clinically relevant lowering of blood pressure. Conventional treatment using blood pressure-lowering medication typically brings about a decrease in diastolic blood pressure of the same level (Collins et al., 1990; Collins & MacMahon, 1994; Gueyffier et al., 1997; Blood Pressure Lowering Treatment Trialists' Collaboration, 2000), which in the long run lowers the risk of strokes by an estimated 30% and the risk of ischemic cardiac death by 30%. A meta-analysis involving one million people calculates that a reduction in systolic blood pressure of just 2 mmHg reduces stroke mortality by 10% and ischemic cardiac death mortality by 7% among middle-aged people (Lewington et al., 2002). These calculations coincide with findings from earlier analyses (Collins et al., 1990; Cook et al., 1995).

Possible mechanisms

The blood pressure-lowering effect of physical training is assumed to be multifactorial but appears to be independent of weight loss. The mechanisms include neuro-hormonal, vascular, and structural adaptations. The anti-hypersensitive effect includes decreased sympathetically induced vasoconstriction in a fit condition (Esler et al., 2001) and a decrease in catecholamine levels. Hypertension often occurs in conjunction with insulin resistance and hyperinsulinemia (Zavaroni et al., 1999; Galipeau et al., 2002). Physical training increases insulin sensitivity in the trained muscle and thus reduces hyperinsulinemia. The mechanisms include increased postreceptor insulin signaling (Dela et al., 1993), increased glucose transporter (GLUT4) mRNA and protein (Dela et al., 1994), increased glycogen synthase activity (Ebeling et al., 1993) and hexokinase (Coggan et al., 1993), low release and increased clearance of free fatty acids (Ivy et al., 1999), and increased transport of glucose to the muscles due to a larger muscle capillary network and blood flow (Saltin et al., 1977; Mandroukas et al., 1984; Coggan et al., 1993).

Prolonged hypertension leads to hypertrophy and in the long term also to systolic dysfunction (Takenaka et al., 1988; Yasuda et al., 1992; Tarumi et al., 1993; Robillon et al., 1994). Many patients are characterized by chronic low-grade inflammation with increased levels of, for example, C-reactive protein (Pradhan et al., 2001). The latter has a negative prognostic value (Duncan & Schmidt, 2001; Abramson et al., 2002). Physical training augments diastolic filling in the left ventricle (Kelemen et al., 1990; Levy et al., 1993), increases endothelial vasodilator function (Higashi et al., 1999a, b), and induces anti-inflammatory effects (Febbraio & Pedersen, 2002).

Type of training

All patients with hypertension (both those receiving medical treatment as well as those not receiving treatment) benefit from physical training, which should either in the form of endurance training, dynamic strength training or isometric training.

Contraindications

In accordance with guidelines from ACSM, people with blood pressure >180/105 should not begin regular physical activity until after pharmacological treatment has been initiated (relative contraindication) (American College of Sports Medicine, 1993). An increase in risk of sudden death or stroke in physically active people with hypertension has not been ascertained (American College of Sports Medicine, 1993; Tipton, 1999). ACSM advises caution in the case of high-intensity dynamic training or strength training with very heavy weights. Heavy strength training can lead to very high pressure in the left ventricle (>300 mmHg), which can be potentially dangerous. In particular, patients with congestive hypertrophy should refrain from heavy strength training. Other precautions depend on comorbidity.

Coronary heart disease

Background

The term coronary heart disease (CHD) refers to a pathophysiological condition where a decrease in blood flow to the heart muscle causes ischemia, i.e., reduces oxygen supply. The most common cause is atherosclerotic constriction in the coronary arteries, but myocardial ischemia can also occur in patients with heart valve disease, hypertrophic cardiomyopathy, severe hypertension and abnormal tendency toward coronary spasm. Level of physical activity and cardio-respiratory fitness correlate with cardiovascular endpoints in healthy people and in patients with CHD (Myers et al., 2002).

Evidence-based physical training

There is solid evidence demonstrating the effect of physical training on patients with CHD. Physical training improves survival rates and is assumed to have a direct effect on the pathogenesis of the disease.

A Cochrane Review from 2011 aimed at determining the effectiveness of exercise-based cardiac rehabilitation (exercise training alone or in combination with psychosocial or educational interventions) on mortality, morbidity and health-related quality of life of patients with CHD (Heran et al., 2011). The study included men and women of all ages who have had myocardial infarction (MI), coronary artery bypass graft (CABG), or percutaneous transluminal coronary angioplasty (PTCA), or who have angina pectoris or coronary artery disease defined by angiography. The Cochrane systematic review included 47 studies randomizing 10 794 patients to exercise-based cardiac rehabilitation or usual care. In medium to longer term (i.e., 12 or more months follow-up) exercise-based cardiac rehabilitation reduced overall and cardiovascular mortality [RR: 0.87 (95% CI: 0.75, 0.99) and 0.74 (95% CI: 0.63, 0.87), respectively], and hospital admissions [RR: 0.69 (95% CI: 0.51, 0.93)] in the shorter term (<12 months follow-up). Cardiac rehabilitation did not reduce the risk of total MI, CABG, or PTCA. In 7of 10 trials reporting health-related quality of life using validated measures was there evidence of a significantly higher level of quality of life with exercise-based cardiac rehabilitation than usual care. Thus, it was concluded that exercise-based cardiac rehabilitation is effective in reducing total and cardiovascular mortality (in medium- to long-term studies) and hospital admissions (in short-term studies) but not total MI or revascularization (CABG or PTCA). The latter review is in agreement with previous meta-analyses (Jolliffe et al., 2000; Taylor et al., 2004).

Physical training of patients with CHD was found to reduce total cholesterol and triglyceride levels and systolic blood pressure. Many of the subjects in the training groups had stopped smoking (OR = 0.64; 95% CI: 0.50–0.83) (Taylor et al., 2004).

Possible mechanisms

The mechanism behind the prognostic gain from physical training is undoubtedly multifactorial and includes training-induced increased fibrinolysis, decreased platelet aggregation, improved blood pressure regulation, optimized lipid profile, improved endothelium-mediated coronary vasodilation, increased heart rate variability and autonomic tone, a beneficial effect on a number of psychosocial factors and a generally higher level of supervision of patients. Physical training is believed to have a beneficial effect by enhancing CRF, reducing myocardial oxygen demand at a certain exercise level, having a beneficial effect on autonomic and coronary endothelial function and improving cardiovascular risk profile, including blood pressure, HDL/LDL ratio, weight, glycemic control, and psychological well-being (Ades, 2001; Giannuzzi et al., 2003).

Type of training

The recommendation is to offer cardiac rehabilitation that includes physical training as a key component to all patients with CHD. Before training is commenced, there should be an evaluation of exercise capacity in order to create an individual training program. The recommended method for evaluating exercise capacity is a symptom-limited exercise test. Trained personnel (physiotherapist, nurse, laboratory assistant) under a doctor's supervision can carry this out. It is difficult to make precise recommendations about the duration, frequency and intensity of the training due to a lack of comparable studies. From 1995 to 2007, the American Heart Association and the American College of Cardiology guidelines (Smith et al., 2001) recommended aerobic training lasting 20–60 min 3–5 times a week at an intensity of 50% to 80% of the patient's maximum level (defined as VO_{2max}, maximum heart frequency, or maximum symptom-limited exercise capacity). The training can be continual or interval, e.g., walking, running, step machine, cycling, rowing, or stair walking. The aerobic training presumably should be backed up by strength training and training intensity should be increased as the patient's exercise capacity increases.

Physical training is also advisable for patients with angina pectoris who are not candidates for revascularization (Thompson et al., 2003). It is not clear how long the supervised training program should be, but the bulk of the studies that were part of the above-mentioned meta-analysis involved a duration of 6–24 weeks with a weighted average of approximately 11 weeks. The effect was not determined by duration but by the overall "training dose" and no difference was found in mortality after training programs involving a generally large dose as opposed to a low dose (Taylor et al., 2004). Lengthier training programs are aimed at ensuring that the patient achieves a training effect and partly at helping to incorporate new exercise habits. The working group assessed that training should extend over 12 weeks, with a shorter program or longer program for selected patient groups after assessment. In areas with scant provision of facilities by the local authorities, it is recommended that a training program be put together in conjunction with the hospital.

Based on the above, the following is recommended:

- Physical exercise is advisable for all patients with stable CHD. In the case of acute coronary disease (ACD), training can be embarked on 1 week after revascularized STEMI/NSTEMI and 4–6 weeks after CABG.
- All patients who have been hospitalized with ACD and/or are not fully revascularized should be examined by a cardiologist before any training program is initiated.
- In order to organize an individual training program, the training should be preceded by an assessment of exercise capacity. The recommended method for this is a symptom-limited exercise test, which can be carried out by trained personnel (physiotherapist, nurse, laboratory assistant) under a doctor's supervision.
- Supervised training with individually organized training programs after an initial exercise test: 2–5 30–60-min sessions a week at an intensity of 50–80% of maximum exercise capacity.
- Twelve weeks of organized aerobic training and possibly interval training combined with resistance training, especially for the elderly and patients with muscle weakness.
- Daily low-intensity training (walking) over 30 min, increasing the level under the supervision of the rehabilitation team.

Contraindications

The following contraindications are in agreement with a European Working Group (Gianuzzi & Tavazzi 2001).

- Acute CHU (AMI or unstable angina), until the condition has been stable for at least 5 days
- Dyspnea at rest
- Pericarditis, myocarditis, endocarditis
- Symptomatic aortic stenosis
- Severe hypertension. There is no established, documented borderline blood pressure value deemed to be the cut-off point for increased risk. Generally it is recommended that demanding physical exercise be avoided in the case of systolic BP >180 or diastolic BP >105 mmHg
- Fever
- Serious non-cardiac disease

Heart failure

Background

Heart failure is a condition where the heart is unable to pump sufficiently to maintain blood flow to meet the metabolic needs of the peripheral tissue (Braunwald & Libby, 2008). Heart failure is a clinical syndrome with symptoms such as fluid retention, breathlessness, or excessive tiredness when resting or exercising, and with objective symptoms of reduced systolic function of the left ventricle at rest.

Asymptomatic left ventricular dysfunction is often the precursor of this syndrome. Symptoms vary from very light restriction of function to seriously disabling symptoms. Heart failure is often divided into left-sided (the most frequent and best researched type) and right-sided heart failure and into acute (pulmonary edema, cardiogenic shock) and chronic heart failure. Heart failure is often caused by ischemic disease, but can also be caused by, for example, hypertension or valvular heart disease (Braunwald & Libby, 2008).

Maximum oxygen uptake (VO_{2max}) is lower in patients with heart failure (Sullivan et al., 1989b; Cohen-Solal et al., 1990; 2001c). This is caused, among other things, by the reduced pumping function of the heart and by peripheral conditions in the muscles (Massie et al., 1988; Sullivan et al., 1990; 2001c). A common symptom with heart failure patients is muscle atrophy, tiredness, and reduced muscle strength (Wilson et al., 1993; Anker et al., 1997; Harrington et al., 1997). Heart failure patients are characterized by defects in the renin–angiotensin system, increased levels of cytokines, also TNF (Bradham et al., 2002), increased noradrenalin (Jewitt et al., 1969), and insulin resistance (Paolisso et al., 1991). These metabolic conditions can all be significant factors in the development of muscle atrophy with heart failure (Anker et al., 1997), although no direct link between VO_{2max} and noradrenalin (Notarius et al., 2002) has been found. Thus, heart failure patients tend to have poor fitness, poor muscle strength and muscle atrophy. The characteristic symptom of tiredness is presumably related to diminishing physical ability. While there was a consensus in the 1970s that patients with all stages of heart failure should be advised to refrain from physical activity and be prescribed bed rest (McDonald et al., 1972), the consensus now is the opposite (2001c).

Evidence-based physical training

International guidelines recommend physical training for patients with CHF after a large number of studies have demonstrated the beneficial effect on central and peripheral factors and on function level, New York Heart Association (NYHA) class and quality of life, without presenting any significant risks (Hunt et al., 2005; Swedberg et al., 2005). The effect of physical training on patients with heart failure has been assessed in numerous meta-analyses (Lloyd-Williams et al., 2002; Piepoli et al., 2004; van Tol et al., 2006; Haykowsky et al., 2007; Hwang & Marwick, 2009; Davies et al., 2010a; Davies et al., 2010b).

There is consistent evidence of the beneficial effect of training patients with heart failure. A definite impact on heart failure-related hospitalization, physical function and quality of life has been identified. The studies were carried out on stable patients in NYHA class II and NYHA class III, and most of the studies excluded patients with competing diseases, such as diabetes or chronic obstructive pulmonary disease.

A 2010 Cochrane Review assessed the effect of physical training on patients with congestive heart failure. The analysis identified 19 randomized controlled trials that compared training over a minimum of 6 months with a non-exercise control group. The 19 studies included 3647 patients, the majority of them men in NYHA class II–III with a left ventricular ejection fraction of less than 40%. Unlike several other earlier analyses, which were based on fewer studies, no significant difference in mortality was found between the training group and the control group. There was an insignificant effect of the same magnitude as in earlier studies. Heart failure-related hospitalizations were significantly lower in the exercise group (RR: 0.72, 95% CI: 0.52–0.99). Furthermore, a clear enhancement of quality of life was ascertained (SDM: −0.63, 95% CI: −0.80 to 0.37) in the exercise group (Davies et al., 2010b).

The randomized trials generally included CHF patients with systolic failure (EF <40%), documentation for the effect of training with isolated diastolic failure is sparse. The latest randomized clinical trials on physical training were carried out with heart failure patients who were presumably following a more optimal program of medical treatment compared to the initial studies. For example, in a 2009 study, 94% of the patients were being treated with beta blockers and angiotensin receptor blockers and 45% had an implanted defibrillator or pacemaker (Flynn et al., 2009).

A Cochrane Review from 2014 (Taylor et al., 2014) updated the Cochrane review previously published in 2010 (Davies et al., 2010b) and had focus on mortality, hospitalization admissions, morbidity, and health-related quality of life for people with heart failure. Randomized controlled trials of exercise-based interventions with 6-month follow-up or longer compared with a no exercise control that could include usual medical care. The study population comprised adults over 18 years and was broadened to include individuals with HFPEF in addition to HFREF. The authors included 33 trials with 4740 people with heart failure predominantly with HFREF and New York Heart Association classes II and III. This latest update identified a further 14 trials. There was no difference in pooled mortality between exercise-based rehabilitation vs no exercise control in trials with up to 1-year follow-up (25 trials, 1871 participants: risk ratio (RR): 0.93; 95% CI: 0.69–1.27, fixed-effect analysis). However, there was trend toward a reduction in mortality with exercise in trials with more than 1 year of follow-up (6 trials, 2845 participants: RR: 0.88; 95% CI: 0.75–1.02, fixed-effect analysis). Compared with control, exercise training reduced the rate of overall (15 trials, 1328 participants: RR: 0.75; 95% CI: 0.62–0.92, fixed-effect analysis) and heart failure specific hospitalization (12 trials, 1036 participants: RR: 0.61; 95% CI: 0.46–0.80, fixed-effect analysis). Exercise also resulted in a clinically important improvement in disease specific health-related quality of life measure. Two studies indicated exercise-based rehabilitation to be a potentially cost-effective use of resources in terms of gain in quality-adjusted life years and life years saved.

Regarding mode of exercise, a meta-analysis showed that in clinically stable patients with heart failure with reduced ejection fraction vigorous to maximal aerobic interval training is more effective than traditionally prescribed moderate-intensity continuous aerobic training for improving peak oxygen uptake (Vo2) (Haykowsky et al., 2013). The latter conclusion was supported by yet another meta-analysis (Ismail et al., 2013).

Possible mechanisms

Training increases myocardial function assessed at maximum minute volume (Sullivan et al., 1988; Coats et al., 1992; Demopoulos et al., 1997; Dubach et al., 1997; 2001c), increases systemic arterial compliance (Hambrecht et al., 2000; Parnell et al., 2002), increases stroke volume (Hambrecht et al., 2000), counteracts cardiomegaly (Hambrecht et al., 2000), induces positive changes in the exercising muscle (Sullivan et al., 1988; Adamopoulos et al., 1993; Hambrecht et al., 1995; 2001c), and increases the anaerobic threshold (Sullivan et al., 1988; Sullivan et al., 1989a; Hambrecht et al., 1995; Kiilavuori et al., 1996; Meyer et al., 1996; 2001c). Exercise reduces the sympathetic nervous system and the renin–angiotensin system (Coats et al., 1990; Coats et al., 1992; Kiilavuori et al., 1995; 2001c). Exercise further induces muscle cytochrome C oxidase activity, which leads to reduced local expression of proinflammatory cytokines and inducible nitric oxide synthase and increases insulin-like growth factor (IGF-1) (Schulze et al., 2002). Thus, physical training is able to inhibit the catabolic processes in the heart failure patient and counteract muscle atrophy. Physical training lowers the concentration of circulating TNF receptors 1 and 2 (Conraads et al., 2002), TNF and FAS-L (Adamopoulos et al., 2002), and the quantity of circulating adhesion molecules (Adamopoulos et al., 2001) in patients with heart failure. Physical training lowers the expression of cytokines in the skeletal muscle (Gielen et al., 2003) and in the blood stream (LeMaitre et al., 2004).

Type of training

Many studies have demonstrated a beneficial effect from interval training, which is possibly more effective than moderate continual aerobic training (2001c; Wisloff et al., 2007). Patients can start on interval training, beginning on a low exercise capacity, and gradually increase duration, frequency, and intensity (2001c).

Practitioners used to be reluctant to recommend resistance training out of concern that increased vascular resistance would increase cardiac load more than aerobic training. There is no evidence that a combination of aerobic and resistance training produces better or worse results than aerobic training alone (Haykowsky et al., 2007).

Based on the above, the following is recommended:

- Training is recommended for all heart failure patients in NYHA function class II–III on a fully titrated medication regimen and well compensated for 3 weeks.
- All patients should be assessed by a cardiologist before embarking on a training program.
- For the sake of caution and in order to determine individual exercise capacity, the training should be preceded by a symptom-limited exercise test.

- A supervised, tailored training program is recommended after an initial exercise test:

Training programs for heart failure patients with very low exercise capacity must be structured with short daily sessions of low-intensity exercise, gradually increasing duration as the program progresses. When the patient is able to train for 30 consecutive minutes, training frequency should be cut down to 2–3 sessions a week and training intensity gradually stepped up. As a rule, training is not recommended for patients in NYHA IV, although there are studies in which selected patients trained without presenting any hazards.

Contraindications

The following contraindications are in agreement with a European Working Group (2001c).

Relative:

- > 1.8 kg weight increase over 1–3 days
- Decrease in systolic BP during exertion (exercise test)
- NYHA IV
- Complex ventricular arrhythmia when resting or during exertion (exercise test)
- Heart frequency at rest > 100

Absolute contraindications:

- Worsening of functional dyspnea or newly occurring dyspnea at rest over 3–5 days
- Significant ischemia at low exertion (< 2 METS or 50W)
- Acute illness or fever
- Recent thromboembolism
- Active pericarditis or myocarditis
- Moderate/difficult aortic stenosis
- Valve insufficiency requiring surgery
- AMI within the preceding 3 weeks
- Newly occurring atrial fibrillation

Intermittent claudication

Background

Arterial insufficiency in the lower limbs (lower limb ischemia, leg ischemia) is a chronic obstructive disease in the aorta below the outlet of the renal arteries, iliac artery and the arteries in the lower limbs probably caused by atherosclerosis. It is estimated that at least 4% of all people above the age of 65 have peripheral arteriosclerosis, which in 50% of cases causes intermittent pain (intermittent claudication). A minority of patients experience the progression of peripheral arteriosclerosis, which results in pain while at rest and ulcerations. Owing to the realization that medical treatment of the disease has limited efficacy, the international consensus today is that physical training is a key factor in the treatment of patients with intermittent claudication (TASC, 2000). As the intermittent claudication becomes more severe, function level decreases and quality of life becomes affected. Increasing pain when walking and the consequent fear of moving gradually causes the patient to become static and socially isolated. In the long term, this leads to deterioration of fitness and the progression of arteriosclerosis, reduced muscle strength and muscle atrophy, trapping the patient in a vicious circle of poor fitness, pain, and social isolation. Physical activity can be used to interrupt this vicious circle and directly affect the pathogenesis of the disease by increasing fitness and muscle strength, changing pain thresholds and the perception of pain, allaying fear, and preventing disease progression.

Evidence-based physical training

There is solid evidence demonstrating the beneficial effect of physical training on patients with intermittent claudication. A Cochrane Reviews from 2014 (Lane et al., 2014) included 30 trials, involving a total of 1816 participants with stable leg pain. The follow-up period ranged from 2 weeks to 2 years. The types of exercise varied from strength training to polestriding and upper or lower limb exercises; generally supervised sessions were at least twice a week. Most trials used a treadmill walking test for one of the outcome measures. Twenty trials compared exercise with usual care or placebo, the remainder of the trials compared exercise to medication or pneumatic calf compression. Overall, when taking the first time point reported in each of the studies, exercise significantly improved maximal walking time when compared with usual care or placebo: mean difference (MD) 4.51 min (95% CI: 3.11–5.92) with an overall improvement in walking ability of approximately 50% to 200%. Walking distances were also significantly improved: pain-free walking distance MD 82.29 m (95% CI: 71.86–92.72) and maximum walking distance MD 108.99 m (95% CI: 38.20–179.78). Improvements were seen for up to 2 years. The effect of exercise, when compared with placebo or usual care, was inconclusive on mortality, amputation, and peak exercise calf blood flow due to limited data. At 3 months, physical function, vitality, and role physical were reported to be improved with exercise in two trials. At 6 months, five trials reported outcomes of a significantly improved physical summary score and mental summary score secondary to exercise. The authors concluded that exercise programs are of significant benefit compared with placebo or usual care in improving walking time and distance in people with leg pain from intermittent claudication who were considered to be fit for exercise intervention.

This was obtained without any demonstrable effect on the patients' ankle blood pressure measurements. The results were not conclusive for mortality and amputation.

In a controlled study, physical training was compared with percutaneous transluminal angioplasty (PTA) and the finding was that there was no significant difference after 6 months (Creasy et al., 1990). A review article by Chong et al. (2000) assessed the results of physical training (9 studies, 294 patients) and PTA (12 studies, 2071 patients). The authors concluded that it was essentially impossible to compare the effect of two treatments in one non-controlled study design, but reported that the effect of PTA was minimally better than training, although PTA involved the risk of serious side effects.

A randomized study compared the effect of (a) physical exercise alone, (b) surgery, and (c) physical exercise + surgery. All groups achieved the same effect on walking distance, but there were side effects in 18% of the patients who underwent surgery (Lundgren et al., 1989).

Another randomized study compared the effect of physical training and antithrombotic therapy (Mannarino et al., 1991). A significantly larger improvement in walking distance was recorded for the group that exercised (86%) compared with the group that received medication (38%). A meta-analysis found that training programs were substantially cheaper and involved fewer risks than either surgery or PTA (de Vries et al., 2002). Furthermore, a meta-analysis has shown that quality of life increases with walking distance (Regensteiner et al., 2002).

A recent review analyzed the safety of supervised exercise training in patients with intermittent claudication (Gommans et al., 2015). There has been concern regarding the safety of performing supervised exercise training because intermittent claudication patients are at risk for cardiovascular events. The review selected 121 articles, of which 74 met the inclusion criteria. Studies represent 82 725 h of training in 2876 patients with intermittent claudication. Eight adverse events were reported, six of cardiac, and two of non-cardiac origin, resulting in an only all-cause complication rate of one event per 10 340 patient-hours.

Possible mechanisms

Physical training programs for patients with heart failure increase local production of the vascular endothelial growth factor (VEGF) (Gustafsson et al., 2001), which induces the production of collaterals and thus increases blood flow. The formation of VEGF is stimulated by muscle contractions during ischemia. This is presumably a key mechanism, which also explains the importance of training beyond the pain threshold. However, a clinical effect of exercise that does not affect ankle blood pressure has been demonstrated (Tan et al., 2000), and there is generally a poor correlation between ankle blood pressure and improvement of walking distance (Hiatt et al., 1990). Physical activity increases endothelial function in the lower limbs (Gokce et al., 2002). We assume that the effect of the physical training is to a large degree linked to improved fitness and increased muscle strength. Furthermore, the patients' experience of being able to pass the pain threshold probably has a psychological effect and consequently their perception of pain changes.

Type of training

The vast majority of studies only assess the effect of walking exercise measured with a treadmill test, while there is little information on other forms of training. One study found beneficial effects from Nordic walking compared to a non-exercising control group (Langbein et al., 2002). Nordic walking involves walking using poles in both hands, which partly provide support and partly force the patient to move the upper body, increasing overall exertion. There is limited information on the importance of walking speed or intensity, but strong evidence to suggest that the effect is increased if training is carried out until the onset of ischemia symptoms. Controlled trials provide some, albeit limited, evidence that supervised training is more effective than unsupervised training (Regensteiner et al., 1996; Bendermacher et al., 2006; Wind & Koelemay, 2007; Shalhoub et al., 2009). The effect of training is reinforced if the patient quits smoking (Jonason & Ringqvist, 1987) and the amount of training is a determining factor in efficacy (Nicolai et al., 2010).

Physical activity should preferably be in the form of walking exercise, which should initially be supervised through regular visits to a therapist. In many cases, training can take place in the home and it should take place at least 3 days a week. The patient should walk until just past the onset of pain and then take a short break until the pain has receded, after which the walking exercise should be resumed. Training sessions should be at least 30 min each time and the training program should be lifelong and supervised in the initial 6 months. Feedback is in the form of a patient logbook recording walking distance, distance/time before onset of pain and training frequency. Walking distance should be tested before and after 3 months, and subsequently once a year. Ischemic pain does not necessarily occur in the case of bike exercise, which is the reason why walking exercise is preferable. If bike exercise is chosen, the patient must be instructed to pedal using the front of the foot and the same training principles apply as for walking.

Contraindications

There are no general contraindications. Supervised exercise training can safely be prescribed in patients with intermittent claudication because an exceedingly low all-cause complication rate is found. Routine cardiac screening before commencing exercise training is not required.

Pulmonary diseases

Chronic obstructive pulmonary disease

Background

Chronic obstructive pulmonary disease (COPD) is characterized by an irreversible decrease in lung function. Advanced-stage COPD is a long and painful process of gradually increasing and ultimately disabling breathlessness as the main symptom. Today the international consensus is that rehabilitation programs are an important part of COPD treatment, which follows from the realization that drug therapy for COPD is inadequate.

A vicious cycle of deterioration in physical capacity, shortness of breath, anxiety, and social isolation develops. Rehabilitation can break this cycle by introducing physical training, psychological support and networking with other COPD patients (Rugbjerg et al., 2015).

Reduction in muscle strength is a major cause of reduced exercise capacity and physical functional level (Hamilton et al., 1995). A minor study showed that muscle mass in the quadriceps was approximately 15% less and muscle strength about 50% lower in elderly men with COPD than in healthy, physically inactive peers (Kongsgaard et al., 2004).

Evidence-based physical training

The positive impact of physical exercise for patients with COPD is well documented. A 2015 Cochrane Review/meta-analysis (McCarthy et al., 2015) added to previous meta-analyses (Lacasse et al., 1996; Lacasse et al., 2002; Lacasse et al., 2007; Salman et al., 2003). The 2015 update includes 65 RCTs involving 3822 participants. A total of 41 of the pulmonary rehabilitation programs were hospital based, 23 were community based and one study had both a hospital component and a community component. Most programs were of 12-week or 8-week duration with an overall range of 4–52 weeks. The authors found statistically significant improvement for all included outcomes. In four important domains of quality of life (Chronic Respiratory Questionnaire (CRQ) scores for dyspnea, fatigue, emotional function, and mastery), the effect was larger than the minimal clinically important difference of 0.5 units. Statistically significant improvements were noted in all domains of the St. George's Respiratory Questionnaire, and improvement in total score was better than 4 units. Both functional exercise and maximal exercise showed statistically significant improvement. Researchers reported an increase in maximal exercise capacity [mean $W_{\max}$ (W)] in participants allocated to pulmonary rehabilitation compared with usual care. In relation to functional exercise capacity, the 6-min walk distance mean treatment effect was greater than the threshold of clinical significance. The subgroup analysis, which compared hospital-based programs vs community-based programs, provided evidence of a significant difference in treatment effect between subgroups for all domains of the CRQ, with higher mean values, on average, in the hospital-based pulmonary rehabilitation group than in the community-based group. Subgroup analysis performed to look at the complexity of the pulmonary rehabilitation program provided no evidence of a significant difference in treatment effect between subgroups that received exercise only and those that received exercise combined with more complex interventions.

Studies show that rehabilitation programs lead to fewer hospitalizations and thus save resources (Griffiths et al., 2000; Griffiths et al., 2001). Most studies use high-intensity walking exercise. One study compared the effect of walking or cycling at 80% of $VO_{2\max}$ vs working out in the form of Callanetics exercises and found that high-intensity training increased fitness while the workout program increased arm muscle stamina. Both programs had a positive effect on the experience of dyspnea (Normandin et al., 2002). Oxygen treatment in conjunction with intensive training for patients with COPD increased training intensity and thus improved fitness in one study (Hawkins et al., 2002), but not in another (Wadell et al., 2001). It is recommended that oxygenation therapy should be provided at the end of training if the patients are hypoxic or become desaturated during the training (American Thoracic Society, 1999). Training to music gave better results than without music (Bauldoff et al., 2002), presumably because patients who run with music perceive the physical exertion to be less, even though they are doing the same amount of exercise. Specific training for inspiratory muscles increased the stamina of these muscles but did not give the patients a lower perception of dyspnea or improved fitness (Scherer et al., 2000). Thus, strong evidence exists that endurance training as part of pulmonary rehabilitation in patients with COPD improves exercise capacity and health-related quality of life. However, dyspnea limits the exercise intensity. Therefore, resistance training, which may cause less dyspnea, could be an alternative. Moreover, low muscle mass is associated with increased risk of mortality (Marquis et al., 2002).

A recent systematic review (Iepsen et al., 2015b) compared the effect of resistance and endurance training. The authors included eight randomized controlled trials (328 participants) and found that resistance training appeared to induce the same beneficial effects as endurance training. It was therefore recommended that resistance training should be considered according to patient preferences when designing a pulmonary rehabilitation program for patients with COPD. The same authors performed another systematic review (Iepsen et al., 2015a) in which they assessed the efficiency of combining resistance training with endurance training compared with endurance training alone. For this analysis, they included 11 randomized controlled trials (331 participants) and 2 previous systematic reviews. They found equal improvements in quality of life, walking distance, and exercise capacity. However, they also found moderate evidence of a significant increase in leg muscle strength favoring a combination of resistance and endurance training and recommend that resistance training should be incorporated in rehabilitation of COPD together with endurance training.

Possible mechanisms

Physical activity does not improve lung function in patients with COPD but increases CRF via the effect on the muscles and the heart. Patients with COPD have chronic inflammation, which may be a cause of the decrease in muscle strength observed in COPD patients. Patients with COPD have higher TNF levels in blood (Eid et al., 2001) and muscle tissue (Palacio et al., 2002). TNF's biological impact on muscle tissue is manifold. TNF affects myocyte differentiation, induces cachexia, and thus a potential decrease in muscle strength (Li & Reid, 2001). A Danish study showed that smoking inhibited protein synthesis in the muscles, which can potentially also lead to loss of muscle mass (Petersen et al., 2007). Training can presumably have an impact on this process. Another Danish study showed that physical training counteracted the increase in protein degradation seen in people with COPD (Petersen et al., 2008).

Type of training

All patients with COPD, particularly the more severe cases, benefit from physical training. Initially the physical training must be supervised, individually tailored and include a combination of endurance training and strength training. Endurance training can be walking or cycling at 70–85% of VO_{2max} (Morgan et al., 2001). Supervised training over 7 weeks produced better results with regard to a number of respiratory parameters than a 4-week program (Green et al., 2001).

Contraindications

No general contraindications. The training should take competing diseases into account. For patients with low oxygen saturation (SaO_2 <90%) and dyspnea when at rest, exercising with oxygenation is recommended.

Bronchial asthma

Background

Bronchial asthma (asthma) is a chronic inflammatory disorder characterized by episodic reversible impairment of pulmonary function and airway hyper-responsiveness to a variety of stimuli (National Institute of Health, 1995). Allergies are a major cause of asthma symptoms, especially in children, while many adults have asthma without an allergic component. Environmental factors, including tobacco smoke and air pollution, contribute to the development of asthma.

Physical exercise poses a particular problem for asthmatics as physical activity can provoke bronchoconstriction in most asthmatics (Carlsen and Carlsen, 2002). Regular physical activity is important in the rehabilitation of patients with asthma (Orenstein, 1995). Asthmatics need to be taught how to prevent exercise-induced symptoms in order to benefit, just like other people, from the positive effects of physical activity against other diseases. With children in particular, it is important that they are taught how physical activity can be adapted to asthma due to its importance for their motor and social development.

Exercise-induced asthma can be prevented by warming up thoroughly and by using a number of anti-asthma drugs, e.g., short- or long-acting beta-agonists, leukotriene antagonists, or chromones. Another way to help eliminate some exercise-induced symptoms is to adjust the prophylactic treatment so that the asthma and thus airway responsiveness are under control. Regular intake of anti-asthma medicine, especially inhaled steroids, is crucial to enabling physical training. Moreover, 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, and tobacco smoke. Some studies (Clark and Cochrane, 1988; Garfinkel et al., 1992; Malkia and Impivaara, 1998), but not in others (Santuz et al., 1997), have found physical fitness to be poor in asthmatics. Irrespective of how physically fit the patient is, guidance and medicine are important to enabling all asthmatics the opportunity to be physically active without worrying about the symptoms.

Evidence-based physical training

A Cochrane Review from 2013 (Carson et al., 2013) included randomized trials of people over 8 years of age with asthma who were randomized to undertake physical training or not. Physical training had to be undertaken for at least 20 min, two times a week, over a minimum period of 4 weeks. Twenty-one studies including 772 participants were included. Physical training was well tolerated with no adverse effects reported. None of the studies mentioned worsening of asthma symptoms following physical training. Physical training showed marked improvement in cardiopulmonary fitness as measured by an increase in maximum oxygen uptake; however, no statistically significant effects were observed for forced expiratory volume in 1 second, forced vital capacity, minute ventilation at maximal exercise, or peak expiratory flow rate. It was concluded that physical training showed a significant improvement in fitness, though no effects were observed in other measures of pulmonary function.

A Cochrane study concluded that swimming training is beneficial for children and adolescents with asthma (Beggs et al., 2013).

A non-controlled trial showed that it is possible for adult asthmatics to participate in high-intensity training (Emtner et al., 1996). The patients trained in an indoor swimming pool at 80–90% of maximum oxygen uptake (VO_{2max}) for 45 min, initially once a week and then twice a week for 10 weeks. Physical fitness improved and there were fewer cases of exercise-induced asthma attacks, less anxiety in connection with physical exertion and less of a feeling of dyspnea. At the 3-year follow-up examination, 68% of the patients were still physically active and trained one to two times a week (Emtner et al., 1998). Physical training has a positive effect on the psycho-social morbidity and quality of life of asthma patients (Mendes et al., 2010; Turner et al., 2011).

Possible mechanisms

Physical activity does not improve lung function in patients with asthma, but it does increase cardiorespiratory condition via its effect on the muscles and heart. A common hypothesis (Ram et al., 2000) is that physical training in asthmatics helps reduce ventilation during exertion, thus reducing the risk of provoking an asthma attack during physical activity. It is also possible that physical training induces an anti-inflammatory effect in the lungs (Silva et al., 2010).

Type of training

The physical training program must be individually tailored and should primarily consist of aerobic training of moderate to high intensity, for example, running, cycling, playing ball, or swimming. Some patients benefit from local treatment with beta-2 agonists or leukotriene antagonists 10–20 min prior to training (Tan and Spector, 2002). The treatment must be prescribed by a doctor and it is important that daily prophylactic treatment is optimal. Warming up at light intensity for about 15 min is also beneficial. The recommendation for individuals who are unfit is to start training at low intensity and then gradually increase to moderate intensity, just as the duration of the physical activity should be increased gradually. After 1–2 months, the training should be carried out at least 3 days a week.

Contraindications

In cases of acute exacerbation of asthmatic symptoms, a pause in training is recommended. If the patient has an infection, a break in training is recommended until the patient has been asymptomatic for 1 day, after which time training can gradually be resumed.

Cystic fibrosis

Background

Cystic fibrosis is the most commonly occurring autosomal recessive, genetic, potentially life-threatening disease (Varlotta, 1998). Incidence among Caucasians is one in 2500. Cystic fibrosis is a system disease, but the predominant symptom is progressive obstructive pulmonary disease, which over time leads to respiratory failure and respiratory heart disease (Davis et al., 1996). Diminished pulmonary function restricts physical development, resulting in lower fitness and muscle function and the patients often develop osteoporosis (Ott and Aitken, 1998) and diabetes (Riggs et al., 1999). Evidence exists that patients with cystic fibrosis have reduced physical fitness (Bradley and Moran, 2002) and exercise has been identified as an independent predictor of mortality and morbidity in cystic fibrosis patients (Nixon et al., 1992; Moorcroft et al., 1997).

Moreover, exercise intolerance is associated with reduced pulmonary function (Moorcroft et al., 1997) as well as daily activity levels (Troosters et al., 2009) and infections (van de Weert-van Leeuwen et al., 2014). The goal of physical training for cystic fibrosis patients is to:

- Mobilize the mucus in the lungs and to stimulate an increase in mucociliary transport (Dwyer et al., 2011a)

- Achieve a satisfactory level of fitness and strength to be able to maintain a normal capacity for exercise
- Maintain normal mobility, especially of the chest, to ensure that mucus clearance therapy is effective (Vibekk, 1991; Lannefors et al., 2004)
- Prevent osteoporosis and diseases related to physical inactivity (Borer, 2005)
- Increase self-confidence (Ekeland et al., 2004).

In theory, physical training may lower the risk for diabetes and infectious episodes.

Evidence-based physical training

In general, the evidence is poor for the effect of physical training in patients with cystic fibrosis, but it has been found that physical activity improves exercise capacity, slows the decline in lung function, and improves quality of life in patients with cystic fibrosis (Dwyer et al., 2011b; Hulzebos et al., 2013).

In a Cochrane review from 2008 (Bradley and Moran, 2002), seven studies which included 231 participants met the inclusion criteria. The review provided some but limited evidence from both short- and long-term studies that aerobic or anaerobic physical training has a positive effect on primary outcomes (exercise capacity, strength, and lung function) but improvements are not consistent between studies.

A systematic 2010 meta-analysis assessed the effect of physical exercise on children with cystic fibrosis. The analysis covered only four randomized controlled trials (Schneiderman-Walker et al., 2000; Selvadurai et al., 2002; Klijn et al., 2004; Orenstein et al., 2004) and included 221 children with cystic fibrosis. The selected studies are strikingly heterogeneous concerning the severity of the cystic fibrosis, duration of the training intervention, and the mix of aerobic exercise and resistance training. All in all physical training was found to have a positive effect on lung function, muscle strength and fitness (van Doorn, 2010).

Inspiratory muscle training has been suggested as a mode of training to improve the lung function and quality of life of people with cystic fibrosis and a Cochrane study from 2013 evaluated the effect of inspiratory muscle training (Houston et al., 2013). Eight studies with 180 participants met the review inclusion criteria. However, it was concluded that there is limited evidence to suggest that this treatment is either beneficial or not. More recent evidence suggests that interval exercise training can improve exercise capacity even in severely affected adults with cystic fibrosis (Gruber et al., 2014).

Possible mechanisms

Physical activity improves fitness and muscle strength, allowing the patient to be active physically. Physical training increases pulmonary function by clearing lung secretions (O'Neill et al., 1987). It also increases patients' self-confidence and physical well-being. Furthermore, exercise protects against osteoporosis and diseases linked to physical inactivity.

Type of training

The physical training should be individually tailored and supervised and include aerobic training and strength training (Wilkes et al., 2009; Karila et al., 2010).

Contraindications

If the patient has an infection, a break in training is recommended until the patient has been asymptomatic for 1 day, after which time training can gradually be resumed.

Musculo-skeletal disorders

Osteoarthritis

Background

Osteoarthritis (degenerative arthritis, degenerative joint disease) is the most common joint disease and one of the most common chronic diseases. Virtually everyone over the age of 60 shows signs of osteoarthritis in at least one joint (Wilson et al., 1990). The prevalence of radiologically verified osteoarthritis of the hip or knee is 70% among people over the age of 65 (Wilson et al., 1990). Loss of articular cartilage is a dominant factor in the pathogenesis of osteoarthritis and is accompanied by joint deformation, bone sclerosis, capsule shrinkage, muscle atrophy and varying degrees of synovitis (Wilson et al., 1990). The clinical and radiological findings combined lead to diagnosis. Radiologically, the cartilage space appears narrower than normal and there is evidence of a loss of articular cartilage, bone spurs, meniscus degeneration, and subchondral sclerosis bone marrow edema. The radiological changes do not appear until later in the progression of the disease. Rest pain and joint tumors gradually appear.

Pain and the resulting level of diminished fitness and muscle strength restrict the patient's physical activity. Osteoarthritis is related to old age (Felson et al., 1987; Miedema, 1994), overweight, and poor muscle function (Slemenda et al., 1998), but also occurs in younger individuals who have placed inappropriate strain on a joint, often as a result of joint injury. Patients with osteoarthritis have a low physical activity level (Semanik et al., 2012), low muscle strength, and impaired muscle function (Roos et al., 2011; Segal and Glass, 2011).

Evidence-based physical training

There is strong evidence that physical exercise, both aerobic and resistance training, has an effect on self-reported pain and general level of functioning in individuals with osteoarthritis in the knee and hip joints (Zhang et al., 2010). The effect of resistance training on osteoarthritis in the knee and hip joints is comparable to peroral non-steroidal anti-inflammatory drugs and acupuncture, and the effect of aerobic training on knee osteoarthritis is comparable to intra-articular corticosteroid injections. There is evidence of a positive effect on pain and function with various types of physical training in patients with osteoarthritis (Zhang et al., 2010; Fransen et al., 2015).

A recent meta-analysis from 2015 (Fransen et al., 2015) evaluated the role of exercise in patients with knee osteoarthritis. In total, data from 44 trials (3537 participants) indicated that therapeutic exercise provides short-term benefit such as reduced pain, improved physical function, quality of life, and improved quality of life. In addition, 12 included studies provided 2- to 6-month data on 1468 participants indicating sustainability of treatment effect for pain and physical function. Individually delivered programs tended to result in greater reductions in pain and improvements in physical function, compared to class-based exercise programs or home-based programs.

A meta-analysis from 2014 (Juhl et al., 2014) included 48 randomized controlled trials and 4028 patients, also focusing on knee osteoarthritis. Similar effects in reducing pain were found for aerobic, resistance, and performance exercise. Single-type exercise programs were more efficacious than programs that included different exercise types. The effect of aerobic exercise on pain relief increased with an increased number of supervised. More pain reduction occurred with quadriceps-specific exercise than with lower limb exercise and when supervised exercise was performed at least three times a week. No impact of intensity, duration of individual sessions, or patient characteristics was found. Similar results were found for the effect on patient-reported disability. The authors conclude that an exercise programs for knee osteoarthritis should have one aim and focus on improving aerobic capacity, quadriceps muscle strength, or lower extremity performance.

A meta-analysis from 2008 comprising 18 studies with 2832 patients with knee osteoarthritis 55–74 years of age found that self-reported measurements of pain, physical functioning, muscle strength, gait speed, and balance improved in 56–100% of the studies. There was also an improvement in strength in musculus quadriceps femoris (Lange et al., 2008). Another meta-analysis from 2008 of nine studies comprising 1234 patients allowing a study of the effect of physical training on hip osteoarthritis found that it had a general positive effect (Hernandez-Molina et al., 2008). Current knowledge suggests that all exercise (not just strength training) has an effect on symptoms as long as it is being done.

A meta-analysis from 2014 (Waller et al., 2014) examined the effect of therapeutic aquatic exercise (TAE) on symptoms and function in patients with lower limb osteoarthritis. Eleven randomized controlled studies were selected. The meta-analysis showed a significant TAE effect on pain, self-reported function and physical. Additionally, a significant effect was seen on stiffness and quality of life, suggesting that TAE is an effective alternative in managing symptoms associated with lower limb osteoarthritis.

Possible mechanisms

There are no steadfast reasons to believe that exercise has a direct effect on the pathogenesis of the disease. Twelve weeks of training thus had no effect on the disease markers (chondroitin sulfates) in the synovial fluid (Bautch et al., 2000). Studies do exist, however, indicating a lowered concentration of IL-10 in the synovial fluid (Helmark et al., 2010) and increased glycosaminoglycan content in the cartilage (Roos and Dahlberg, 2005) after exercise. The latter *in vivo* cartilage monitoring study in patients at risk of knee osteoarthritis who begin exercising indicates that adult human articular cartilage has a potential to adapt to loading change. This could indicate a possible disease-modifying effect from the exercise, influencing the inflammation, and/or cartilage loss.

In terms of the training effect on impairments, the immediate mechanism of action is straightforward, namely through improved balance, muscle strength and endurance, although only a few studies have evaluated this in people with osteoarthritis (Fitzgerald et al., 2004).

There is a dearth of studies that shed light on the mechanisms of the analgesic effect of training. Isolated training of the pelvic muscles results in less knee pain in patients with knee osteoarthritis (Bennell et al., 2010). This indicates that it is not necessary to train the affected joint, but that exercise has a positive effect per se on pain.

Type of training

As mentioned above, there are an extensive number of studies showing that physical exercise improves general functioning in daily life and results in less pain. It should be emphasized that osteoarthritis patients as a group are heterogeneous. Physical training programs for osteoarthritis patients as a group should be individualized and supervised initially and focus on either improving aerobic capacity, quadriceps muscle strength, or performance. Over time, the supervised training can be adjusted to self-training with little or no follow-up by a professional. The training does not have to focus the affected joint(s).

Contraindications

In cases of acute joint inflammation, the affected joint should rest until the drug treatment has taken effect. If pain worsens after training, a break should be taken and the training program modified. It is important that especially young people with osteoarthritis resulting from a joint injury avoid sports that involve heavy pressure on the joints, especially with an axial compressive load or twisting. This applies to, e.g., basketball, football, handball, volleyball, and high-intensity running on hard surfaces.

The type of training should be altered if there is any sign of acute joint inflammation and/or a worsening of symptoms. Training joints other than the one(s) affected will have a positive effect. If there is any sign of acute joint inflammation and/or a worsening of symptoms, the nature of the training can be changed for a period from, for example, land-based training to water-based training, or from strength training to fitness training. Severe overweight may be a relative contraindication for weight-bearing exercise with less weight loss prior to initiating training as a mechanical overload may promote progression of the disease.

Osteoporosis

Background

Osteoporosis is a disease characterized by a decrease in bone mass and change in microarchitecture, and hence reduced bone strength. Patients with osteoporosis have a higher risk of bone fracture. Osteoporosis occurs in some cases as an independent disease (primary osteoporosis), and in others as a result of other diseases (secondary osteoporosis). Osteoporosis leads to a decrease in bone mineral density and no symptoms are generally apparent before bone fracture occurs.

The age-adjusted incidence of osteoporotic fractures is steadily rising in Europe. Within the last 20–30 years, the incidence of vertebral fractures has increased by a factor of 3–4 for women and by a factor of over four for men. The incidence of hip fracture has also risen by a factor of 2–3, mostly for men (Obrant et al., 1989). Owing to accelerated bone loss during menopause, osteoporosis has been perceived as a disease that predominantly affects women. However, this ignores: (a) the significant age-adjusted increase in osteoporotic fractures over the last 30 years (Obrant et al., 1989); (b) the significant intra-European differences in incidence of hip fracture (Kanis, 1993); (c) the significant intra-European differences in gender ratio with regard to hip fracture (Kanis, 1993); and (d) the fact that fracture incidence is rising faster for men than for women (Obrant et al., 1989). The maximum bone mass reached at the age of 20–25 is known as peak bone mass and is primarily genetically determined. Intake of calcium and vitamin D are also important for protection against osteoporosis, and vitamin D and calcium supplements are effective in reducing the occurrence of fractures (Fairfield and Fletcher, 2002). Other factors that are significant for the development of osteoporosis are smoking, early menopause, and lack of physical activity. Lack of weight-bearing physical activity during childhood plays a role (McKay et al., 2000). A longitudinal study from the Netherlands, in which adolescents were monitored over a 15-year period showed that daily physical activity in childhood and adolescence is closely linked to bone density in the back and hips at the age of 28 (Kemper et al., 2000).

A 2010 meta-analysis found evidence that weight-bearing physical activity increases bone strength in children, but found insufficient evidence for the same effect in adults (Nikander et al., 2010). Bone loss due to immobilization is due to an acceleration in the remodeling process, caused by an increased negative balance per turnover (Krolner and Toft, 1983). The clinical consequences of immobilization are significant. A study showed that immobilization due to a tibia fracture led to major loss in bone density in the hips, both on the fractured side and on the contralateral side (Van der Wiel et al., 1994). In a follow-up study, it was shown that bone density in the hip on the fractured side still had not normalized 5 years later (van der Poest et al., 1999). Furthermore, a meta-analysis has shown that just 3-week bed rest doubles the risk of hip fracture in the following 10 years (Law et al., 1991).

Excessive physical activity can also have unintended negative consequences, also for the bones. Girls with secondary amenorrhea due to physical exercise can lose bone mass and become sterile (although this is reversible) with decreased libido (Helge, 2001). Hormonal factors (especially estrogen withdrawal around the menopause) have been the focus of attention in osteoporosis research, prevention, and treatment, but today epidemiological clinical and bone studies indicate that mechanical factors (physical exercise) play a strong role in bone health. To sum up, a decline in the level of physical activity among the general population is presumably one of the main reasons for the general rise in the incidence of hip fracture throughout the last 30 years.

Evidence-based physical exercise

Evidence shows that aerobic exercise can increase bone mineral density (BMD), while a combination of resistance training and balance training prevents the risk of falls and fractures in elderly people.

A Cochrane review from 2011 (Howe et al., 2011) included 43 RCTs (27 new in this update) with 4320 participants and found that the most effective type of exercise intervention on BMD for the neck of femur appears to be non-weightbearing high force exercise such as progressive resistance strength training for the lower limbs. The most effective intervention for BMD at the spine was combination exercise programs compared with control groups. Fractures and falls were reported as adverse events in some studies, but there was no effect on numbers of fractures. Overall, the quality of the reporting of studies in the meta-analyses was low, in particular in the areas of sequence generation, allocation concealment, blinding, and loss to follow-up. The authors concluded that exercise has the potential to be a safe and effective way to avert bone loss in post-menopausal women.

A 2000 meta-analysis identifies 35 randomized controlled trials that also assess the effect of aerobic exercise and strength training, but also include studies of pre-menopausal women (Wallace and Cumming, 2000). The conclusion is that both aerobic exercise and strength training have an effect on the BMD of the spine in both pre- and post-menopausal women. Aerobic exercise has an effect on the BMD of the hip, but there are not enough studies to provide conclusive evidence of the effect of strength training on the BMD of the hips.

A randomized controlled trial investigated the effect of physical training on BMD in patients with rheumatoid arthritis (RA) ($n = 319$) (de Jong et al., 2003). The intervention group took part in two weekly training sessions lasting 75 min. Each session consisted of bicycle fitness training, strength training in the form of circuit training and weight-bearing sport in the form of volleyball, football, basketball, or badminton. The training program was evaluated every 6 months for up to 24 months. The intensive physical training, which included weight-bearing sports, suppressed bone mineral loss (de Jong et al., 2004a) and thus coincided with an earlier RA study that found moderate, yet positive effects from dynamic exercise on bone mineral content (Westby et al., 2000). Strength training alone had no effect on bone mineral content in RA patients (Hakkinen et al., 1999; Hakkinen et al., 2001).

A randomized controlled trial included 65- to 75-year-old women diagnosed with osteoporosis ($n = 93$) (Carter et al., 2002). The women were randomized for a 20-week exercise program consisting of two times 40-min sessions/week. The program consisted of balance and strength training. There was a positive effect on both balance and muscle strength; however, BMD was not examined after training. On the other hand, 10 weeks of balance and strength training, as described in the last study (Carter et al., 2002) was not effective (Carter et al., 2001). Another randomized controlled trial also included elderly women diagnosed with osteoporosis (Iwamoto et al., 2001). The women were randomized for control ($n = 20$), 2 years' training ($n = 8$) or 1 year of training followed by 1 year without training ($n = 7$). The program consisted of daily walks and fitness. The training brought about significant improvements in BMD, which reverted to the levels in the control group after 1 year without training.

In the case of elderly patients, an important aspect of training is to strengthen their sense of balance and to prevent falls (Skelton and Beyer, 2003). Prospective cohort studies focusing on fractures all indicate 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 prevented fractures associated with falls. An Australian randomized trial (Day et al., 2002) included 1090 seventy- to 84-year-olds who lived at home. The interventions involved (a) physical training in groups; (b) home visits with a view to preventing falls in the home; or (c) optimizing eyesight. There were eight groups, defined according to how many of the interventions the subject was allocated to.

The physical training consisted of suppleness exercises, strength training of the legs and balance exercises. Sense of balance was significantly improved in the training group. Physical training lowered the risk of fall to 0.82 (95% CI: 0.70–0.97, $P < 0.05$). When all interventions were implemented, the reduction in risk was 0.67 (95% CI: 0.51–0.88, $P < 0.004$).

A 2002 meta-analysis (Robertson et al., 2002) involved 1016 women 65–97 years of age. Muscle training combined with balance training was found to reduce the risk of fall to 0.65 (95% CI: 0.57–0.75) and the risk of fractures to 0.65 (95% CI: 0.53–0.81). The program was equally effective for people with our without a history of falls, but the 80+ year olds gained the most from it.

A Danish study (Beyer et al., 2007) included women 70–90 years of age with a history of recent fall. The patients were randomized to a control group ($n = 33$) and to a training group ($n = 32$), which underwent a training program involving moderate strength training and balance exercises twice a week for 6 months. The training resulted in improvement of muscle strength, extension/flexion of the upper body, walking speed, and sense of balance. This progress was still evident 6 months after the intervention.

An older meta-analysis from 1995 (Province et al., 1995) and a number of more recent studies confirm that balance training and other types of physical training have a positive effect on the quality of life of elderly people and on the risk of fall (Hongo et al., 2007; Madureira et al., 2007; Rosendahl et al., 2008; Shigematsu et al., 2008a, b; Beling and Roller, 2009; Persch et al., 2009; Salminen et al., 2009; Arnold and Faulkner, 2010; Bautmans et al., 2010; Burke et al., 2010; Cakar et al., 2010; Madureira et al., 2010; Shirazi et al., 2007).

Mechanisms

The positive impact of physical activity is the same for both sexes and is due, among other things, to an increase in the cross-sectional area of the bones and thus larger bones. Furthermore, physical training increases muscle strength, thereby improving sense of balance and reducing the risk of fall.

Type of training

Evidence shows that weight-bearing exercise in childhood prevents osteoporosis. There is also evidence showing that aerobic training has a positive effect on BMD, while the effect of strength training on BMD is less well illustrated. In the case of RA patients, it was found that intensive physical training alone did not have an effect on BMD. There is clear evidence that combined strength training and balance training prevents the risk of fall and fractures.

Physical activity should thus ideally be a combination of aerobic training, preferably weight-bearing exercise, and strength training. In the case of elderly patients, the emphasis should be on strength training and balance training, e.g., Tai Chi. The training should be supervised initially and take place in groups. Training can also be a part of a daily regimen. Obviously, some patients benefit from weight loss.

Contraindications

No general contraindications. In the case of patients diagnosed with osteoporosis, the physical training program should include activities that involve little risk of fall.

Back pain

Background

"Backache" is defined as fatigue, discomfort, or pain in the lower region of the back, sometimes with the pain radiating to the leg(s), but with no specific duration or degree of discomfort specified. Anatomically the lower back or lumbar region is defined as the part of the body from the bottom of the ribcage to below the buttocks. Typical diagnoses used in clinical practice are: lumbago, muscle infiltration, facet joint syndrome, scoliosis, osteoarthritis, and osteoporosis. In daily clinical practice, it is important to distinguish between inflammatory conditions (such as Bechterew's disease) and degenerative conditions. It is also important to make a distinction between acute and chronic pain with or without root pressure.

Low back pain is one of the most common complaints that affect 60–80% of all adults at least once during their lifetime (Sandanger et al., 2000; Ihlebaek et al., 2006). In 70–80% of cases, making a specific diagnosis is not possible, even after a thorough and precise examination. The diagnoses for which there is a clear link between observable anatomic changes and pain include spinal stenosis, discitis, infectious spondylitis, sacroiliitis, osteoporotic fractures, and spinal tumors. There is a less clear link in the case of spondylosis, disk degeneration, spondylarthritis, slipped disk, Scheuermann's disease, and scoliosis. Sedentary occupations have been suspected of being a risk factor for low back pain, but a recent meta-analysis did not find any scientific evidence to back this assumption (Sandanger et al., 2000; Ihlebaek et al., 2006).

Evidence-based physical training

Chronic back pain and exercise. A meta-analysis from 2011 involving 3180 people with back pain and joint pain concludes that a wide range of non-supervised activity can help to relieve pain (Kelley et al., 2011) and a meta-analysis from 2015 concludes that multidisciplinary biopsychosocial rehabilitation interventions were more effective than usual care (Kamper et al., 2015).

A 2010 Cochrane Review (Schaafsma et al., 2010), which updates an earlier review from 2003 (Schonstein et al., 2003) analyzed whether physical training has a significant effect on working capacity, assessed in terms of sick leave rates. The analysis included 23 randomized controlled trials involving a total of 3676 subjects. Physical training was found to have no effect on sick leave rates among patients with acute back pain. The results were less clear for patients with sub-acute back pain; however, a sub-group analysis pointed to the beneficial effect of physical training in the workplace. When the data from five studies are pooled, physical training is found to have some effect in the case of patients suffering from chronic back pain. It was also found that physical training plus cognitive therapy was no more efficacious in reducing pain and sick leave rates than just physical training on its own.

Another meta-analysis from 2010 (Oesch et al., 2010) included only studies on patients with non-acute, non-specific low back pain. The analysis included 20 randomized controlled trials and found physical training to have a significant long-term effect compared to no exercise or conventional treatment (OR: 0.66, 95% CI: 0.48–0.92) but no short-term effect (OR: 0.80, 95% CI: 0.51–1.25). The analysis concluded that physical training as an intervention had moderately positive long-term effects on working capacity when assessed in terms of absence from work. It was not possible, however, to conclude what the most effective type of physical training was.

Compared to general exercise, core stability exercise is more effective in decreasing pain and may improve physical function in patients with chronic LBP in the short term (Wang et al., 2012).

Bechterew's disease. The Latin name for this disease is *ankylosing spondylitis*. Spondylitis means inflammation of the vertebrae and ankylosing refers to the type of arthritis that tends to cause stiffness of the joints. Patients can have a severe or a mild form of Bechterew's disease and the ensuing symptoms can be correspondingly very painful or not so painful. The degree of severity depends partly on how many years the patient has had the disease.

A meta-analysis from 2015 evaluated the effectiveness of home-based exercise intervention in AS patients. Studies that measured the Bath Ankylosing Spondylitis Functional Index (BASFI), the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), depression, and pain as outcomes were included. A total of six studies comprising 1098 participants were included in the study. Meta-analyses showed that home-based exercise interventions significantly reduced the BASFI scores (MD = −0.39, 95% CI: −0.57, −0.20, $P = 0.001$), BASDAI scores (MD = −0.50, 95% CI: −0.99, −0.02, $P = 0.04$) and depression scores (MD = −2.31, 95% CI: −3.33, −1.30, $P = 0.001$), Thus, home-based exercise interventions can effectively improve the health-related quality of life in patients with AS (Liang et al., 2015).

The latter study was in agreement with a Cochrane Review from 2008, which involved 11 trials with 763 patients and investigated the effect of physical exercise on lumbar mobility. It found that (a) individual, supervised training programs carried out in the home were better than no intervention; (b) supervised group physiotherapy was better than exercises at home; and (c) combined training in a spa adds to the effect of the group physiotherapy (Dagfinrud et al., 2008).

Acute back pain and physical training. According to several meta-analyses (van Tulder et al., 2000; Schaafsma et al., 2010), there is evidence that physical training is not effective in the treatment of acute low back pain. The exercise therapy based on the McKenzie method consists of the therapist letting the patient repeat certain movements to find the direction of movement that reduces symptoms or centralizes symptoms. These exercises can be used to test acute-stage patients. An individual program is put together based on these preferred movements. Ten studies in the meta-analysis (van Tulder et al., 2000) report on the effect of stretching and flexing exercises, seven of which are on the basis of the McKenzie method. Although individual studies report a certain effect, overall evidence of the effect on pain in the short and long term is very threadbare.

The effect of stringent bed rest was assessed in a meta-analysis (Hagen et al., 2000; Hilde et al., 2002) based on four randomized controlled trials ($n = 491$ patients) (Wiesel et al., 1980; Malmivaara et al., 1995; Wilkinson, 1995; Vroomen et al., 1999). The effect of bed rest is compared with general physical activity in patients with acute low back pain. Two high-ranking studies established that sick leave rates among the patients in the physically active group were lower compared to the groups prescribed bed rest.

Back school. A back school is an educational program to inform patients about the anatomy of the back and its function and offer advice on how to prevent and manage back pain (Hørder et al., 1999). Theoretical back schools are often an integral part of rehabilitation programs, in which patients are instructed and take part in an exercise program. The original, traditional back school, which has been the subject of countless randomized trials, typically focused on cautionary advice and teaching patients how to sit or lift correctly. Evidence shows that this type of back school is not very effective (van Middelkoop et al., 2011). Back schools have changed in character in recent years. The emphasis is on instruction and allaying any fears and the message tends to be along the lines of "ignore the pain as much as possible and try to lead your life as normal".

Possible mechanisms

In a number of instances, the pain mechanisms in the case of back pain resemble the pain mechanisms in fibromyalgia, which could be one explanation for why the specific structure of the training program is not necessarily relevant (Jensen et al., 2010). Exercise therapy and back schools are thought to affect pain behavior and tolerance of physical activity. Training increases muscle strength and stability and the irritant that induces the pain is reduced.

Type of training

The general idea is to continue to live a normal life, but, although there is no evidence that particular forms of exercise or training have a particularly beneficial effect, there is no harm in general physical exercise from day one (walking, cycling or swimming).

There is plenty of evidence documenting the effect of dynamic back training, but there is also evidence that dynamic back training is not necessarily better than, say, aerobic (Mannion et al., 1999) or Mckenzie exercises (Petersen et al., 2002). Another study indicates that the effect of recreational exercise is better or at least as good as back exercises (Hurwitz et al., 2005).

In studies which have found the effect of intensive training plus cognitive therapy to be equal to the effect of back surgery, a program was conducted which combined strength training, suppleness training, and fitness training over a minimum of 3 weeks, comprising 25 h. The recommendation for patients with chronic back pain is a program involving a sufficient amount of movement, exercises, and training, possibly with initial supervision and carried out in group sessions. Current thinking presumes that swimming a minimum of one km twice a week is just as effective as back training 2–3 times a week. The program should be adapted to suit the individual patient in terms of motivation, practical feasibility and slotting the program into daily life (Brox et al., 2003; Brox et al., 2006).

Contraindications

Absolute: Any suspected or known recent fracture, tumor or infection in the back.

Relative: Osteoporosis with fracture is a relative contraindication. Regular exercise is recommended after the acute phase has passed, although lifting and bending and particular combinations should be avoided. Spondylolisthesis is not a contraindication, but may necessitate modification of the training program.

A slipped disk is not a contraindication either, as a slipped disk without nerve root irritation should be treated as unspecific back pain. In the case of a slipped disk with nerve root irritation, regular exercise is recommended as long as there is no increase in leg pain. Intensive back training, however, is not advisable. There is sparse documentation for direction-specific exercises (Long et al., 2004).

Rheumatoid arthritis

Background

The occurrence of RA varies among countries and areas of the world. Rheumatoid arthritis occurs in 0.5–1% of the north western population and incidence of the disease is twice as high in women as in men (Alamanos et al., 2006). Disease onset can be at all ages, but is most frequently between 45 and 65. Rheumatoid arthritis is a chronic systemic inflammatory disease that often presents with symmetrical polyarthritis. Extra-articular manifestation of this joint disease involves the heart, lungs, and skin. Joint pain is typically caused by inflammation, but in advanced cases is linked to destruction of the joints. Inflammation, physical inactivity and steroid treatment can result in osteoporosis. Patients with rheumatoid arthritis and restricted movement tend to have considerably reduced muscle strength corresponding to 30–75% of that of non-patients (Ekblom et al., 1974; Nordesjo et al., 1983; Hsieh et al., 1987; Ekdahl and Broman, 1992; Hakkinen et al., 1995) with half the level of endurance (Ekdahl and Broman, 1992). This decrease in muscle function is attributable partly to muscle inflammation and partly to physical inactivity. Mobility is restricted due to swollen joints and destruction of the joints. Patients feel pain when at rest that is worse when they move, experience stiff joints in the morning that are caused by unspecific inflammation and also fatigue that is presumably due to inflammation and physical inactivity. One common consequence of painful joints, restricted mobility, and fatigue is a lower level of physical activity, which leads to deterioration of fitness. The patients who were able to undergo a fitness test were found to be 20–30% below the normal level of fitness (Ekblom et al., 1974; Beals et al., 1985; Minor et al., 1988; Ekdahl and Broman, 1992).

Patients with rheumatoid arthritis have a 50–60% higher mortality rate due to cardiovascular disease (Gabriel, 2008; Lindhardsen et al., 2011). The aim of physical training programs is to increase fitness and muscle strength and to educate patients about suitable ways of moving. A further long-term objective is to prevent early mortality from cardiovascular disease (Wolfe et al., 1994).

Evidence-based physical training

Patients are classified according to level of function: class I = independent; class II = independent with a few problems; class III = reduced ability to act independently; class IV = no or little ability to act independently. There is substantial evidence of the effect of physical training on rheumatoid arthritis, but the vast majority of studies concern class I and II patients, and only very few patients in class III or IV. A 2009 Cochrane Review (Hurkmans et al., 2009) comprising eight randomized controlled trials (Harkcom et al., 1985; Minor et al., 1989; Baslund et al., 1993; Hansen et al., 1993; Lyngberg et al., 1994; Van Den Ende et al., 1996; Sanford-Smith et al., 1998; de Jong et al., 2003) concludes that physical training should consist of training to improve both fitness and strength.

Overall, the findings of the studies overlap. Dynamic physical activity increases fitness and muscle strength, while no or only moderate effect is reported on disease activity and pain. No studies have found increased disease activity as a result of physical training.

One randomized controlled trial included 319 patients with rheumatoid arthritis (de Jong et al., 2003). The intervention group took part in twice-weekly training sessions lasting 75 min. Each session consisted of bike fitness training, strength training in the form of circuit training and weight-bearing sport in the form of volleyball, football, basketball, or badminton. The training program was evaluated every 6 months for up to 24 months so far. The intensive weight-bearing training program increased functional status and physical wellbeing without having a negative effect on disease activity. The training program did not worsen radiological progression, apart from a tendency to increased progression in a smaller group of rheumatoid arthritis patients with severe baseline radiological damage (de Jong et al., 2003).

Studies have shown that aerobic and resistance exercise training programs consistently improve the aerobic capacity, muscle strength, and self-reported functional ability of patients with rheumatoid arthritis (Baslund et al., 1993; Hakkinen et al., 2003; Lemmey et al., 2009; Baillet et al., 2010; Strasser et al., 2011; Stavropoulos-Kalinoglou et al., 2013). Furthermore, aerobic and resistance exercise training programs can improve endothelial function, blood pressure, lipid profile (Stavropoulos-Kalinoglou et al., 2013), and autonomic function (Janse van Rensburg et al., 2012) in patients with RA. Resistance exercise training, or resistance plus aerobic exercise, increases muscle mass (increased skeletal muscle fiber size and cross-sectional area, thigh cross-sectional area, and leg and arm lean masses) (Nordemar et al., 1976; Hakkinen et al., 2005; Marcora et al., 2005; Lemmey et al., 2009; Sharif et al., 2011), and decreases body fat percentage (Hakkinen et al., 2003; Strasser et al., 2011; Stavropoulos-Kalinoglou et al., 2013) and trunk fat mass (Lemmey et al., 2009) in patients with RA.

Several studies have shown that aerobic and resistance exercise programs do not change the number of inflamed joints, radiological joint damage, disease activity, or systemic inflammatory markers (C-reactive protein or erythrocyte sedimentation rate) in patients with low to moderate RA disease activity (Lyngberg et al., 1988; Baslund et al., 1993; Hakkinen et al., 2003; de Jong et al., 2004b; Lemmey et al., 2009), whereas other studies have detected improvements in these parameters (Lyngberg et al., 1988; Neuberger et al., 1997; Van Den Ende et al., 2000; Hakkinen et al., 2003; Metsios et al., 2014).

However, it is recommended that caution is taken with patients who have extensive baseline damage (that is, at the beginning of exercise therapy), as a high-intensity resistance exercise program can lead to increased joint damage in these patients (de Jong et al., 2003).

Possible mechanisms

Patients with RA have a lower level of fitness and lower muscle strength, which can be increased through dynamic training and strength training, respectively. RA is an inflammatory disease characterized by increased levels of circulating TNF (Brennan et al., 1992). The biological effects of TNF on muscle tissue are multiple. TNF induces cachexia and thus deterioration of muscle strength (Li and Reid, 2001). Exercise training induces anti-inflammation and specifically suppresses TNF production (Pedersen et al., 2001; Febbraio and Pedersen, 2002). It has recently been proposes that a "vicious cycle" of chronic inflammation is established in patients with inflammatory rheumatic diseases (Benatti and Pedersen, 2015).

Disease-related excessive production of cytokines might predispose these patients to atherosclerosis, loss of muscle mass, and metabolic disorders such as insulin resistance and dyslipidemia. These comorbidities can be proinflammatory and can lead to disability and decreased physical activity, which are risk factors for the accumulation of visceral fat, thereby further contributing to the network of inflammatory pathways implicated in the onset of metabolic disorders, atherosclerosis, and other chronic diseases.

The prescription of exercise as a potential anti-inflammatory tool is a relatively new concept (Petersen and Pedersen, 2005). Of particular interest for patients with chronic inflammation, each bout of exercise might provoke an anti-inflammatory environment, as muscle-derived IL-6 inhibits TNF production and stimulates the production of the anti-inflammatory cytokines IL-1ra and IL-10. Furthermore, a variety of other myokines might mediate indirect anti-inflammatory effects of exercise. Some of these myokines have been shown to be anabolic. Myokines are also directly involved in prevention of abdominal obesity and thereby might have a fundamental effect on inflammation. Furthermore, some myokines have been shown to have systemic effects on the liver and to mediate cross-talk between the intestine and pancreatic islets, thereby furthering many of the metabolic effects of exercise. Finally, other myokines are of importance for bone health and the endothelial function of the vascular system (Benatti and Pedersen, 2015).

Type of training

All patients with rheumatoid arthritis, both patients with recently diagnosed rheumatoid arthritis and patients with a long history of rheumatoid arthritis, benefit from physical training; however, there is insufficient documentation of the effect of physical training on class III and IV patients. Physical training should ideally be supervised at first, tailored to the individual patient and include moderate- to high-intensity aerobic training and resistance training. Group exercise is beneficial. The exercise program should be incorporated gradually into the patient's daily routine, possibly via patient associations or a sports club.

In the case of patients with joint destruction in the hip, knee, or ankle joints, the aerobic workout should be non-weightbearing to avoid putting any strain on the joints during training. For many patients, cycling, or swimming is preferable to running. Some patients do benefit from weight-bearing activity, which possibly provides greater protection against bone mineral loss. General strength training to train the large muscle groups is effective.

The physical activity should be adapted to the individual patient's disease activity and disease manifestation. In the case of patients with severe problems in the neck area, swimming may be difficult, but water workouts can be advantageous.

The training program should also include progressive strength training for all muscle groups, including the affected joints. Here too, the training should be adapted to the individual patient's disease activity and symptoms. Training on exercise equipment provides greater safety.

It is important, however, that the exercises do not involve too great a weight load. In the case of leg presses, a weight load slightly less than the person's weight is recommended if problems exist with the knee or the feet/ankles. It is also important to be aware of shoulder symptoms and to take care with heavy loads above shoulder height. If the patient is in pain or has swollen wrists it might be a good idea to try a wrist bandage during training on exercise equipment that involves the use of hands. Patients who are unable or unmotivated to visit the fitness center can receive instruction in home exercises using elastic bands or the weight of their body.

The therapist measures muscle strength at the start of training after 3 months and subsequently once a year. The training should be lifelong, supervised for the first 3 months and then regularly monitored with feedback for the rest of the patient's life. Feedback can be in the form of a training logbook kept by the patient, recording pain, and annual testing of fitness and muscle strength, as described above.

Contraindications

There is a lack of information on physical training for patients with severe symptoms, which is why it is recommended at present that such patients commence a training program after medical treatment has been instituted. In the case of sever extra-articular manifestations in the form of pericarditis and pleurisy, physical training is not advisable. In the case of joint surgery, it is important that strength training is supervised and that training is initially with low weight loads. If rheumatoid arthritis is manifested in the upper neck joints, it is important to be extremely careful when doing exercises involving the neck. The training should be supervised and individually tailored.

Cancer

Background

Cancer and cardiovascular disease are the primary causes of premature death in our part of the world. Cancer is the name given to a group of diseases dominated by uncontrolled cell growth resulting in the compression, invasion, and degradation of surrounding fresh tissue. Malignant cells can be transported through the blood or lymphatic fluid to peripheral organs and cause secondary colonies (metastases). The underlying mechanism common to all cancer diseases is changes in genetic material (mutation), which can be caused by environmental factors, such as tobacco, radiation, pollution, infections, or possibly nutrition. Mutations can cause the cell properties to change and the mechanisms that control the cell's life span to be disturbed. Thus, cancer cells can live unhindered and uncontrolled. Cancer symptoms are diverse and depend on tumor type and locality. However, many types of cancer cause weight loss, including loss of muscle mass, as well as fatigue and reduced physical capacity as a result of decreased fitness and muscle atrophy. Patients become physically inactive due to general malaise, poor appetite, demanding treatment regimes (surgery, chemotherapy), radiotherapy, and other factors, or a combination of factors together with their generally difficult situation. Chemotherapy increases risk of infection and leads to physical inactivity and thus loss of muscle mass and a decrease in fitness. It has been estimated that physical inactivity could account for cancer patients' poor physical condition by one-third (Dietz, 1981). Fatigue is one symptom that is not only associated with patients with active or advanced cancers, but is also found with patients who have undergone radical treatment (Loge et al., 1999). This condition affects patients' quality of life and in recent years greater focus has been put on the importance of physical activity to enable cancer patients to function normally and to enhance their quality of life (Thune, 1998; Courneya and Friedenreich, 1999; Courneya et al., 2000; Dimeo, 2001).

Evidence-based training

There is growing epidemiological evidence that a physically active lifestyle protects against the development of colon cancer, breast cancer, endometrial cancer, and prostate cancer (Thune and Furberg, 2001; Samad et al., 2005; Harriss et al., 2009; Wolin et al., 2009; Eliassen et al., 2010; Schmitz et al., 2010; George et al., 2011; Kenfield et al., 2011). In recent years, a number of observation studies have shown that people who are physically active after being diagnosed with breast cancer or colon cancer have a statistically higher chance of survival compared to those who are physically inactive. According to these studies people who are physically active, at least to the extent proposed by general recommendations (www.cdc.gov) almost double their chance of survival (Holmes et al., 2005; Meyerhardt et al., 2006a, b, 2009; Peel et al., 2009; Ibrahim and Al-Homaidh, 2011).

There is ample evidence that physical training for cancer patients has a positive impact on fitness, muscle strength, and physical well-being in the broadest sense (Duijts et al., 2011; McMillan and Newhouse, 2011; Keogh and MacLeod, 2012). Numerous randomized controlled trials have been conducted to determine efficacy of exercise on cancer-related fatigue.

A meta-analysis (Tomlinson et al., 2014) included 72 randomized controlled trials and concluded that exercise had a moderate effect on reducing fatigue compared with control intervention. Exercise also improved depression and sleep disturbance. Exercise effect was larger in the studies published 2009 or later. Taken together, the results suggest that exercise is effective for the management of cancer-related fatigue.

One study (Adamsen et al., 2009) examined the effect of physical training in groups as a supplementary measure in addition to conventional therapy (adjuvant therapy or treatment for advanced cancer). The study involved 269 patients with cancer, of which 73 were men aged 20–65 who represented 21 different cancer diagnoses. Patients with metastases in the brain or bones were excluded from the program. The program included a combination of high-intensity fitness training, resistance training, relaxation, and massage 9 h a week over 6 weeks. This intervention was found to reduce fatigue, improve quality of life, improve aerobic capacity, muscle strength, physical and functional activity, and emotional well-being.

Physical activity both during and after treatment can increase quality of life and reduce fatigue in women with breast cancer (Alfano et al., 2007; Valenti et al., 2008; Chen et al., 2009; Smith et al., 2009) and physiotherapy for women with breast cancer after surgery can prevent lymphedema (Torres et al., 2010).

One meta-analysis (McNeely et al., 2006) included 14 randomized controlled trials of people with breast cancer. The study concluded that physical training improves quality of life, fitness, and physical ability, and reduces fatigue. There are also several studies showing that physical activity can help alleviate the psychological burden on cancer patients while they are undergoing chemotherapy (Midtgaard et al., 2007; Love and Sabiston, 2011).

Possible mechanisms

Physical activity increases fitness and muscle strength, which relieves fatigue and strengthens physical ability. Physical exercise is also thought to boost patients' self-confidence and psychological well-being. Exercise may reduce tumor growth via several mechanisms including (a) vascularization and blood perfusion, (b) immune function, (c) tumor metabolism, and (d) muscle-to-cancer cross-talk. Insight into these mechanistic effects is emerging, but experimental intervention studies are still needed to verify the cause-effect relationship between these mechanisms and the control of tumor growth (Pedersen et al., 2015).

Amount of training

Cancer patients should aim to exercise according to generally recommended levels of physical activity (www.cdc.gov). Initially the training should be individually tailored and supervised. It should ideally include both aerobic training and resistance training. Cancer patients who have completed their therapy typically feel tired as well as physically and, in some cases, mentally weak. Patients benefit from a mixture of moderate and high-intensity aerobic training combined with resistance training. The aerobic physical exercise should start at a low intensity and be gradually stepped up to moderate and finally high intensity, gradually increasing the duration of the training at the same time. The aerobic training should be combined with resistance training, which also starts at a low exertion level and short durations.

It is recommended that training should be supervised but that relative and absolute contraindications should be observed. Even hospitalized and bed-ridden patients can profit from physical training (Dimeo et al., 1999), but there is sparse information about exercise during chemotherapy or radiotherapy. It is important to emphasize that this patient group is so heterogeneous that standard proposals make no sense and for many, especially elderly cancer patients, the focus ought to be on retaining mobility and physical ability.

Contraindications

It is advised that patients undergoing chemotherapy or radiotherapy with a leukocyte count below $0.5 \times 10(9)/L$, hemoglobin below 6 mmol/L, thrombocyte count below $20 \times 10(9)/L$, temperature above 38 °C should not exercise. Patients with bone metastases should avoid resistance training with heavy weights. In the case of infection, it is recommended that training be interrupted for at least one whole day without symptoms, after which time training should be slowly resumed.

Perspective

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 its effect. The accumulated knowledge is now so extensive that it has to be implemented.

Although there still is a need to define the most optimal type and dose of exercise, to explore if high-intensity interval training as well as one-legged training or other newer exercise modalities will have a place for specific diagnoses, it is now time that the health systems create the necessary infrastructure to ensure that supervised exercise can be prescribed as medicine.

Moreover, it is important that society in general support a physical active lifestyle. People do not move, when you tell them to. People move when the context compels them to do so. In order to enhance the physical activity level of a population, accessibility is important. There is a need for political statements and laws about “health consequences”. Just as politicians always should consider gender and ethnic issues, they should also consider health aspects, including how infrastructure and architecture may influence the population’s physical activity level.

Key words: physical activity, physical training, type 2 diabetes, cardiovascular, cancer, neuropsychiatric.

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