34. Metabolic syndrome

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Summary

Metabolic syndrome consists of a cluster of factors such as abdominal obesity, insulin resistance, dyslipidemia and hypertension. In addition, factors such as impaired fibrinolysis, inflammatory status, high levels of uric acid and a fatty liver are not uncommon. Metabolic syndrome increases the risk of cardiovascular disease, type 2 diabetes, dementia, Alzheimer's disease and some common forms of cancer. An increase in the prevalence of metabolic syndrome is evident in the general population, primarily owing to a lack of physical activity in combination with a high energy intake, a poor diet, stress and psychosocial factors.

A high level of physical activity and fitness reduce the risk of metabolic syndrome while physical activity affects all integral components. In order to prevent and treat metabolic syndrome, it is recommended that sedentary time is reduced and moderately strenuous physical activity carried out daily for a minimum of 30, but preferably 60 minutes. Further positive effects are achieved by exercising moderately and regularly 2–3 times a week for a minimum of 30 minutes. Aerobic fitness training may well be combined with adapted strength training.

Individuals with metabolic syndrome are often at risk of developing secondary conditions and it is consequently important that individual risk analyses are performed and, if required, examinations and recommendations for physical activities are adapted to the individual in question. Equally important is the follow-up of the physical activity recommendations.

Definition

Prevalence/Incidence

Many international reports show an alarmingly high prevalence of metabolic syndrome among men, women and children. The prevalence of metabolic syndrome varies depending

on the definition used (1). According to a European Study (DECODE) of 6,156 men and 5,356 women without diabetes and between the ages of 30–89 from Finland, Sweden, Poland, the Netherlands, the United Kingdom and Italy, the age-standardised prevalence was 16 per cent among men and 14 per cent among women (2). The study also showed that the prevalence increases with age. American studies show a high prevalence among both men and women (3–5).

Today, metabolic syndrome is also common in populations with a traditionally low rate of cardiovascular diseases and mortality. In Greece, the overall prevalence of metabolic syndrome among healthy, middle-aged men (n = 1,128) and women (n = 1,154) was 20 per cent (6). The prevalence of metabolic syndrome was higher among the men (25%) than the women (15%) and increased with age. The prevalence of metabolic syndrome is considerably higher in high-risk populations. Approximately 53 per cent (7) of obese patients in Italy were found to suffer from metabolic syndrome compared with 45 per cent (8) of patients in the Netherlands with cardiovascular disease. Among 3,770 English women aged 60–79, just under 30 per cent were found to suffer from metabolic syndrome (9). The result of a Swedish population-based study of 4,232 individuals (aged 60, 78% participation rate) showed that 26 per cent of the men and 19 per cent of the women had metabolic syndrome according to NCEP/ATP III criteria (10, 11). Extremely alarming are reports on the high prevalence of metabolic syndrome among children and young people (12).

Risk factors for metabolic syndrome

Metabolic syndrome is the result of complex interactions between environment and genes. A change in lifestyle with less physical activity, unhealthy food and drinking habits and an imbalance between energy intake and energy expenditure in addition to chronic stress and psychosocial factors are some fundamentally important reasons for the increase in metabolic syndrome (13–19).

Despite the difficulties in measuring physical activity and the variety of methods used, a large number of international and national reports agree that the majority of adults and children are physically inactive today. Only about 20 per cent of the population is sufficiently physically active (13).

A majority of more recent studies indicate a strong link between the level of physical activity or fitness and the prevalence of metabolic syndrome. A Swedish study of men and women aged 60 showed a strong dose-response relationship between reported physical activity in leisure time and metabolic syndrome (11). Individuals exercising moderately at least twice a week for a minimum of 30 minutes had a 70 per cent lower risk of developing metabolic syndrome compared with individuals reporting low levels of leisure time physical activity (less than 2 hours light physical activity per week). The relationship was not affected by factors such as gender, education, civil status, smoking or intake of fruit, vegetables and alcohol (see Figure 1).

Similar findings were made in other cross-sectional studies and prospective studies where an inactive lifestyle and/or poor fitness were closely linked to the existence of metabolic syndrome (20–25).

Many national and international reports indicate an increase in overweight and obesity among both children and adults (26–28). The waist circumference of children and adults has increased comparatively more than their weight. Today, nearly half of Sweden's adult population is overweight (BMI ≥ 25) and approximately 10 per cent suffers from obesity (BMI ≥ 30). The prevalence has doubled since the 1980s (29). Abdominal obesity is closely linked to metabolic syndrome (30).

The pathogenesis of metabolic syndrome

The pathogenesis of metabolic syndrome is complex with interactions between genetic and lifestyle factors (19, 20, 31). Overweight and abdominal obesity are principal and recurrent clinical characteristics which, together with insulin resistance in skeletal muscles, adipose tissue and liver, play a central role in the development of metabolic syndrome. A typical dyslipidemia with high levels of triglycerides, low HDL and high ApoB plus small, dense, oxidation prone and very atherogenic LDL particles is a common and important subcomponent of metabolic syndrome. Post-prandial (following food intake) hyperlipidemia and high levels of serum-free fatty acids have also been found. Hypertension is another recurrent condition. Other subcomponents include a reduced fibrinolytic capacity, inflammatory activity, high levels of uric acid, a reduced endothelial function and fatty liver (29, 30). See Fact Box 1.

Most common symptoms – what are the consequences of metabolic syndrome?

Metabolic syndrome is often a symptom-free condition detected in connection with a health check or other contact with the healthcare services. The various subcomponents of metabolic syndrome are common in an adult population (11), but are often symptom-free. High blood pressure, obesity, incipient diabetes or a silent coronary artery disease may naturally result in symptoms such as excessive fatigue or exertion-induced discomfort or chest pains. Abdominal obesity may lead to snoring, insomnia, daily fatigue and a lower quality of life (31, 32).

Metabolic syndrome increases the risk of major public illnesses, type 2 diabetes, dementia, Alzheimer's disease plus other more common forms of cancer. Many cross-sectional studies and prospective studies indicate that individuals with metabolic syndrome have an elevated risk of cardiovascular disease (1, 2, 34–37). This elevated risk applies to all cardiovascular diseases (1, 2) plus cognitive function, dementia and mortality in general (36–38). It also applies to both men and women (39).

The risk of developing type 2 diabetes is considerably higher for individuals with metabolic syndrome while diabetics with metabolic syndrome have a worse prognosis than those without (34, 35).

A number of epidemiological studies over the past few years have also linked metabolic syndrome to prostate cancer (40) and other more common forms of cancer such as colon cancer and breast cancer (41–44). Hyperinsulinemia may be one mechanistic link (45).

Diagnostics

Metabolic syndrome has many definitions. However, all definitions include abdominal obesity/overweight, insulin resistance and disturbed glucose/insulin homeostasis, typical dyslipidemia and hypertension. The four most commonly used definitions are those proposed by WHO (46), the European Group for the Study of Insulin Resistance (EGIR) (47), the National Cholesterol Education Program (NCEP/ATP III) (10) and the International Diabetes Federation (IDF) (48). More recently, a separate definition relating to children was also proposed (12). The definition proposed by American NCEP/ATP II is most commonly used and appropriate for clinical practice (see the Fact Box below).

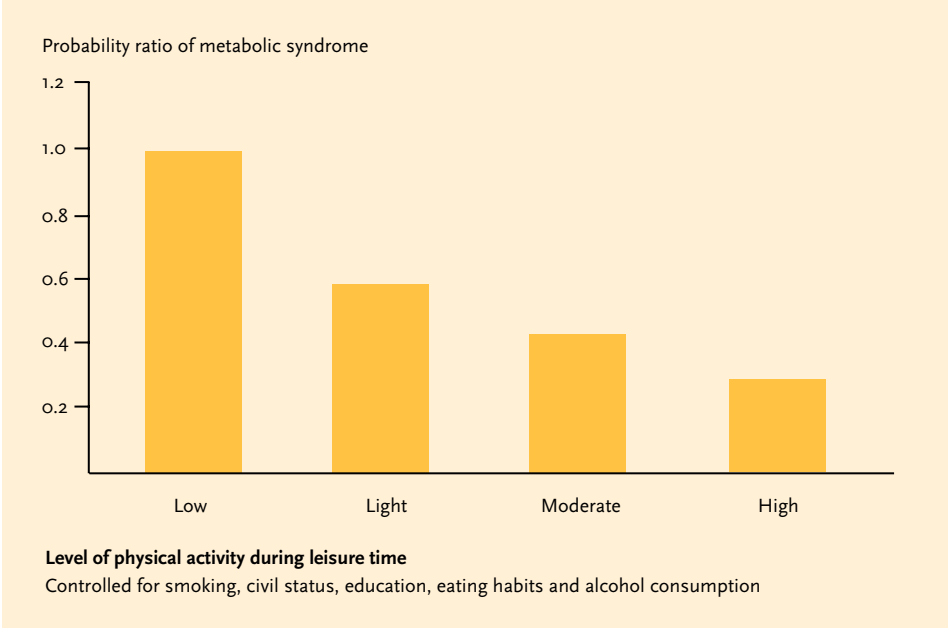

Figure 1. A dose-response relationship between the level of physical activity during leisure time and the occurrence of metabolic syndrome in 60-year-old Swedish men and women.

Criteria for clinical diagnosis of metabolic syndrome, NCEP/ATP III:
Any of five constitute diagnosis of metabolic syndrome

- Waist circumference > 102 cm for men and > 88 cm for women.
- S-triglycerides ≥ 1.7 mmol/l (or drug treatment)
- HDL cholesterol < 1.03 mmol/l for men and < 1.3 for women (or drug treatment)
- Blood pressure ≥ 130/ 85 mm Hg (or drug treatment)
- Fasting glucose ≥ 5.6 mmol/l (or drug treatment)

Treatment

Prevention and treatment of metabolic syndrome is based on changing lifestyle (1, 19, 49–53). Increased physical activity is the cornerstone in the treatment of metabolic syndrome. The treatment should always be individualised and focus on weight loss and reduced abdominal obesity through increased physical activity and improved food patterns. Recommendations on the consumption of food and alcohol follow general dietary guidelines, but have to be adapted to the individual (53). Advice on nicotine replacement therapy and stress management may also be relevant.

Pharmacological treatment of different subcomponents is also a possibility (51, 52) as lifestyle modifications will not counteract the effects of any treatment. However, today's advanced and professional prevention and treatments are always based on changing lifestyle.

Treatment is aimed at lessening the risk of future diseases through the reduction of various risk factors.

Effects of physical activity

Close association between physical activity and metabolic syndrome

A growing number of epidemiological studies indicate that there is a strong dose-response relationship between the level of physical activity or fitness and metabolic syndrome (see "Most common symptoms") (25). For example, the prevalence of the metabolic syndrome is 70 per cent lower in 60-year-old men and women who exercise with a moderate intensity at least twice a week, even when taking into account other relevant factors such as food and alcohol intake, education and smoking (11).

Physical activity reduces the health risk associated with metabolic syndrome

Overweight or abdominally obese men and women who exercise regularly are at much lower risk of cardiovascular disease than those who are inactive (55–57). In an American study, more than 21,000 men aged 30–83 were monitored during an average period of eight years for the purpose of studying cardiovascular diseases and mortality. A fit but

overweight or abdominally obese man was at a lower risk than an unfit man of normal weight (54). When monitoring 88,000 healthy middle-aged women for a period of 20 years as part of the so-called Nurses Health Study, it became evident that physical activity could reduce the risk of coronary disease associated with abdominal obesity (55).

A systematic review of the literature and 10 prospective studies regarding the relationship between physical activity and the risk of type 2 diabetes showed that regular daily physical activity of a moderate intensity for a minimum of 30 minutes would considerably reduce the risk of coronary heart disease (56). A Finnish study monitored 2,017 healthy men and 2,352 healthy women aged 45–64 for an average period of 9.4 years. The risk of type 2 diabetes was reduced by 60–70 per cent among subjects reporting a high level of physical activity compared with subjects reporting a low level of physical activity. These findings apply equally to overweight people and people of a normal weight (57). A follow-up of 1,263 American men with type 2 diabetes showed that the mortality was 50 per cent lower among those reporting to be physically active during a prospective 15-year study (58). Similar findings were made in a study of 3,708 Finnish men and women with type 2 diabetes over a period of 19 years. A moderate or high level of physical activity was associated with a significantly improved prognosis regardless of weight, blood pressure, smoking or blood lipids (59). Moderate physical activity during work, leisure time or as a means of transportation is generally associated with an improved prognosis for type 2 diabetics (60).

A large number of case-control studies and prospective studies have likewise shown a link between the level of physical activity and the cancer forms associated with metabolic syndrome, e.g. prostate cancer, colon cancer and breast cancer (61–63).

Multiple effects of physical activity on metabolic disorders

The effects of physical activity on the metabolic disorders included in metabolic syndrome are evident from a number of clinical studies and have also been summarised in several review articles (19, 64–70). There are many mechanisms behind the preventive effects of physical activity and they are not yet fully known, but include a positive effect on the lipoprotein metabolism. Physical activity increases the blood flow in muscles and adipose tissue and increases lipoprotein lipase activity, reduces triglycerides and increases HDL levels. The particle size and susceptibility to oxidation of LDL particles are also positively affected by increased physical activity. The antihypertensive effects of physical activity are well documented. Peripheral insulin sensitivity and glucose tolerance are improved (66, 67). Physical activity reduces abdominal obesity and bodyweight (68, 69). Thrombogenesis and haemostasis are also positively affected (70). The IGFBP-1, endothelial function and inflammatory markers have also been shown to be affected (19, 68). Because of the multiple effects, increased physical activity is a beneficial way in which to prevent and treat metabolic syndrome.

There are currently no randomised primary prevention studies of the effects of increased physical activity among individuals with metabolic syndrome regarding future incidence or mortality from cardiovascular disease or cancer.

However, randomised primary preventive intervention studies on overweight men and women with reduced glucose tolerance and metabolic syndrome have shown that a combined dietary intervention and increased physical activity regimen can substantially (58%) reduce the risk of developing type 2 diabetes (71–74). The independent effects of increased physical activity are still partially unknown even though a Chinese four-armed study (diet, exercise, diet and exercise or control) indicated that the recommendations given on food intake and exercise were equally effective, each resulting in a risk reduction of 40 per cent (72). Post hoc analyses of the Finnish Diabetes Prevention study indicate that there is also a strong link between the reduction of risk and increased physical activity when taking into account other relevant factors such as eating habits (74). According to the Norwegian ODES Study, increased physical activity in combination with a change in diet may considerably reduce the prevalence of metabolic syndrome as compared with a control group during a 12-month follow-up period (65).

Newly developed molecular biology techniques and molecular genetics based on animal and human research models have over the past few years provided us with a greater understanding of the cellular mechanisms of metabolic syndrome as well as the molecular biology and molecular genetics behind the positive effects of physical activity.

Indications

Increased physical activity is of extensive importance to both primary and secondary prevention of metabolic syndrome. Today, different components (overweight, abdominal obesity, insulin resistance, high blood pressure, lipid disorder, etc.) in addition to metabolic syndrome are so common among the general public that prevention aimed at the individual is no longer enough. Population-based measures undertaken to increase physical activity among children and adults are also needed to reduce the risk of chronic diseases and premature deaths in the future.

Prescription

Reduce sedentary time

Many prospective studies have shown that the number of hours spent in front of the TV is related to the future risk of obesity and diabetes in both men and women (75, 76). There is also a link between the number of hours spent in front of the TV or the computer and the prevalence of metabolic syndrome among men, women and children (77, 78). A dose-response relationship is reported between sedentary time and mortality from all causes and cardiovascular disease (79, 80). Energy expenditure when walking (4.8 km/hour) is approximately 400 per cent more than when resting, e.g. lying in the sofa or sitting on a chair (20 kilojoule/minute compared with 5 kilojoule/minute) (81). In view of this, limiting inactivity is just as important as promoting physical activity.

Advice on physical activity for the prevention and treatment of metabolic syndrome

Individuals with metabolic syndrome should be encouraged to engage in daily physical activity of moderate intensity for a minimum of 30 minutes or 60 minutes if overweight, e.g. a brisk walk (82, 83). Additional health benefits are obtained if, in addition to daily physical activity of 30–60 minutes, some form of exercise is performed 2–3 times a week.

The activities recommended for the prevention or treatment of metabolic syndrome incorporate some form of aerobic fitness training such as walking, Nordic walking, jogging, swimming, cycling, etc. These activities can also be combined with a certain amount of strength training. Muscle mass decreases with age as a result of inactivity. Studies have shown that the lack of muscle strength affects the development of metabolic syndrome while strength training can have an effect on insulin sensitivity, for example (84).

Exercise should be done regularly for a minimum duration of 30 minutes. The recommended daily amount of physical activity can be accumulated through several separate episodes (for example 10 plus 10 plus 10 minutes) throughout the day (85). The exercise should be of a moderate intensity, approximately 60–70 per cent of maximum capacity, i.e. to the point when you begin to perspire and quicken your breathing. The same recommendations are essentially given for the prevention and treatment of cardiovascular diseases, type 2 diabetes and obesity or for maintaining generally good health (82).

The fact that a small amount of physical activity is better than no physical activity at all is common sense and was recently verified by a randomised controlled study of overweight and inactive postmenopausal women (82). The effect of various doses of exercise on general fitness was tested and a clear dose-response relationship was found. As little as 50 per cent of the recommended dose (according to the general guidelines) had a clear beneficial effect on aerobic fitness.

Constructive advice on exercise

A good knowledge of physical activity and health and recent recommendations and guidelines is not always enough. The approach taken by the caregiver as to the importance of lifestyle and lifestyle intervention in connection with metabolic syndrome is essential and requires pedagogical skills in addition to good scientific knowledge. All caregivers, i.e. staff categories, should be offered the opportunity of learning about the effects of physical activity and how to recommend exercise/give advice on physical activities so that all such recommendations and advice are given in unison. This would reinforce the credibility of the recommendations and advice given.

Giving advice on physical activity requires perceptiveness and a patient-centred approach. The patient is often embarrassed about his or her lifestyle, inactive life and obesity, etc. and it is therefore important not to add to this feeling of guilt. The general advice given on physical activity must always be adapted to the individual and transformed into concrete recommendations on exercise. It is important to form a picture of the patient's life circumstances and motivation to change. The information given must be neutral and not convey the caregiver's own opinion of physical activity. The patient should be informed about what type of physical

activity is suitable and the intensity, frequency and duration recommended in order to achieve the optimal effect. In addition, the concept of 50–70 per cent of maximum capacity should be explained to the patient, i.e. all forms of activities of an easy to moderate intensity up to the point when you begin to perspire and your breathing quickens.

The patient should also be given advice on suitable local activities and physical activity on prescription (FaR®) for the purpose of individual training or, if appropriate, modified exercise. Exercise referrals or physical activity on prescription (FaR®) has been in practice for decades in Sweden and New Zealand, for example (87, 88). According to national studies, approximately one third of the healthcare centres in Sweden follow this practice (89). Patients and the general public can also obtain information on physical activity and health in booklets available for purchase from dispensing pharmacies, for example. The use of a pedometer is a simple way in which to stimulate increased physical activity and monitor the effects of the prescriptions issued. When carrying a pedometer for a couple of weeks, the patient becomes aware of the degree of activity performed in different situations. A joint discussion on the subject of reasonable targets or sub-targets can also be advantageous.

Follow up on the advice given and give feedback

It is important that the advice on physical activity is followed up to ensure compliance and accomplishment. The time that such a follow-up is to take place must be chosen on an individual basis, although six weeks is generally considered an appropriate interval. By then, most people will have had time to make certain changes as verified by their pedometer or diary with positive effects on their waist circumference or metabolic variables. The waist circumference, which can easily be measured in clinical practice and by the patient, is strongly linked to the prevalence of metabolic syndrome in general and to several of the metabolic variables encompassed by metabolic syndrome (90–93). Prospective studies have also shown that waist circumference is linked to the future risk of coronary heart disease, intima-media thickness of the carotid arteries and death (94–98). Elevated blood pressure, lipids, blood glucose, etc. should also be monitored.

Risks and the need for health checks

Excess exertion can increase the risk of a stroke, myocardial infarction or sudden death in high-risk individuals. Such events are dramatic, but unusual. Much more common are injuries due to overloading or overtraining such as tendon inflammation and large joint disorders.

There are generally very few contraindications of increased physical activity. However, some men and women with metabolic syndrome are considered to be high-risk individuals because of the presence of multiple risk factors. Consequently, all advice or recommendations relating to exercise must be preceded by an appropriate assessment and individual risk analysis. An emergency examination and treatment should always be performed

in case of untreated, very high blood pressure or blood glucose levels as well as acute symptoms from the heart and circulation (e.g. TIA, unstable angina, peripheral circulation disorders).

However, professionally recommended physical activity in connection with metabolic syndrome rarely constitutes a risk. Following a standard analysis of cardiovascular symptoms and a family history in addition to a thorough physical examination of the heart and arteries, measurement of height, weight, waist circumference and blood pressure plus the taking of samples for an evaluation of the metabolic condition, it is important to determine whether further analysis such as an exercise test or ultrasonography is required. The patient is informed about warning signals and how to recognize them, as well as the importance of starting slowly and gradually increasing the amount and intensity of any activity. In this way, many types of injuries due to overloading can be prevented and avoided. The benefits of a good pair of shock absorbing shoes cannot be stressed enough, especially for an overweight person.

Interactions with drug therapy

There are a large number of pharmacological agents available for individuals with metabolic syndrome and information about interactions can be obtained from other sources. With the exception of insulin treatment and other pharmacological treatments of diabetes where there is a risk of hypoglycaemia, the risk of any adverse interaction, as a result of increased physical activity on the recommendation of a competent professional, is relatively atypical. Successful changes in lifestyle and increased physical activity may however necessitate a dose reduction. Hence, a regular follow-up is particularly important when lifestyle changes are combined with pharmacological treatment.

Contraindications

There are very few contraindications of physical activity in connection with metabolic syndrome, but they must be taken into consideration (also refer to “Risks”). Absolute contraindications include acute symptoms from the heart and circulation or a pending cardiovascular event (e.g. TIA, stroke, unstable angina, heart attack, acute peripheral circulation disorders), acute bleeding, hypoglycaemia or hyperglycaemia, significantly elevated blood pressure, infection accompanied by fever and poor health in general. As regards relative contraindications such as elevated cardiovascular risk, please refer to the section on “Risks”. Healthcare personnel who give advice on physical activity should always carry out a risk analysis even though the personal responsibility of the patient should not be overlooked. Physical activity and exercise is a natural part of our existence that brings enjoyment and contributes to an enhanced quality of life.

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