26. Diabetes mellitus – type 2 diabetes

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Summary

Type 2 diabetes represents 80–90 per cent of all diabetes and is a chronic disease characterised by hyperglycemia and other metabolic disorders. The basis of treatment is measures that reduce insulin resistance, above all increased physical activity, weight loss in the case of overweight, and stopping the use of tobacco. If these lifestyle measures are not enough to properly control the disease, there are a number of different medications in tablet form, and insulin.

Generally speaking, it can be said that, by leading to a decreased sensitivity to insulin, physical inactivity is a significant risk factor for type 2 diabetes, and several studies have shown that the development of type 2 diabetes can be prevented through exercise training combined with dietary guidelines. Regular exercise for type 2 diabetes has a positive effect on both insulin sensitivity and other risk factors for cardiovascular disease, for example, blood lipid profile and blood pressure. This is of great importance since the risk for developing cardiovascular disease is three to four times higher in diabetes. Several studies also report improved glucose control. It is recommended that the patient perform a minimum of 30 minutes of medium intensity physical activity daily, such as a brisk walk, cycling or similar activity adapted to his or her overall physical condition and lifestyle. Further health effects and aerobic fitness can be achieved if this is combined with somewhat more intensive exercise at least 2–3 times per week, such as a fitness class, tennis, swimming, skiing or similar, depending on the individual's interests.

Definition

Type 2 diabetes is a chronic disease characterised by hyperglycemia (elevated or abnormally high blood sugar levels) and other metabolic disturbances, including metabolism of lipids and haemostasis. The disease was earlier called adult-onset or non-insulin-dependent diabetes, but these descriptions should no longer be used.

Prevalence/Incidence

Type 2 diabetes represents 80–90 per cent of all diabetes. The total prevalence in the Nordic countries is 4–5 per cent of the population over 20 years of age, but rises sharply after the age of 50–60 years. Approximately 20 per cent of people over the age of 70 years are affected. In recent years, the disease has been shown in children with a genetic predisposition and who also have other risk factors, for example, overweight and physical inactivity. Globally, the incidence of type 2 diabetes is increasing dramatically, above all in India, the Middle East, China, USA and parts of Latin America. The actual prevalence is often unknown, as the disease can develop quite insidiously and not be detected until a health check-up is performed. It has been estimated that the number of undiagnosed patients with type 2 diabetes make up at least half or even the same number of patients already known to have diabetes. In a small portion, approximately 5 per cent, of patients earlier counted as type 2 diabetics, the genetic background has been established. These people carry different types of mutations in transcription factors or glucokinase (Maturity Onset Diabetes of the Young, MODY), which is inherited as autosomal dominant and leads to diabetes in the early years (to be distinguished, however, from type 2 diabetes in children with the risk factors mentioned above).

Cause

Hyperglycemia in type 2 diabetes most often develops due to insufficient insulin secretion and reduced insulin sensitivity (insulin resistance). Insulin resistance presents, at least in pronounced disease, both in the liver and in extrahepatic (outside the liver) tissues, principally in the skeletal muscle (1, 2). This leads to a pathologically increased glucose production from the liver and reduced glucose uptake in the muscles. However, insulin resistance cannot, on its own, lead to hyperglycemia/diabetes, but a concurrent defective secretion of insulin from the beta cells in the islets of Langerhans is also required. Type 2 diabetes develops in genetically predisposed individuals via a stage of reduced glucose tolerance. Heredity is considered polygenous, but which genes are responsible for defects in insulin secretion and/or insulin sensitivity is not yet fully established. Of the known candidate genes associated to an increased risk for type 2 diabetes, most appear to have more significance for insulin secretion than for insulin resistance (3–7).

Risk factors

Most of the lifestyle factors that are known to increase the risk for type 2 diabetes reduce insulin sensitivity (8–14). These include overweight, physical inactivity and the use of tobacco. There is also evidence that a fat-rich and fibre-poor diet, as well as psychosocial stress, independent of body weight, can lead to an increased risk for developing type 2 diabetes (10).

Pathophysiological mechanisms

The molecular mechanisms behind defective insulin secretion and insulin resistance are still unclear. Insulin release is reduced primarily when stimulated with glucose, but also when stimulated with other agents, such as certain amino acids. The beta cell defect is likely primary, but some studies have shown that the defect may arise as a result of "exhaustion" (high demand on secretion and concurrent insulin resistance). Even the toxic effect of hyperglycemia (glucotoxicity) and dyslipidemia (lipotoxicity) can aggravate beta cell function as well as insulin sensitivity, though these toxic effects can largely be reversed by good metabolic control.

Symptoms and prognosis

In most patient with type 2 diabetes, the disease develops insidiously and with few symptoms. The diagnosis can be made at health check-ups or when more symptoms appear due to higher blood glucose levels, for example, in the case of a serious infection or other concurrent disease. One can then observe increased urination and increased thirst, but rarely significant weight loss. Other symptoms that should lead one to think of type 2 diabetes are skin and urinary tract infections, polyneuropathy (disease of the peripheral nerves), impotence and cardiovascular disease. As in other diabetes, there is a risk in type 2 diabetes for developing late complications in the eyes, nerves, kidneys and cardiovascular system. The risk of myocardial infarction or stroke is 3–4 higher, and it is not uncommon that type 2 diabetes is detected in patients with acute cardiovascular disease.

Diagnostics

Diabetes is defined as a fasting plasma glucose of 7.0 mmol/l or higher, symptoms of diabetes and random plasma glucose measurements of over 11.0 mmol/l, or plasma glucose over 11.0 mmol/l two hours after intake of 75 g glucose (oral glucose tolerance test).

Treatment

The basis of treatment on measures that reduce insulin resistance, mainly increased physical activity (8, 9, 12–20) and a fibre-rich diet containing a maximum of 30 per cent fat (primarily mono- and polyunsaturated) and 50–60 per cent complex carbohydrates. Any use of tobacco should be stopped. If these lifestyle measures are not enough to properly control the disease, there are a number of different kinds of oral medications and insulin (21).

Metformin is the drug of choice, the main effect of which is the reduction of glucose production in the liver, while sulfonylureas or glinides are used to stimulate insulin secretion. Glitazones (thiazolidinediones) can be used in combination with either metformin or insulin-stimulating drugs to increase insulin sensitivity, above all in muscle. Newer drugs are analogues to the intestinal hormone GLP-1 (glucagon-like peptide), such as exenatide, or enzyme inhibitors that increase the endogenous level of GLP-1, such as sitagliptin. These drugs improve plasma glucose levels by, among other things, increasing the endogenous insulin secretion and inhibiting glucagon secretion. Acarbose inhibits the breakdown of disaccharides in the intestine. Type 2 diabetes is a progressive disease, however, and after 5–10 years of treatment a large majority of patients fail on these peroral drugs. Insulin treatment can then be required in order to maintain acceptable control, especially if weight loss occurs. Today, insulin treatment is most often given in combination, for example, with metformin. Primary insulin treatment can be necessary if the patient with type 2 diabetes has high blood glucose levels at onset. In many cases a transition to peroral therapy can occur later, however.

Effects of physical activity

Effect of acute exercise

In healthy individuals, physical exercise does not normally lead to changes in the blood sugar concentration, even if maximal exertion can lead to increased blood sugar levels. This generally also applies to type 2 diabetics with only dietary treatment, and it is unusual that physical exercise leads to hypoglycemia in this patient group. These individuals therefore do not normally need to think about eating more in connection with an exercise session, as long as the physical exercise is not strenuous or long-lasting (e.g. a marathon race) (22). In people with type 2 diabetes who receive insulin treatment, sulfonylurea drugs or glinides, however, moderate to strenuous exercise leads to a fall in blood sugar concentration during the exertion itself, a change that can remain up 12 hours after the exercise is finished. In the course following very strenuous exercise, on the other hand, hyperglycemia can arise due to increased plasma hormone levels, which stimulate the liver's glucose production, together with a reduction in the sugar uptake of the skeletal muscle post-exercise (23, 24).

Effects of regular exercise training

Regular exercise training in type 2 diabetics leads to an increase in the insulin sensitivity of the tissues even at rest. An increased insulin sensitivity with training is also seen in non-diabetics, but is of particular importance in type 2 diabetics and other patient groups that normally already have a reduced insulin sensitivity at rest (12, 13, 15–20, 25). It can generally be said that, by leading to a lower sensitivity to insulin, physical inactivity is a risk factor for type 2 diabetes, and several studies have shown that the development of type 2 diabetes can be prevented through exercise training.

An interesting finding is that there is a reversed relationship between the amount of exercise training and the risk of developing type 2 diabetes (10). Because type 2 diabetes is associated with a 3–4 times higher risk for myocardial infarction and stroke, it is also important that exercise training in this patient group has an impact on the risk factors for heart disease, in addition to through the increased insulin sensitivity, also through leading to an improved blood lipid profile and lower blood pressure (16–19, 22, 26). An interesting question is also whether blood sugar control is affected by exercise training in type 2 diabetics, since good blood sugar control reduces serious late complications in diabetes. The research data in this area was negative for a long time, but recent studies have shown that improved blood sugar control can be achieved with exercise training, especially for younger age groups (27). A recently published study, in which non-insulin-treated type 2 diabetics (39–70 years) were randomly assigned to endurance training, strength training, combined training or to a control group without training, for 6 months, showed improved blood sugar control, measured as glucosylated haemoglobin (HbA1c), in all training groups. Significant best outcomes were shown in the sample group where fitness and strength training were combined (28). In a randomised study, researchers were able to show that lifestyle treatment (physical activity 2–3 times per week and dietary counseling) were as effective at reducing HbA1c in a group of tablet-treated type 2 diabetics with poor blood sugar control as starting insulin treatment (29).

Indications

Primary prevention

A number of randomised prospective studies and epidemiological observation studies suggest good primary prevention effect from physical activity in individuals with reduced glucose tolerance (11–14, 30–33). In some of these studies, regular exercise was combined with weight loss (approx. 5%) (30, 31), whereas other large prospective studies have shown a diabetes-preventive effect with physical activity as the only intervention (32–34). An example of the latter that can be noted is the study in the Chinese city of Da Qing (32), in which 577 individuals with impaired glucose tolerance were divided into four groups, among them a group with only exercise training as treatment. After 6 years, 68 per cent of the individuals in the untreated control group had developed type 2 diabetes, compared to only 41 per cent in the exercise group.

Secondary prevention

Regular physical activity is an important part of the treatment of type 2 diabetes (12, 13, 16–20, 34). By contributing to good metabolic control (see above), it is likely that also the development of late diabetic complications can be reduced.

Prescription

Medium intensity physical activity, a minimum of 30 minutes per day of brisk walking, cycling or similar activity, adapted to the individual's overall physical condition and lifestyle. It is important to include warm-up and cool-down components of a lower intensity. Further health and aerobic fitness effects can be achieved if this is combined with somewhat more intensive exercise at least 2–3 times per week, for example, a fitness class, tennis, swimming, or skiing. Strength training is also recommended (Table 1). If cardiovascular symptoms are present the strength training should be less strenuos than shown in the table, for example 12–15 repetitions instead of recommended 8–12. In the case of eye symptoms, even lighter weights should be used, for example,15–20 repetitions of each exercise. In order to avoid a rise in blood pressure, lifts should be done on exhalation and the muscles relaxed during inhalation. For aerobic fitness and strength training, each session should begin with a warm-up and end with a cool-down period of 5–10 minutes each, including careful stretching of tight muscles and soft tissues.

Physical activity aimed at weight loss should be combined with a reduced calorie intake. Hypoglycemia seldom occurs in connection with exercise and extra intake of carbohydrates is therefore not necessary. Patients receiving insulin treatment or taking insulin-stimulating peroral drugs may become hypoglycemic, however, especially if they do not have pronounced insulin resistance (hypoglycemia in connection with physical activity is also discussed under the heading of Effect of acute exercise in this chapter and the chapter on type 1 diabetes).

Table 1. General recommendations for physical activity in type 2 diabetes mellitus (35).

Type of training	Examples of activities	Frequency	Intensity	Duration
Basic activity	Walking, climbing stairs, gardening. It is also desirable to increase standing/walking time at work and at home.	Daily	So talking is still possible, 30–50% of maximal oxygen uptake; 12–13 acc. to Borg's scale.	> 30 min.
Aerobic fitness training	Nordic walking, jogging, cycling, swimming, skiing, skating, fitness class/aerobics/dance, ball sports, rowing.	3–5 times/week	Until out of breath Begin slowly and gradually increase to 40–70% of maximal oxygen uptake; 13–16 acc. to Borg's scale*.	20–60 min.
Strength training	Movements using the body as resistance, resistance bands, weights, weight/resistance equipment.	2–3 days/week	Until or near muscular exhaustion for each exercise**.	8–10 exercises, with 8–12 reps of each exercise

* Level of exertion may need to be reduced in the case of retinal, renal or cardiovascular complications as well as autonomic dysfunction.

** Replace with easier exercises in the case of retinal, renal or cardiovascular complications.

Functional mechanisms

Even though it is unusual for physical exercise to lead to hypoglycemia in people with type 2 diabetes, the blood sugar concentration changes in connection with exercise more often in type 2 diabetics than in non-diabetics. This has to do with the marked increase in sugar uptake for the skeletal muscle during exertion due to a non-insulin-dependent increased permeability of sugar to the muscle cells. In healthy non-diabetic individuals, the increased sugar uptake of the skeletal muscle is compensated for during exertion by an increased release of glucose from the liver due to an increase in the hormone glucagon as a result of the exertion, while insulin levels fall. In people with type 2 diabetes, this compensation is sometimes not sufficient and leads to lower blood sugar, possibly due to the fact that the insulin concentration in the blood is often elevated in these people, which can result in insufficient release of glucose from the liver (23, 24). The increased blood sugar concentration seen in type 2 diabetics in the course following a vigourous exercise session is considered to be connected to remaining high concentrations of so-called counter-regulating hormones post-exercise (24).

The increased insulin sensitivity with regular exercise can be explained by changes at different levels, for example, a changed body composition, with less fat and more muscle, and cellular changes in the skeletal muscle, such as increased concentrations of glucose transporter proteins and glycogen synthase (13, 25).

Functional tests/Need for health check-ups

In some cases, especially in older patients or in the case of long diabetes duration, it is appropriate to conduct a stress test or other examination to assess heart status. The presence of peripheral neuropathy, impaired sensation, impaired joint function, eye complications (proliferative retinopathy) and kidney disease should also be assessed. The latter are necessary because elevated blood pressure during activity may aggravate eye problems and the development of kidney disease. And finally, one should examine the feet with respect to loss of feeling, uneven loading, pressure sores and corns and calluses, as well as the possible presence of sores.

Interactions with drug therapy

Physical activity increases both insulin sensitivity and insulin-independent glucose uptake in muscle, and thus amplifies the insulin effect. This can be of practical importance in certain patients receiving insulin treatment or insulin-stimulating peroral drugs.

Contraindications

Relative

Caution with concurrent heart disease. In the case of peripheral neuropathy there is a risk for injuries to the feet and joints. In the case of eye complications (proliferative retinopathy) there is a risk for exacerbation of eye status (uncommon). In the case of autonomic neuropathy, physical activity that is too intensive can be associated with risks (hypotension and lack of early warning signs for cardiac ischaemia). In the case of kidney disease, high blood pressure (systolic pressure of 180–200 mmHg) can aggravate the development of the disease.

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