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Diabetology lecture notes for medical students

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BEFEKTETÉS A JÖVŐBE

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Chapter 1.
Introduction and pathophysiology
Dr. István Wittmann

The frequency of diabetes, its outstanding importance in the development of cardiovascular and tumour-associated morbidity and mortality, and the medical intervention of the field in the last years, make it necessary that we provide an easy-to-upgrade, electronic format teaching material to support the learning of the students.

Changing perspectives in diabetology

Studies over the last years indicate that one of the major causal factors related to type 2 diabetes mellitus, insulin resistance, is not the only hormone resistance that can characterize this type of diabetes. This field of medicine is related by several common-onset hormone resistances to endocrinology; the immunological mechanisms present in type 1 diabetes relate it to immunology, and through complications it is connected to obesitology, lipidology, hypertension, cardiology, neurology, angiology, ophthalmology, nephrology and so on.

Diabetes leads to systemic alterations, thereby damaging all parts of the body. Thus the study of diabetes promotes the learning of a holistic approach. In order to do this, let us familiarize ourselves with relationships between hormonal resistances and cardiovascular complications.

Hormone resistance and cardiovascular diseases

Insulin resistance plays a major role in the development of type 2 diabetes mellitus; however, it is frequently already present in obesity without diabetes and in impaired glucose tolerance. Moreover, it can also be detected in non-obese smokers, which suggests that insulin resistance may also occur without any increase in abdominal fat mass. As a result, insulin resistant patients may be divided into two groups, those with and those without obesity.

Obesity-associated insulin resistance

According to a widely accepted perspective, the major cause in obese patients for the pathomechanism of insulin resistance is subclinical inflammation. According to the hypothesis of subclinical inflammation, in obesity the abdominal fat cells undergo a phenotype change, and produce among other elements cytokines (e.g. TNF-alpha) that flood the circulation. The cytokines will be able to activate the NAD(P)H oxidase enzyme by

binding to cytokine receptors of endothelial and parenchymatous cells, while the enzyme will in turn overproduce superoxide. The overproduction of superoxide leads to intracellular oxidative stress, which leads to an altered phosphorylation of an important factor in the signalling of insulin, namely insulin receptor substrate 1 and 2 (IRS1, IRS2). Exactly what happens is that the inhibitory serine phosphorylation will outweigh the activating tyrosine phosphorylation of IRS-1 and -2. As a consequence, insulin signalling via the IRS-pathway decreases. It is important to emphasize that resistin, which is well-known for inducing insulin resistance, and which originates from the abdominal fatty tissue, can lead to insulin resistance via the same pathomechanism.

As the insulin signalling is able to run through the other pathways in an undisturbed manner (insulin resistance is selective), and hyperinsulinaemia develops in the circulation because of the loss of metabolic effects, there will be an increased insulin influence over other pathways. This is the way, an increased vasoconstriction (increased endothelin-1 secretion) and mitogenity develop in insulin resistance, along with in impaired glucose-lowering and vasodilatory effect. This mechanism may also play a role - via increased mitogen activity - in the development of increased risk of cancer in diabetes and obesity.

One important question to be asked is where the phenotype change of the abdominal fat cells originates from. Why does the abdominal fat cell differ from the subcutaneous fat cell? One possible explanation is that the gut flora changes in obesity and type 2 diabetes mellitus, and that those types of bacteria will overgrow in the colon, the lipopolysaccharide of which is able to pass through the bowel wall and reach the abdominal fat cells, driving them to phenotype change. This is underlined by the fact that a transient antibiotic therapy is able to influence insulin resistance. According to another explanation, the abdominal fat cells produce aldosterone, which is able to transform the cells in an autocrine manner. A third explanation is that the fat cells produce an aldosterone (or mineralocorticoid) releasing factor that is able to promote aldosterone production in the adrenal gland. For the mechanism of action of aldosterone, see below.

As a consequence, we can say that insulin resistance in obesity is mainly due to oxidative stress developed due to cytokines, resistin and aldosterone.

Insulin resistance in the non-obese

Common thinking in the field focuses nearly exclusively on the insulin resistance of obese persons, and far fewer data are available regarding insulin resistance in persons with a normal body mass.

From this group, a hormonal disease that is well-known not to be associated with obesity arises, hyperthyreodism. In hyperthyroidism, interleukin-6 overproduces in the subcutaneous fatty tissue, and the elevated levels of circulating tumour necrosis factor alpha and higher interleukin-18 are made responsible for the development of insulin resistance. All three cytokines could lead to insulin resistance through the abovementioned mechanism, through the production of superoxide free radical. The effect of hyperthyroidism on blood glucose is attenuated by the hyperkinetic circulation.

While obesity-associated increased aldosterone production surely contributes to insulin resistance (see above), in primary hyperaldosteronism there is no correlation of plasma aldosterone levels and body mass index, i.e. a lean patient can also be insulin resistant. The explanation for this is that aldosterone is able by binding to its mineralocorticoid receptor to activate the NAD(P)H oxidase enzyme. The superoxide free radical that is formed can have an effect on insulin signalling similar to that of cytokines. Here, we also have to emphasize that angiotensin II, by activating the same mechanism, decreases the insulin response of the cells.

Smoking markedly increases the risk of insulin resistance, type 2 diabetes and metabolic syndrome. In this case it is not the obesity, but other components of the metabolic syndrome that make up the diagnosis of the syndrome. Some water-soluble component of cigarette smoke is able to inhibit insulin-signalling via the IRS-1. According to our own in vitro data, cigarette smoke decreases the activating phosphorylation of Akt (protein kinase B), which may lead to the development of insulin resistance. As the effect can be avoided using antioxidants, a free radical mechanism can be hypothesized.

In consequence we can say that the same intracellular effects can lead to insulin resistance in the non-obese as in the obese.

Insulin resistance of the beta cells

The proper efficacy of insulin is required for the insulin secretory effects of the beta cells of the pancreatic islands. When activated under normal circumstances, the insulin receptors on the surface of the beta cells ensure the resistance of the beta cells against apoptosis. Glucagon-like peptide-1 (GLP-1) has a synergistic effect on these processes. In the case of insulin resistance, insulin also exerts less influence over the beta cells, meaning that insulin secretion will also decrease. As we will see later on, in such cases the beta cells also become resistant towards GLP-1.

We can draw the conclusion that in the case of the beta cells, insulin resistance goes hand-in-hand with lower rates of insulin secretion.

The breakthrough phenomenon

The "breakthrough phenomenon" is well-known. The principle is that in type 2 diabetes mellitus, an intensive insulin therapy of 2-4 weeks, using either the conservative method or an insulin pump, is able to break through insulin resistance. Here the insulin resistance of the beta cells also disappears, and insulin secretion also improves due to the breakthrough. *Conclusions from the breakthrough phenomenon are:*

1. *Insulin resistance is reversible, i.e. it is not due to irreversible DNA-damage.*
2. *We need a therapy of 2-4 weeks to achieve the breakthrough, i.e. it is not effective instantaneously.*
3. *The success of a breakthrough of a couple of weeks may indicate that we can find reversion of some sort of protein damage in the background.*

Insulin resistance and mortality

According to a study in non-diabetics, the greater the degree of insulin resistance, that is, the higher the value of the $HOMA_{IR}$, the higher the risk of total mortality. From time to time the possibility arises that in type 2 diabetes the endogenous hyperinsulinaemia or the high exogenous insulin dose may increase cardiovascular risk; however, there is no real proof of this. In diabetes it is hard to diagnose, as it is virtually impossible to distinguish the effect of a large insulin dose from that of the effect of insulin resistance.

In conclusion we can say that according to studies in non-diabetics, it may be more likely that insulin resistance, or even more likely the subcellular processes lying behind it, are directly connected with increased mortality.

Insulin resistance is at the same time incretin resistance

In human preliminary studies it was observed that GLP-1 infusion given to healthy persons (reaching a 46 pmol/l plasma level) could increase the insulin plasma levels at 120 minutes to 4000 pmol/l. Conversely, in patients with type 2 diabetes the plasma GLP-1-level of 41 pmol/l led to an insulin level below 500 pmol/l. It can be concluded that in insulin resistant type 2 diabetics GLP-1 is also less effective, i.e. there is a GLP-1-resistance. When a dose of GLP-1 three times higher (leading to a plasma level of 126 pmol/l) was given to the

same patients, insulin production rose, reaching a value of around 4000 pmol/l observed in healthy persons.

In conclusion we can say that in type 2 diabetes GLP-1 resistance is present besides insulin resistance.

The breakthrough of incretin resistance

In the abovementioned population, a follow-up study was also carried out, within which the blood glucose of the patients with type 2 diabetes was normalized using a four-week intensified insulin therapy, i.e. a classic breakthrough was performed. The efficacy of GLP-1 before and after the insulin treatment was tested. It was found that after the four weeks of breakthrough the effect of GLP-1 on the increase of insulin secretion and glucagon secretion improved significantly. This suggests that a close to euglycaemic state over duration of four weeks decreases the GLP-1 resistance of alpha- and beta cells.

In conclusion we can say that a near-euglycaemic state due to intensified insulin therapy can lead to a breakthrough of GLP-1-resistance of the alpha- and beta-cells.

The insulin-resistant are also erythropoietin-resistant

In adults, the erythropoietin required for erythropoiesis is produced in the tubulo-interstitial fibroblasts of the kidney. Where there is renal damage, the production decreases; therefore, nephrologic patients frequently require erythropoietin therapy. Our observations show that red blood cell formation in diabetic patients with renal disease is lower than in patients with renal disease without diabetes, but with similarly impaired kidney function and erythropoietin levels. Others have found out that in dialyzed patients with or without diabetes, the erythropoietin dose (obviously reflecting the extent of erythropoietin resistance) shows a close connection with the value of the $HOMA_{IR}$ index, i.e. the higher the $HOMA_{IR}$ is, the higher was the erythropoietin requirement of the dialyzed patients. According to an interesting observation, the IRS-2-Akt pathway – the impairment of which is responsible for the development of insulin resistance – also plays a role in the intracellular signalling of erythropoietin.

In conclusion we can say that among diabetic and non-diabetic dialyzed patients, insulin-resistant patients are also erythropoietin-resistant.

Erythropoietin resistance and mortality

A connection has been found between the erythropoietin dose and mortality. As a result, a new tendency has evolved in nephrology to use the smallest possible dose of

erythropoietin. However, similarly to the case of insulin, with erythropoietin the question also arises whether erythropoietin itself is harmful, or the source of the increased risk rather the hormone resistance behind high doses of erythropoietin? Investigations are yet to be carried out, but on the analogy of insulin, and also because of the same signaling pathways, it seems more probable that cellular changes behind hormone resistance play a role.

It may be hypothesized that it is rather the alterations in the background of erythropoietin resistance and not the higher erythropoietin dose itself that is responsible for the increase in mortality.

The insulin resistant are also leptin resistant

Basic scientific research has shown that in the IRS-Akt pathway the phosphorylation of the IRS component is changed by oxidative stress and is responsible for insulin resistance and is common in the signalling of insulin and leptin. Probably this can also lead to leptin resistance based on the abovementioned facts. Indeed, plasma insulin and leptin levels show a tight correlation in healthy persons and in patients with polycystic ovary syndrome.

In conclusion we can say that the insulin-resistant are also leptin-resistant.

Leptin resistance increases mortality

According to a clinical study, in non-diabetic persons, the risk of cardiovascular morbidity and mortality is higher in elderly (mean age=79 years) patients with leptin levels above the median than in patients with leptin levels below the median. Again, the question could be raised whether it is the higher hormone level or the hormone resistance behind the higher hormone levels that account for the increase in risk?

We can assume the same as it is more or less proven for insulin resistance, namely that maybe not the high leptin level itself, but the subcellular alterations behind the hormone resistance could be the common cause.

The insulin resistant can also be acethylcholine resistant

It was also discovered that the same signalling (IRS-Akt) is also of importance in the vasodilatory effect of acetylcholine, thus also acetylcholine resistance can be present in insulin resistance, and both can lead to the elevation of blood pressure and to tissue ischemia.

Based on studies carried out in patients with hypertension, the possible beneficial effect of inhibitors of the renin-angiotensin-aldosterone system on the risk of diabetes rises again and again. These antihypertensive medications decrease the intracellular production of

superoxide and hydroxyl free radicals by decreasing the angiotensin-II- and aldosterone-triggered activation of the intracellular NAD(P)H oxidase. This is then able to lead to a decrease in blood pressure (increase in the efficacy of acetylcholine and insulin) and an improvement of metabolism (increase in the efficacy of insulin and leptin).

As a counterargument it is often presented that in a part of clinical trials (corresponding to the principles of evidence-based medicine) the RAAS-inhibition did not have an effect on the development of diabetes mellitus. The cause for that can be, that patients with a low risk (and thus a low level of activation of the RAAS) were included into the negative trials, thus the efficacy of RAAS-inhibition was also low. On the contrary, if patient with a high chance of developing diabetes were studied, the inhibition of the RAAS decreased the risk of diabetes markedly.

In conclusion we can say that insulin resistance may be concomitted by acetylcholine resistance.

The 'root' of the metabolic syndrome

In the light of the abovementioned data, we may assume that the cause for the association of haemodinamic (hypertension) and metabolic (carbohydrate and lipid metabolism) disorders may be damage to the abovementioned common IRS-Akt signalling pathway. This is present in both obese and non-obese patients with metabolic syndrome. Thus it may not be insulin resistance that is the cause, but rather one of the symptoms of the metabolic syndrome. The real cause lies deeper, in ntracellular signalling, and principally damage of the IRS-Akt signalling due to oxidative stress. Thus the increase in cardiovascular risk present in the metabolic syndrome is in part a consequence of damage due to the components of the metabolic syndrome (obesity, hypertension, rise in triglyceride levels, decrease in HDL-cholesterol levels and carbohydrate metabolism-disorder), while on the other hand the intracellular signalling damage (which is also the cause of the metabolic syndrome) directly damages the blood vessels, the kidneys and the heart. In blood vessels, a decrease in vasodilation develops due to this signalling malfunction.

We may assume that the metabolic syndrome has its roots in the signalling disorder of the IRS-Akt pathway, that insulin resistance is only a sign of that, and that the signalling malfunction behind the metabolic syndrome may therefore be one important cause of the association of the metabolic syndrome and cardiovascular diseases.

The significance of the first phase of insulin secretion

The first phase of insulin secretion starts to decrease in obese patients already in the phase of normal glucose tolerance (**Figure**). The consequence is the rise in plasma glucose in the early postprandial phase, which may lead to an increase in the second phase of insulin secretion. This disproportional rise of the second phase may be so great that it can lead to hypoglycaemia. In some cases, type 2 diabetes is recognized upon this late postprandial hypoglycaemia.

Because of the increased workload, the second-phase hypersecretion of insulin goes along with an increased secretion of the amylin hormone, as insulin and amylin can be found in the same secretion granula. This overproduction of amylin causes a local amyloidosis in the islet cells of the pancreas and thus destroys the beta cells; moreover, in the later phase, the alpha cells as well. Thus in advanced type 2 diabetes not only will insulin (and amylin) production be impaired, but the secretion of contrainsular glucagon will be lost as well, and this will lead to a worsening in the counter-regulation to hypoglycaemia.

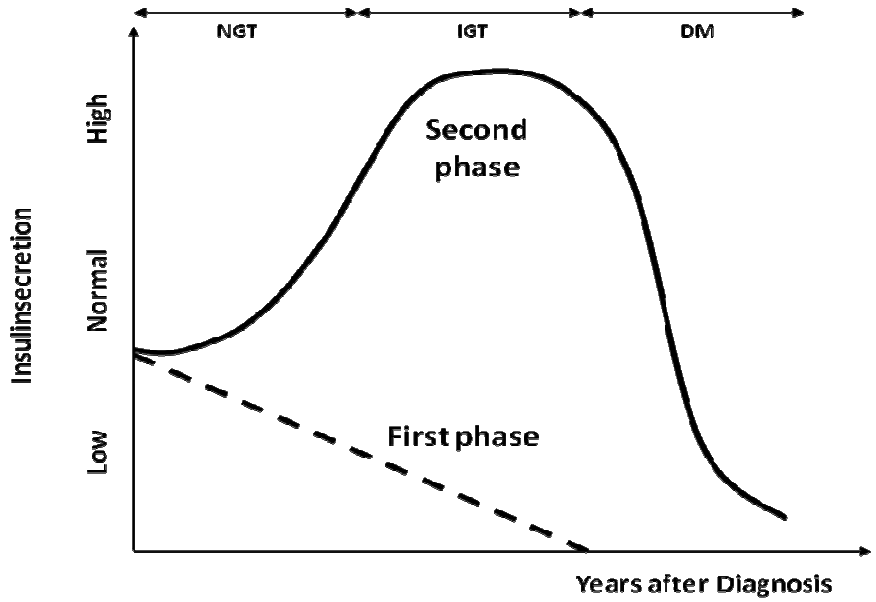

Figure: Changes in the first and second phases of insulin secretion as a function of diabetes duration in the phase of normal glucose tolerance (NGT), impaired glucose tolerance (IGT) and diabetes mellitus (DM). Shematic image.

The role of organ and tissue damage in the development of type 2 diabetes mellitus

Adipose tissue

Visceral adipose tissue is more insulin resistant than subcutaneous tissue. In the background, the gut flora is altered, and lipopolysacharid is able to translocate through the

bowel walls, reaching the visceral fat cells by binding to their surface receptors, activating the NAD(P)H oxidase enzyme and bringing them to a phenotype change. Then the visceral fat cells will produce cytokines, growth factors and the earlier mentioned mineralocorticoid-releasing factor.

The visceral fat tissue becomes insulin resistant, initiating lipolysis, an important contributor to diabetic lipotoxicity.

Furthermore, these processes are accompanied by the deposition of ectopic fat tissue; that is, fat cumulates around the blood vessels and the heart, between muscle fibres, in the liver, etc. This fatty tissue damages the organ it has appeared in, directly *in loco* through the cytokines produced.

Liver

An increased hepatic glucose production and efflux can be observed in the liver in diabetes. This plays an important role in the development of hyperglycaemia, and especially in the rise of the fasting blood glucose.

Another important process in the liver is the fat accumulation known as non-alcoholic fatty liver disease (NAFLD), which is the most important cause of cryptogenic cirrhosis. NAFLD shows also a tight connection with insulin resistance.

Skeletal muscles

The glucose uptake of skeletal muscles is regulated by insulin at two levels. The first level is the nutritive praecapillary arterioles. The skeletal muscle is not always equally perfused. Insulin causes these nutritive praecapillary arterioles to open, and in this way insulin is able to reach the skeletal muscles. In cases of insulin resistance, this process does not take place, there is an insufficient perfusion, added to which the glucose transporter of the muscles, GLUT4, is not translocated to the cell membrane from the intracellular pools, and so the glucose uptake of the muscles will be lower.

Kidney

Gluconeogenesis

Two organs share fasting glucose production: the liver and the kidneys. The hepatic glucose efflux comes in part from glycogenolysis, and in part from gluconeogenesis. Gluconeogenesis, however, is the sole he source of renal glucose efflux **(Table.).** This

gluconeogenesis increases in diabetes, and the higher the fasting glucose, the more glucose is produced by the kidneys, which is of course unfavourable to metabolism.

Table: Glucose efflux of the liver and the kidneys in a fasting state in healthy persons

Liver-derived	**75–80%**
Glycogenolysis	**45–50%**
Gluconeogenesis	**25–30%**
Kidney-derived	**20–25%**
Glycogenolysis	**0**
Gluconeogenesis	**20–25%**

Sodium-glucose cotransporter-2

The tubular epithelial cells of the proximal tubuli of the kidney reabsorb glucose from the primary filtrate. Sodium-glucose cotransporter-2 (SGLT2) is responsible for 90% of reabsorption, while sodium-glucose cotransporter-1 (SGLT1) for the remaining part. In diabetes, we can observe an increased expression and activity of SGLT2, which contributes to maintaining hyperglycaemia.

Central nervous system

The central nervous system plays a part not only in the regulation of appetite and eating, but also in the direct regulation of blood glucose. From the portal vein, afferentation leads via the vagal nerve to the central nervous system, which is influenced directly by GLP-1. On the efferent side, nervous system regulation plays a role in the initiation of the first phase of insulin secretion. This takes place in the first 5-10 minutes of alimentation, where there cannot as yet be any absorption of nutrients.

The first phase of insulin secretion will decrease, and later diminish in insulin resistance. However, if we break though the insulin resistance via intensified insulin therapy, the first phase of the secretion of insulin can be restored. This makes it probable that insulin resistance can also develop in the central nervous system, and its cessation may influence the carbohydrate metabolism in a favourable way.

Chapter 2.
Types, diagnosis and epidemiology of diabetes mellitus
Dr. István Wittmann

According to the present-day classification of diabetes the following types can be differentiated:

1. Type 1 diabetes mellitus
   - With autoimmune mechanism
   - Idiopathic
2. Type 2 diabetes mellitus
3. Other, specific types
   - Genetic dysfunctions of the beta cells
   - Genetic defects of insulin function
   - Forms related to diseases of the exocrine part of the pancreas
   - Endocrinopathies
   - Types induced by drugs and chemicals
   - Infection-related
   - Unusual forms of the immunopathogenic diabetes
   - Genetic syndromes associated with diabetes
4. Gestational diabetes

Prediabetes (high risk of diabetes) and the diagnosis of diabetes

The major components of the diabetes mellitus syndrome are the following:
First, one has to mention the osmotic diuresis-induced polyuria due to osmotic diuresis. Being a small molecular weight substance, glucose is able to pass freely through the barriers in the renal glomeruli; and because of its high serum level, the tubular reabsorption system is not able to reabsorb it completely, and so it will appear in the urine. The polyuria will lead to polydypsia. On the other hand, glucosuria will lead to energy wasting and in this way to weight loss. The compensatory reaction to weight loss is polyphagia.

Glucose is a reducing sugar that can set up Schiff-base bonds with free amino groups of amino acids and proteins. This bond is stabilized due to a re-arrangement process, and eventually leads to the formation of advanced glycation end-products. The process is called non-enzymatic glycation. Glycation impairs protein functions, and in this way functions of the antibodies as well. At the same time, in hyperglycaemia lesion of the cells responsible for

immunocompetence also develops. These two processes lead to immunosupression in diabetes, increasing the risk of infections.

Diabetes may lead pruritus, i.e. itching of the skin, in part directly through non-enzymatic glycation of components of the skin, and in part indirectly, through diabetic neuropathy.

The symptoms mainly developing in type 1 diabetes mellitus are abdominal pain and Kussmaul breathing, the cause of which is diabetic ketoacidosis.

Thus the most important diabetic symptoms are:

1. Polyuria-polydypsia
2. Weight loss - polyphagia
3. Risk of infection
4. Pruritus
5. Abdominal pain and Kussmaul breathing (in Type 1)

The diagnosis of praediabetic states (also called states with a high risk of diabetes) and diabetes mellitus is based on fasting and 2 hours venous plasma glucose values (in an oral glucose tolerance test, OGTT). According to present regulations, this has to happen using validated measurements of central laboratories. A further method used mainly in the United States is based on haemoglobin A_{1c} (HbA_{1c}) measurement. According to this, we can diagnose diabetes by a value above 6.5%.

The diagnostic criteria are summarized in the following table. It is important to emphasize that in the absence of the abovementioned symptoms, all measurements have to be repeated in order to ensure accuracy of diagnosis.

Table: Diagnosis of praediabetes (high risk of diabetes) and diabetes mellitus

	Venous plasma glucose concentration, (mmol/l, laboratory measurement)
Normal glucose tolerance: Fasting blood glucose and 2-hour value of OGTT	 ≤ 6.0 < 7.8
Impaired Fasting Glucose, IFG: Fasting blood glucose and 2-hour value of OGTT	 6.1-6.9 < 7.8

Impaired Glucose Tolerance, IGT Fasting blood glucose and 2-hour value of OGTT	 ≤ 6.0 7.8-11.0
Impaired fasting glucose + impaired glucose tolerance (IFG+IGT) Fasting blood glucose and 2-hour value of OGTT	 6.1-6.9 7.8-11.0
Diabetes mellitus Fasting blood glucose or 2-hour value of OGTT	 ≥ 7.0 ≥ 11.1

Epidemiology of diabetes mellitus

Diabetes has turned everywhere into a population healthcare problem. There are populations where it is of extreme frequency (e.g. half of the Pima Indian population has diabetes). In most countries the number of recognized cases reaches up to 5-10% of the population. According to estimates, there exists the same volume of unrecognized diabetics as the number of recognized diabetes cases, meaning that 10-20% of the population may suffer from diabetes. We know from other estimates that the number of cases with prediabetes (high risk for diabetes) is roughly equal to the number of cases with diabetes, so we may conclude by stating that at least 20% of the population suffers from some sort of carbohydrate metabolism disorder.

The distribution within the diabetes group may be of interest. Approx. 90% of diabetics suffer from type 2, while 5-10% from type 1 diabetes mellitus. Gestational diabetes and the other specific forms of diabetes may attribute to 1% of the total number of cases.

A recent finding is that abnormal childhood obesity is becoming more and more widespread, thus type 2 diabetes may become manifest in the early adulthood.

We have also only recently become aware of the fact that insulin resistance may develop in the form of weight gain in young type 1 diabetic patients. In such cases, the patient has two types of diabetes: both type 1 and type 2.

Chapter 3.
Pregnancy and diabetes mellitus: Gestational diabetes

Dr. András Szilágyi

Definition

Pregnancy can be complicated by three types of diabetes: type 1 and type 2 diabetes mellitus and gestational diabetes. Pregestational diabetes is defined as diabetes mellitus that existed before pregnancy. To this group belong type 1 and type 2 diabetes, incidence of which has shown an increase in recent times.

Gestational diabetes (GDM) is defined as glucose intolerance diagnosed during pregnancy, regardless of whether it is treated with insulin or purely with diet or whether this condition maintains or resolves after delivery.

Epidemiology (See also in related chapter)

While there is a trend in delayed childbearing, the association between type 2 diabetes and pregnancy is expected to be more frequent. Prevalence of type 1 diabetes among women of childbearing age is estimated to be approximately 0.3%. GDM is more common, the prevalence being about 3-6 % according to Hungarian data, although this does depend upon screening methods.

Etiology, pathogenesis

Insulin resistance increases by 30-90% in pregnancy. Anti-insulin, diabetogenic hormones secreted by the placenta play important roles in this process, among which the role of human placental lactogen (HPL) has to be highlighted. Maternal insulin production increases to compensate for insulin resistance. If this increase is insufficient, the compensation will be inadequate, resulting in GDM.

The insulin metabolising effect of the placenta also contributes to the emerging insulin need.

Maternal and foetal complications in diabetes and pregnancy

Maternal complications: Hypo-and hyperglycaemia, diabetic ketoacidosis, higher rate of infections, preeclampsia, polyhydramnion, ophtalmologic complications.

Foetal complications: malformations, miscarriage, intrauterine death, preterm birth, macrosomia, placental insufficiency, intrauterine growth retardation, hypertrophyc

cardiomyopathy, polyhydramnion, birth injury, infections, delayed foetal lung maturity, polycytaemia, and postnatal hypoglycaemia, hyperbilirubinemia and hypocalcemia.

Diagnostic evaluation

Screening for and diagnosis of GDM

There is no worldwide accepted unified approach to screening and diagnosing GDM. In Europe the standard OGTT (2- h 75 g oral glucose tolerance test) recommended by WHO is the applicable test to determine GDM.

Plasma glucose measurements before OGTT (fasting plasma glucose or zero minute) and the 2 hour values are recommended for screening and diagnostic purposes, according to WHO recommendations.

Fasting plasma glucose of 7 mmol/l or higher (≥126 mg/dl) supports the diagnosis of GDM, and in this case OGTT is not recommended.

Normal fasting glucose with 2-hour plasma glucose over 7.8 mmol/l (>140 mg/dl) also indicates GDM.

GDM is also diagnosed when a random plasma glucose is 11.1 mmol/l or higher (≥200 mg/dl), confirmed through a second test, or when HbA1c is >6.5%.

In 2010 the International Association of the Diabetes and Pregnancy Study Groups ((IADPSG) recommended new criteria relating to 75 g OGTT for screening GDM (FPG ≥5,1 mmol/l, 1-hour ≥10,0 mmol/l, 2-hour ≥ 8.5mmol/l) although these have not been widespread as yet. According to these criteria the prevalence of GDM is higher.

All pregnant women should be screened for gestational diabetes at 24-28 weeks' gestation.

Women who are at very high risk should undergo early testing (OGTT) at 12-16 weeks' gestation. The criteria for very high risk are as follows: obesity, family history of diabetes, hypertension, presence of glucosuria, previous delivery of an LGA (large for gestational age) infant, previous delivery of an infant with malformation, previous intrauterine foetal death, habitual abortion.

Management

Type 1 diabetes mellitus and pregnancy

The goal of insulin therapy is to achieve normoglycaemia and to prevent such complications as foetopathy. Insulin therapy must be continuously corrected because insulin needs increases by 2-3 times during pregnancy.

In late gestation (after the 36 weeks'), insulin need usually diminishes, although excessive reduction in insulin need might mean a poor prognostic sign referring to placental insufficiency. After delivery, insulin needs decreases markedly within hours.

Besides insulin treatment, dietary therapy is of great importance in maintaining normoglycaemia and ensuring optimal conditions for foetal growth.

In addition to maintaining normoglycaemia, intrauterine monitoring of the foetus is indispensable during prenatal care in order to achieve a good perinatal outcome.

From 26-28 weeks of gestation tests for evaluating foetus and foetal well being are necessary (ultrasonography, Doppler flowmetry, Nonsterss test, Oxytocin stress test etc)

Type 2 dabetes mellitus and pregnancy

Normoglycaemic metabolic management must be initiated before conception with type 2 diabetic women as well. It is also important that oral antidiabetic agents should be discontinued before pregnancy begins, although this issue is controversial in the case of insulin sensitizers (metformin) which are permitted in early pregnancy.

In early pregnancy some type 2 diabetic patients can be controlled solely with a diet regime. More than 50% of these women require insulin treatment as their pregnancy advances.

Management of GDM

Implementation of an optimal diet is the first step in the management of GDM, although even in obese patients extreme caloric restriction is not recommended.

Daily caloric intake should reach 1600 kcal with a 150-160g carbohydrate content distributed among 5 meals throughout the day. Blood sugars should be maintained between 3.5-7 mmol/l.

An inappropriate diet results primarily in elevated postprandial glucose levels which exceed 7.0 mmol/l. In such cases, the administration of short–acting insulin products before meals (1-3 shots/day) might help to achieve normoglycaemia.

When over-high fasting plasma glucose is the primary alteration the treatment should be complemented with bedtime NPH insulin. Twice daily doses of intermediate-acting insulin might also be required. The daily insulin need is approximately 0.7-1.0 U/ kg.

The administration of rapid acting insulin analogues seems to be safe during pregnancy. There is no sufficient experience regarding use of long-acting insulin analogues (although detemir can be given).

Inadequately treated GDM is associated with higher perinatal morbidity and mortality. Both the achievement of normoglycaemia and an intensive monitoring of foetus and placental function during pregnancy and delivery play important roles in prevention of this high morbidity and mortality. Initiation and frequency of use of intrauterine foetal diagnostic tests (nonstress test, oxytocin challenge test, flowmetry of foetal vessels etc.) depend on the severity of diabetes and the existence of possible complications.

Prognosis and care after delivery

In most cases, GDM will resolve itself soon after delivery. These patients have a significantly higher risk of developing type 2 diabetes during their lifetime. Incidence rate can reach as much as 50% over a period of 7 years. For this reason, postpartum follow up will be of great importance. In this, the first step is the reclassification of maternal glycaemic status at 6 weeks after delivery or following the end of breastfeeding. This is also true for determining whether the definitive diagnosis was purely GDM or pregestational diabetes which had existed prior to, but recognised only during, pregnancy.

Chapter 4.
Therapeutic plan and targets in diabetes mellitus
Dr. István Wittmann

After diagnosis, diabetes mellitus should be classified, i.e. it has to be decided which type of diabetes is the patient is suffering from. Where there is a possibility of monogenic inheritance, a centre should be contacted which has a professional approach to and experience in the diagnosis and therapy of such cases.

It must be established what complications have already developed. We should not forget that according to estimations the onset of type 2 diabetes is between 5-10 years prior to the time of diagnosis. It is of equal importance that micro- and macrovascular complications may already develop at the IGT phase. We may also then state that they are not diabetes-associated, but carbohydrate dysmetabolism-associated micro-and macrovascular complications.

At the time of diagnosis and at the initiation of a new follow-up one should consider the following:

Case history

1. Total internistic case history
2. Age and diabetes duration
3. Eating habits, physical activity, body weight
4. Complications and concomitant diseases
5. Diabetes education
6. Initial or previous HbA_{1c} value(s), data from the blood glucose 'diary'
7. Previous antidiabetic, antihypertensive therapy
8. Hypoglycaemic history (also hypoglycaemia awareness)

Physical examination to be carried out:

A total internistic physical examination, including measurement of height, body weight, abdominal circumference, blood pressure, signs of orthostasis, and a thorough examination of the feet, should be carried out.

Laboratory tests to be carried out:

HbA_{1c}, lipid profile (total cholesterol, LDL-, HDL-cholesterol, triglyceride), liver function tests, routine urine test, estimated GFR and in type 1 also TSH.

Consultations to be carried out

Dietetitian, ophthalmologist, maybe a dentist.

Target range instead of target value

Nowadays we consider setting target ranges rather than target values as the appropriate approach. This consideration comes from the observation that both blood glucose and HbA_{1c} show a biphasic relation with mortality, that is, there exists an ideal range where mortality is smallest. Underlying and beyond that, one has to face an increase in mortality rate. This range may be individually different regarding following influencing factors:

1) Susceptibility to and history of hypoglycaemia, treatment predisposing to hypoglycaemia
2) Age, duration of diabetes, life expectancy
3) Presence of micro- and macrovascular complications
4) Accompanying diseases
5) Motivation and medical adherence of the patient
6) Social and financial status of the patient

Susceptibility to and history of hypoglycaemia, treatment predisposing to hypoglycaemia

With an increase in the duration of diabetes, the susceptibility to hypoglycaemia will increase due to a loss of secretion of glucagon (due to destruction of the alpha cells), and due to sympathetic neuropathy and nephropathy. The presence of severe hypoglycaemia in the past history of the patient increases the chance of hypoglycaemia. Therapy using sulphonylureas and insulin or overtight glycemic control increases the risk of hypoglycaemia.

Age, duration of diabetes, life expectancy

According to the above, an advanced age and longer duration of diabetes brings on a predisposition to hypoglycaemia. On the other hand, with the decrease in life expectancy, a very tight control is not justified.

Micro- and macrovascular complications

Accordingly, both sympathetic neuropathy and nephropathy predispose to hypoglycaemia. On the other hand, an overfast and complete normalization of the carbohydrate metabolism in a patient with high average glucose levels may worsen the diabetic retinopathy. Furthermore, hypoglycaemia may lead to further damage to the cardiac status in a patient with an already established ischemic disease; moreover, it may lead to provocation of arrhythmias and thus sudden death.

Accompanying diseases

In the case of an actual, severe, ongoing infection or an operation with general anaesthesia and the opening of a body cavity, one has to switch to insulin therapy and has to halt other antidiabetics, including metformin.

Motivation and medical adherence of the patient

In the chronic phase of diabetes therapy it is not the doctor who treats the patient, but the patient who is treating himself, in best cases following medical advice. Therefore it is an important question as to whose advice the patient is adhering. Unfortunately, he does not want to follow the advices of his own doctor, as the doctor can 'only' state the present-day stance of science. On the other hand, unofficial 'advisers' say what the patient wants to hear, and so the patient is of course more willing to accept their advice.

One important problem in cases of a relatively mild initiation into the onset of (type 2) diabetes is that the patient does not feel any special complaint. As a result, his state of motivation is low, despite our therapeutic options being most effective in this phase. In cases of more advanced diabetes, the complications will bring on the motivation of the patient, but our therapeutic options have already become pretty impaired by this phase of the disease.

According to our own surprising data, 30-40% of diabetics have already discontinued their medication only 1 year after its initiation.

Social and financial status of the patient

Diabetes means a psychic and financial load upon the whole family of the patient. Accepting this is a great medical achievement. It is of great importance to find out who does the cooking in the family. The education of this person has to run parallelly with that of the patient. Where there is deterioration of carbohydrate metabolism, besides the usual causes (infection, changes in working habits or lifestyle etc.) one also has to consider family

problems. I have observed that even if the patient indicates another cause, this is most frequently the real one.

Glycaemic markers and target ranges

HbA_{1c} is the most important marker in the follow-up to diabetes. It shows glycated haemoglobin, thereby indicating the average glycaemia of the past three months. Limitations to the value of HbA_{1c} are as follow: anaemia, iron deficiency, blood transfusion, dialysis and haemoglobinopathies.

Fructosamine displays the value of glycated albumin. Accordingly, it represents the average glycaemia of the past two weeks. It can be used in any type of diabetes, but is of special importance in cases of pregnancy. It cannot be evaluated properly in cases of protein loss (e.g. abnormal albuminuria, protein-losing enteropathies) and an accelerated protein turnover (e.g. hyperthyroidism).

Glycaemic target ranges are as follow:

HbA_{1c} in type 1:	6.5-7.5%
HbA_{1c} in type 2:	6.0-8.0%
Praeprandial plasma glucose:	4.4-7.2 mmol/l
Postprandial plasma glucose:	<10.0 mmol/l

Chapter 5.
The basics of the non-pharmacological therapy of diabetes mellitus

Dr. József Rinfel

The non-pharmacological therapy of diabetes mellitus is referred to as lifestyle modifications that have two major parts, namely dietetotherapy and therapy based on physical activity. In a wider sense, psycho-social support and patient education can also be mentioned here. The fulfilment of these is not only fundamental to successful patient care, but also a marker of good cooperation between physician and patient. Putting these parts of patient care into daily practice often exceeds the boundaries of conventional medical practice, hence the cooperation of different specialists (dietetitian, physiotherapist, educator etc.), but knowing the basics is inevitable for persons with a general medical degree.

Lifestyle is regarded as a determinant in the development of type 2 diabetes mellitus, the worldwide rapid spread of the disease showing a connection with obesity and a sedentary lifestyle: changing this lifestyle may be a key to prevention, as well. Several epidemiological studies have provided proof of this. Efficient and consequent lifestyle changes, if initiated in time, may prevent approx. 50-60% of type 2 diabetes cases.

Once developed, treatment of the disease also requires a proper diet and daily physical activity. The elements of this should be tailored to the patient, taking into consideration the properties and level of cooperation of the patient and adjusted to the actual pharmacological therapy. However, changthese in lifestyle can only be successful with the cooperationof the patient! It is of high importance that the patient understands what they should do, and how and why they should do it.

Besides providing a good metabolic control, keeping a proper diet and doing regular physical activity is also needed for body weight control and for the quality of life. Data also prove that it may also delay or prevent the development of complications.

Dietetotherapy

The aim of prescribing a diet is to provide optimal nutrition to the individual. This has general rules, but the unique properties of each patient, concomitant diseases, and related pharmacologic therapy make it necessary to make individual recommendations to the particular patient.

Diabetes mellitus is a complex metabolic disorder; and so several conditions have to be taken into account simultaneously when planning the diet. Alterations in the background of

type 2 diabetes mellitus include the delay of the early prandial phase of insulin secretion, insulin resistance and the frequently-observed obesity, all of which represent problems to be solved. With insulin therapy, the effect of preparations employed on blood glucose levels also makes regular timing of meals necessary.

It is therefore absolutely necessary that the patients should be able to properly plan his own diet, determining besides daily calorie intake the ratio of major components of food (carbohydrates, proteins, fat), and choosing food by taking into account regarding quality criteria, timing of meals and the carbohydrate content of individual meals.

Differences in the ability of carbohydrates to raise blood glucose levels should also be emphasized. Knowing the glycaemic index and application of it while planning the diet may aid in reaching good metabolic control. This may only be reached when using a regular, structured patient education (see the chapter on patient care and education in diabetes).

It is of fundamental importance that the patient should understand and accept the sometimes large modifications of their previous dietary habits. These may sometimes be hard to fit into the usual daily routine, and putting it into daily practice may also be problematic. To overcome these, the involvement of specialists may be useful, and in this regard the participation of dieticians and educators may assist, too, as they may help the patient understand the details of lifestyle prescriptions. Additionally, the involvement of other persons in helping the patient may be useful: the participation of family members in keeping to a diet may improve the rate of success.

The dietetotherapy of diabetics should cover the following:

Energy content of the diet

A diabetic patient with normal body weight needs a calorie intake that is determined by age, height, markers of metabolic controls, and the type, intensity and duration of physical activity. This is around 25-35 kcal/bodyweight kg/day, that would generally come to a daily intake of 1800-2500 kcal (7.6-10.5 MJ).

In the case of insulin resistance, a modest, 5-7 % weight loss may aid the efficacy of insulin. However, restriction of energy intake is usually not sufficient to attain long-term weight reduction and improvement of glycaemic control: for that, regular, daily physical activity is also required. We also have to consider that energy requirement of the elderly is lower than at a younger age.

Composition of the diet

Despite occasional changes in recommendations regarding the composition of the diet, a diet with low fat content and a defined carbohydrate content that is mainly carbohydrate-based is actually widely accepted. (Extreme diets should be avoided; diets preferring extreme proportions may especially carry risks. Unfortunately, doctors also succumb to these despite all the facts at their fingertips!

Accordingly, carbohydrate content should cover approx. 50-60% of the total energy intake, and a protein intake of 0.8-1 g/bodyweight kg/day (approx. 20% of total calories) is suggested, while the remaining calories (approx. 30% of total calories) go to fat.

(*Thus, in the case of a middle-aged person of 70 kg, normal BMI and abdominal circumference with intermediate level of physical activity*

- *the daily energy requirement would be 25x70 ~ 1800 kcal/day*
- *protein intake: 70 g x 4 kcal/g ~ 300 kcal (1500 kcal/day remain)*
- *carbohydrate intake: 1800x0,55 = 1000 kcal (: 4 kcal/g) = 250 g/day*
- *fat intake: 1800 - (300+1000) = 500 kcal (: 9 kcal/g) = 60 g/day*

Thus the daily diet is: 1800 kcal; 70 g protein; 250 g carbohydrates; 60 g fat)

It is also important to know the glycaemic index, and consumption of complex carbohydrates leading to less of a rise in blood glucose levels is recommended, within which one should aim for foods with high fibre content (30 g dietary fibres/day). In this regard, the consumption of vegetables, fruits and whole grains is recommended.

Regarding fat intake, a proportion of saturated fatty acids should be < 10% (but if the LDL-cholesterol level is > 2.5 mmol/l, then a lower proportion of < 7% is suggested). According to the guidelines, the proportion of polyunsaturated fatty acids should be ~ 10 %, with monosaturated between 10-12%. It is also important to decrease the intake of trans fats (fatty acids), as more components of the atherogenic dyslipidaemia (LDL ↓, HDL ↑) may be ameliorated using this approach.

The protein intake is planned in the usual way. In the case of a nephropathy, the amount and composition of protein intake may require changes usually prescribed by the nephrologist.

Frequency of meals

In general, division of the total calorie intake to 5-6x smaller meals is suggested, (3 major meals with intermediate meals, in some cases with a bedtime snack), but with certain

therapies (e.g. prandial glucose regulators, analogue basal/bolus insulin therapy) 3 major meals may be sufficient.

Limiting the carbohydrate content of individual meals in cases of patients with type 2 diabetes mellitus is important, the cause for this is to decrease the "carbohydrate load" related to a meal (see postalimentary hyperglycaemia). On the other hand, in cases of certain secretagogue therapies and insulin substitution we should also try to avoid a pronounced fall in blood glucose, which could lead to the risk of hypoglycaemia.

Other dietary considerations related to diabetes

The diet of diabetic patients should be rich in vitamins and mineral salts and trace elements, but an extra supplementation is not necessary. The use of vitamin complexes is not proven, and in the case of certain antioxidants a large intake is rather risky and harmful!

So-called "dietary products" should be used with caution. Sweeteners should also be used with caution. As a rule, the use of artificial – non-caloric – sweeteners (saccharin, cyclamate, acesulphame-K, aspartam etc.) should be preferred, but temperance is also required with their use. Besides individual sensitivity, thermal stability should also be taken into account, an important consideration in baking and cooking.

It should also be noted that aspartam is a photosensitive substance, decomposing quickly beyond its date of consumption (foods lose their sweet taste in this case), the degradation products contain phenylalanine, and may therefore carry risk for patients with known phenylketonuria

No potential side effects or risks considering non-caloric sweeteners have as yet been proven, thus when used according to prescriptions, a significant health risk related to their use does not need to be considered.

With sugar-replacement caloric sweeteners (fructose, sorbitol, xylitol, stevia) and food products manufactured with their use, the calorie and carbohydrate content should be considered and calculated into the daily intake.

The consumption of alcohol and other “drugs” should also be considered. In the case of alcohol, besides the physiologic affect of alcohol attention should also be turned to the relative high caloric intake (~7 kcal/g). The consumption of alcoholic drinks with sugar should be definitely avoided. The alcohol intake should be 1 unit for women and 2 units for

men (1 unit = 1-1.5 dl of wine, 3 dl of beer, or 2-3 cl spirits, which corresponds to the consumption of approx. 15 g).

Regarding the consumption of a daily amount of 1-2 dl of dry red wine, protective cardiovascular effects have been observed in the studies.

Of the beverages containing coffeine, a daily quantity of 1-3 espresso and 2-4 cups of tea may be consumed. The stimulants coffeine and tannin do not lead to a rise in blood glucose.

Here we do not cover detailed special dietary considerations related to diabetes (diabetic nephropathy, celiac disease more common in type 1 diabetes, lactose intolerance with an increase in prevalence with ageing) but refer to them only.

Physical activity

As previously referred to, regular physical activity is a necessary part of lifestyle interventions that may not only play a part in the prevention of diabetes melitus, but which is also an integral part of the care of already developed diabetes.

However, the physical activity should be suited to the capacity, fitness, age, accompanying diseases, and pharmacological therapy of the individual patient. The intensity, duration, form and frequency of physical activity should be tailored to the individual.

The diabetic patient should consult his treating physician and a specialist (e.g. physiotherapist, trainer, games master) before the initiation of such activity.

Properly planned and constructed, regular physical activity may lead to a complete improvement of metabolic parameters, and besides blood glucose, lipid parameters and uric acid may also show positive changes. This is inevitable as regards body weight control, the long-term maintenance of which is not possible in the majority of cases without physical activity. Studies have shown that it improves cardio-pulmonal performance and status. The quality of life improves, the burden of the psychological load can be attenuated, it may be beneficial in preventing stress and anxiety-depression disorders. Regular physical training is also a pledge of active senescence, providing a tool that not only maintains physical functions as well as possible, but also slows down mental decline.

Prior to the initiation of a regime of physical activity, a thorough check-up is recommemnded which should cover general status, especially the cardiopulmonal loadability, and diabetes-specific complications (neuro- nephro- retinopathy, osteoarthropathy).

The patient should recognize those physiological states where training may even be harmful: acute metabolic deterioration (blood glucose over 15 mmol/l, the danger of hypoglycaemic episode, ketoacidosis etc.), febrile states, infections, the presence of an autonomic neuropathy, severe renal impairment, proliferative retinopathy, the onset of acute cardiac symptoms etc. In these cases it is required that the exercise be postponed and an extraordinary medical consultation undergone!

On planning an exercise programme, **dynamic exercises** that move large muscle groups and mainly induce an aerobic load (walking, fast walking, bicycle racing, swimming, aquatic work-up etc.) should be given chief emphasis. We should bear in mind what types of movements the condition of the patient enables, and what they would like to do on a daily, regular basis.

Static exercises which improve muscle force and condition may also be included into the training programme, but they should only be carried out when tailored to the individual, under stricter control.

Resistance training aims at the increase of muscle force and changing body composition by increasing the basal metabolic rate; it leads to increased energy consumption.

Stretching may also be advisable, as well as those daily activities (walking, working around the house, stair walking) that we carry out regularly. Arterious vessel exercises may be beneficial to patients with atherosclerosis.

In general, a 3-5 times weekly exercise session of medium-intensity of 15-20 minutes duration is suggested, which can be raised until the patient finds it too difficult.

We should draw attention to the replacement of fluid lost during exercise. During/after exercise a stricter blood glucose control is suggested with an appropriate correction.

Summarizing, the objective of non-pharmacological therapy is to change the lifestyle of the patient. Appropriate dieting and physical activity are major tools in the prevention of type 2 diabetes mellitus, and it should be possible to prevent ~50% of cases of the diseases. In therapy of the metabolic disease that has already developed, lifestyle interventions are also a determining factor, and a successful therapy can only be provided using these approaches, as well.

It is important that dietary changes and suggestions regarding physical activity should be made together and in agreement with the patient. Putting these into practice can be achieved using by educating and continuously motivating the patient.

The level of change in lifestyle mirrors the cooperation between doctor and patient!

Chapter 6.
Non-insulin-like antidiabetic agents
Dr. István Wittmann

These agents are divided into 2 groups:

Oral non-insulin-like antidiabetic agents

Parenteral non-insulin-like antidiabetic agents

Oral non-insulin-like antidiabetic agents can be further classified as having effects that are:

Primarily insulin-dependent

Primarily insulin-independent

There are 2 subgroups of primarily insulin-dependent oral, non-insulin-like antidiabetic agents:

Agents that enhanceenhance the effect of insulin

Agents that increase insulin secretion from the pancreas (insulin secretagogues)

Primarily insulin-dependent, oral, non-insulin-like insulin sensitising agents are as follows:

Biguanides: metformin (buformin is not recommended any more)

Alfa-glucosidase inhibitors: acarbose

Thiazolidinedions (PPAR-gamma-agonists, glitazones): pioglitazon

Primarily insulin-dependent, oral, non-insulin-like agents that increase insulin secretion (insulin secretagogues):

Sulphonylureas: gliclazide, glimepiride, glipizide, gliquidone (glibenclamid/glyburide is now regarded as an obsolete drug)

Prandial glucose regulators (glinides): nateglinide, repaglinide

Dipeptidyl-peptidase-4 (DPP4) –inhibitors (gliptins): alogliptin, linagliptin, saxagliptin, sitagliptin, vildagliptin,

Primarily insulin-independent, oral, non-insulin-like agents:

Sodium/glucose cotrantsporter-2 (SGLT-2) inhibitors (glycoseurics): canagliflozin, dapagliflozin, empagliflozin

Parenteral (injectable) non-insulin-like antidiabetic agents:

Amylin-analogues: pramlintide

Incretin mimetics:

GLP-1-analogues: liraglutide

GLP-1-receptor agonists: exenatide, lixisenatide

Table summarises oral antidiabetic agents in synoptic form. This classification does not involve those human insulin and insulin analogues which are found in Chapter. 7

Table: Non-insulin-like antidiabetic agents

1. **Oral non-insulin-like antidiabetic agents**
    i. Primarily insulin-dependent
        1. Agents that enhance the effect of insulin
            a. Biguanids: metformin
            b. Alfa-glucozidase-inhibitors: acarbose
            c. Thiazolidinedions (insulinsensitisers, PPAR-gamma-agonists): pioglitazone

        2. Agents that increase insulin secretion (insulin-secretagogues)
            a. Sulphonylureas: gliclazide, glimepiride, glipizide, gliquidone
            b. Prandial glucose regulators: nateglinide, repaglinide
            c. Dipeptidyl-peptidase-4-inhibitors: alogliptin, linagliptin, saxagliptin, sitagliptin, vildaglitin,

    ii. Primarily insulin independent
        a. Sodium/glucose cotransporter-2 (SGLT2) inhibitors: canagliflozin, dapagliflozin, empagliflozin

2. **Parenteral non-insulin-like antidiabetc agents**
    a. Amylin-analogues: pramlintide
    b. Incretin-mimetics:
        i. GLP-1-analogue: liraglutide
        ii. GLP-1-receptor-agonists: exenatide, lixisenatide

Primarily insulin–dependent, oral non insulin–like agents that enhance insulin effect (metformin)

Mechanism of action: Metformin decreases hepatic glucose production, enhances insulin sensitivity (decreases insulin resistance), influences intestinal glucose absorption and activates incretin system. Behind these actions, at least in part, is the drug's AMP kinase activating

effect which is not only favourable to metabolism but also decreases tumor mitogenesis through mTOR inhibition.

Advantages: It does not cause hypoglycemia or weight gain. It is also favourable as regards non-alcoholic fatty liver disease (NAFLD). It decreases cardiovascular- and cancer risks.

Indication: Used for treating all patients with type 2 diabetes who are not intolerant, or when there is no contraindication.

Dosage: Should be started with low dose (500 mg once or twice a day). Dosage increases should be made over 2-3 week periods up to the maximal dose of 2550 mg per day (850 mg three times a day). Higher doses are unjustified as efficacy does not increase, but side effects may develop. Extended release formulation is also available, which is tolerated well up to a maximal daily dose of 2000 mg once a day.

Combination: Can be used in monotherapy or in combination with all types of antidiabetic agents.

Contraindications and adverse effects: Metformin is contraindicated in patients with renal impairment, in patients with congestive heart failure or respiratory failure who are at risk of hypoxaemia, in severe liver failure, in pancreatitis and in pregnancy. It should be discontinued in patients undergoing radiologic examinations with iodinated contrast material.

A rare but serious side effect of metformin is lactic acidosis, which is often fatal even today.

Metformin intolerance means a serious adverse reaction, usually with gastrointestinal side effects (bloating, flatulence, diarrhoea), which leads to discontinuation of the drug.

Primarily insulin–dependent, oral, non insulin–like agent that enhances the effect of insulin (acarbose):

Mechanism of action: Alpha-glucoside hydrolase enzyme inhibitor. The inhibition of alpha-glucosidase enzymes leads to decreased intestinal glucose absorption and subsequently to diminished glucotoxicity as well. It enhances the effect of incretin via an as yet unknown mechanism.

Advantages: Does not cause hypoglycemia, is associated with weight loss, and decreases cardiovascular risk.

Indications: It is recommended for obese patients for lowering postprandial hyperglycemia.

Dosage: Should be started with a low dose such as 50 mg once or twice a day, with gradual titration up to a maximal dose of 400mg (100 mg 4 times a day).

Combination: Can be used in monotherapy as well as in combination with all types of antidiabetic agents.

Contraindications and adverse effects: It is rarely used because of common gastrointestinal side effects (bloating, flatulence, diarrhoea).

Primarily insulin–dependent, oral, non insulin–like agent that enhances insulin effect (pioglitazone)

Mechanism of action: It is an agonist of the peroxisome proliferator-activated receptor gamma (PPAR-gamma).

Advantages: The drug is associated with relevant A1C-reduction. It might be beneficial in NAFLD and can also be used in renal impairment

Indications: It is recommended for obese, significantly insulin resistant patients.

Dosage: Dose up-titration is usually not required.

Combination with other antidiabetic agents: Can be used alone or in combination with other antidiabetics except for insulin or some SGLT2-inhibitors.

Contraindications and adverse effects: It is contraindicated in congestive heart failure. An increased incidence of bone fracture has been reported in women who take pioglitazone, therefore it is not recommended for postmenopausal women. Weight gain has also been observed, partly due to fluid retention, but subcutaneous fat accumulation may also occur.

Primarily insulin–dependent, oral, non insulin–like agents that increase insulin secretion (secretagogues): sulphonylureas (gliclazide, glymepiride, glipizide, gliquidone)

Mechanism of action: Sulphonylureas close ATP-sensitive K-channels in the beta-cell plasma membrane, resulting in membrane depolarisation. This opens voltage-gated $\underline{Ca}^{2+}$ channels and the $\underline{Ca}^{2+}$ influx leads to insulin release.

Advantage: The drug leads to significant A1C reduction.

Indications: Sulphonylurea monotherapy is only recommended when metformin intolerance or contraindication occur. It is commonly used in combination with other antidiabetic agents.

Dosage: The most commonly used modified (extended) release form of gliclazide and glymepiride is given once a day, while glipizide and gliquidon are given in two divided doses per day**.**

Combination with other antidiabetic agents: It can be combined with all other antidiabetic agents.

Contraindications and adverse effects: Sulphonylurea efficacy declines relatively rapidly (after a few years of treatment), because these agents are associated with a progressive decline in β-cell (and also alpha cell) function and their action is beta cell dependent. The beta cell

"burnout" is partly a consequence of concomitant amylin secretion, which leads to local amyloidosis causing cell destruction.

Sulphonylureas may induce hypoglycemia and may inhibit hypoglycemic counterregulatory responses via alpha cell destruction. They cause weight gain. Except for gliclazide they also increase cardiovascular and cancer risk. They bind to albumin in circulation and so they may interact with Vitamin K antagonists and NSAIDs. Their metabolisation via citokrom P4502C9 pathway also leads to numerous drug interactions.

Primarily insulin–dependent, oral, non insulin–like agents that increase insulin secretion: prandial glucose regulators (nateglinide, repaglinide)

Mechanism of action: The same as in sulphonylurea**.**

Advantage: They specifically enhance early-phase prandial insulin secretion (prandial insulin releasers) in contrast with sulphonylureas.

Indications: The same as in sulphonylurea. They might be suitable for lifestyles where meals are unpredictable or missed.

Dosage and Combination: They are taken immediately before a meal. If a meal is skipped the medication should also be skipped. It can be combined with all other antidiabetic agents.

Primarily insulin-dependent, oral, non-insulin-like agents that increase insulin secretion dipeptidyl-peptidase-4-inhibitors (alogliptine, linagliptine, saxagliptine, sitagliptine, vildagliptine)

Mechanism of action: The dipeptidyl-peptidase-4 enzyme splits GLP-1 and GIP, making these hormones metabolically inactive. Inhibition of DPP-4 enzyme increases the plasma level and duration of action of these hormones. GLP-1 stimulates insulin secretion in a glucose dependent manner as well as decreasing glucagon release. GIP rather induces insulin secretion alone.

Advantages: They are weight neutral, and are associated with low risk of hypoglycaemia. Their antihyperglycemic effect remains permanent (there is no beta cell "burnout"). They can also be used where there is kidney impairment and seem to be cardiovascularly safe.

Indications: DPP-4 inhibitors can be used in monotherapy and in combination with almost all other antidiabetic agents. They are also effective in kidney failure.

Dosage: Dose up-titration is not required. The dose of some preparations has to be reduced according to the kidney impairment.

Combination with other antidiabetic agents: Some preparation can be applied in monothreapy and all preparation can be used in combination with one or two antidiabetic agents. All the drugs are now available in a combined form with metformin.
Contraindications and adverse effects: Some of them are not recommended in liver disease. If they are added to sulfonylureas hypoglycemia might occur, which requires sulfonylurea dosage reduction. Their side-effect profile is usually comparable to placebo.

Primarily insulin independent oral, non-insulin like agents: SGLT2-inhibitors (canagliflozin, dapagliflozin, empagliflozin)

Mechanism of action: SGLT-2 inhibitors promote glucose and sodium loss in the urine by blocking sodium-glucose cotrasporter 2 in the renal proximal tubular epithelial cells.
Canagliflozin inhibits SGLT-1 in intestinal mucosa as well.
Advantages: SGLT-2 inhibitors can cause weight loss and also lower blood pressure. They are associated with low risk for hypoglycaemia. They moderate glucotoxicity and are cardiovasculary safe.
Indications: Can be used in monotherapy as well as in dual or triple combination therapy.
Dosage: A single daily dose is recommended, gradual dose titration is not required.
Combination with other antidiabetic agents: Can be used in monotherapy and also in combination therapy.
Contraindications and adverse effects: Dapagliflosin is not recommended for use in patients receiving loop diuretics or pioglitason. SGLT-2 inhibitors increase the incidence rate of genital infections thus they are not recommended for patients with a previous history of genital infections. The prevalence of urinary tract infections is comparable to placebo.

Parenteral non-insulin-like antidiabetic agents: incretin mimetics (exenatide, liraglutide, lixisenatide)
Mechanism of action: Incretin mimetics bind to the GLP-1 receptor, stimulate glucose-dependent insulin secretion (such as DPP-4 inhibitors) and decrease glucagon release. According to the most recent classification, these drugs might be classified either as prandial or non-prandial agents.
Prandial agents (exenatide, lixisenatide) have a more notable influence on postprandial blood glucose rise and may slow gastric emptying more significantly. Non-prandial agents like

liraglutid and exenatide LAR (a long acting release (LAR) exenatide formulation with once-weekly dosing) show greater reduction in fasting blood glucose.

Advantages: Incretin mimetics are considerably effective antihyperglycemic agents associated with low risk of hypoglycaemia, and have a favourable impact on weight and blood pressure. Cardiovascular outcome trials performed thus far have confirmed cardiovascular safety.

Indications: Incretin mimetics are recommended as a second or third line therapy (in combination with other antidiabetic agents) for patients with type-2 DM and obesity.

Dosage: Gradual titration is required. Exenatid LAR reaches its maximum effectiveness after several weeks.

Combination with other antidiabetic agents: Can be used in combination with one or two antidiabetic agents and even with insulin.

Contraindications and adverse effects: Nausea may occur, which is usually self limiting, and resolves or at least lessens within a few weeks. GLP-1 agonists are not recommended in severe renal impairment.

Algorithm for the treatment of type 2 diabetes mellitus

Figure shows a treatment algorithm for type 2 DM. Green marking refers to preferred agents, whereas yellow marking refers to agents that can be appropriate for selected patients (acceptable alternatives).

In newly diagnosed type 2 diabetic patients with ketoacidosis, hyperosmolar hyperglycaemic state or markedly elevated blood glucose levels (fasting plasma glucose >13.9 mmol/l, or random plasma glucose > 16.7 mmol/l or A1C >10%), insulin therapy is recommended from the outset.

After initial management of the “acute state”, further chronic therapeutic regimens (e.g.: oral therapy, initial combination therapy regimens etc.) can be considered.

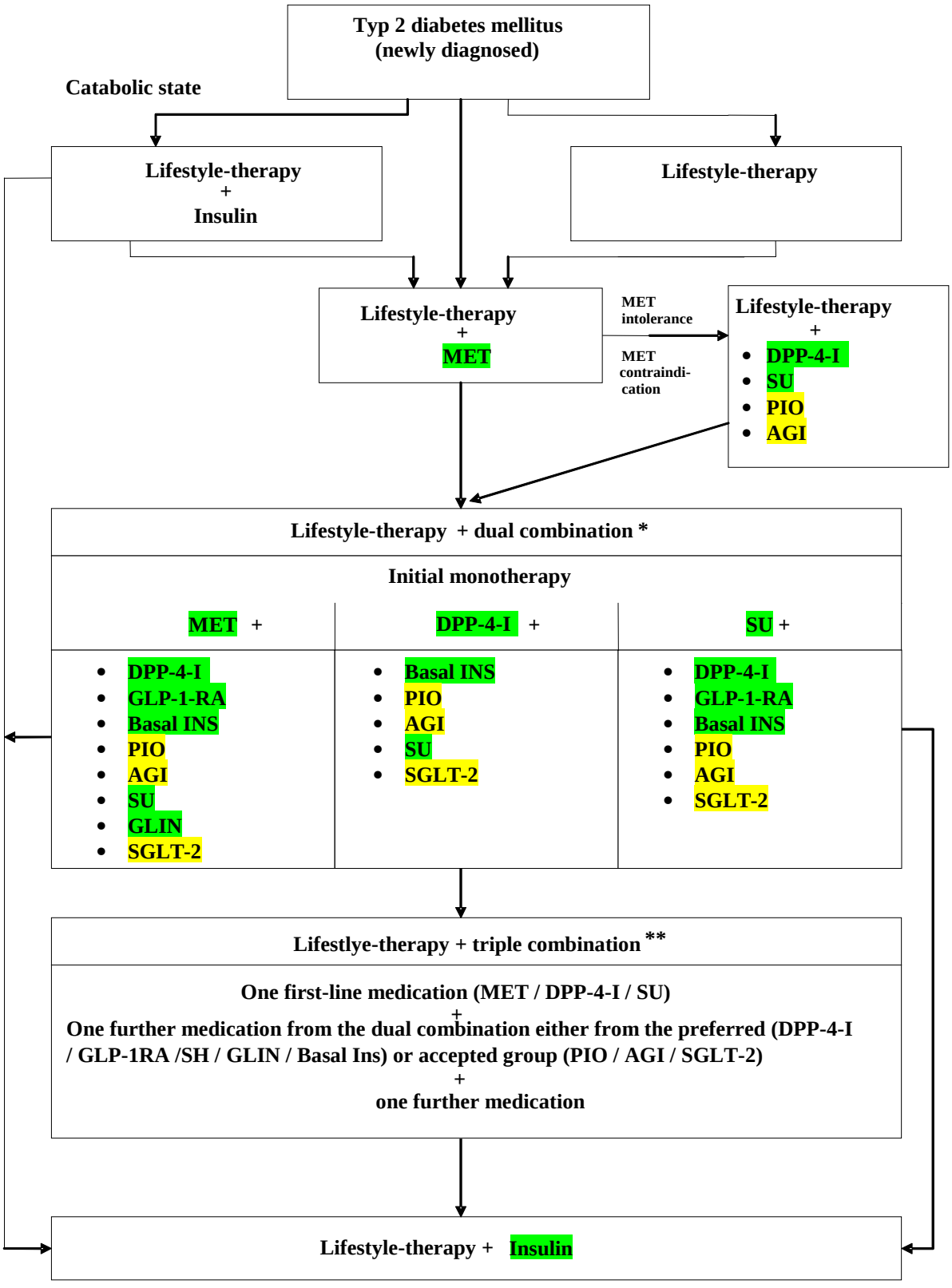
Typ 2 diabetes mellitus
(newly diagnosed)
Catabolic state
Lifestyle-therapy
+
Insulin
Lifestyle-therapy
Lifestyle-therapy
+
MET
MET
intolerance
MET
contraindi-
cation
Lifestyle-therapy
+
DPP-4-I
SU
PIO
AGI
Lifestyle-therapy + dual combination *
Initial monotherapy
MET +
DPP-4-I +
SU +
DPP-4-I
GLP-1-RA
Basal INS
PIO
AGI
SU
GLIN
SGLT-2
Basal INS
PIO
AGI
SU
SGLT-2
DPP-4-I
GLP-1-RA
Basal INS
PIO
AGI
SGLT-2
Lifestlye-therapy + triple combination **
One first-line medication (MET / DPP-4-I / SU)
+
One further medication from the dual combination either from the preferred (DPP-4-I / GLP-1RA /SH / GLIN / Basal Ins) or accepted group (PIO / AGI / SGLT-2)
+
one further medication
Lifestyle-therapy + Insulin

Figure: Algorithm for management of type 2 diabetes mellitus. Abbreviations: MET=metformin, DPP-4-I=dipeptidyl-peptidase-4-inhibitor, SU=sulphonylurea, PIO=pioglitazon, AGI=alpha-glukozidase-inhibitor, GLP-1-RA=GLP-1-receptor-agonist (includink all GLP-1 mimetics), INZ=insulin, SGLT2=sodium-glucose-cotransporter-2-inhibitor, GLIN=glinides (prandial glucose regulators).

When "acute" insulin treatment is not necessary, lifestyle modification and metformin treatment are recommended as first line therapy. The algorithm opens the door to lifestyle modifications alone as an initial therapy, and metformin is considered for use only when lifestyle interventions fail to control blood glucose (A1C is above target after 3 months).

When considering the favourable effects of metformin on cardiovascular- and cancer risk in diabetic population, early metformin therapy is usually preferable. When metformin intolerance or contraindication occurs, DPP-4-I, SU, AGI, or PIO can be used.

If pharmacological monotherapy proves to be insufficient within a relatively short period (3 month) combination therapy becomes necessary.

The recommended combination regimens are listed in Figure.

According to the currently recommended diabetes management guidelines, three-drug combination therapy is required in patients who do not reach their individualised glycemic target within about a 3-6 month period. Some drugs (such as metformin or acarbose) require a gradual up-titration which may last for weeks or months. In this case the lag period before adding other antihyperglycemic agent(s) can be extended.

The main goal of this intensive management approach is to avoid hyperglycaemic periods (A1C above target) lasting for years, which result in severe complications.

It should be noted that according to the changes in patients needs it is possible to raise or reduce drug doses, or even to use step-down therapy (discontinue one or two oral agents or even insulin after weight loss) or to replace antidiabetic agents if new indications or contraindications occur.

Many patients with long-standing-type 2 diabetes eventually require insulin therapy. All types of insulin (human as well as analogue insulin) can be used, such as bedtime insulin, a bi-daily regimen with premix insulin, or intensive insulin therapy (basal bolus regimen) etc. It is important that metformin should be continued unless it has not been become contraindicated. The recommendation to use metformin is based on its (previously mentioned) possible favourable effects on cardiovascular and cancer risk in diabetes. Furthermore, its role in reducing insulin resistance, which results in lower insulin dose requirements, is also beneficial.

Chapter 7.
Insulin treatment
Dr. István Wittmann

Insulin treatment is among the most impressive examples of individually tailored therapies. There are as many insulin regimens as there are patients! For this reason, knowledge of the pharmacodynamic characteristics of various types of insulin is of the utmost importance. Dosing and timing of insulin treatment is recommended according to these pharmacodymanic parameters.

Table: Pharmacodynamic parameters of insulins

Type of insulin	Time of onset (mins)	Time of max. effect (hours)	Duration of action (hours)
Human insulin			
Regular, short-acting human insulin	30	2	5-7
Intermediate (NPH) insulin	60-120	4-6	12-16
Rapid-acting analogues			
Insulin Aspart	10-20	1	2-5
Insulin Glulisine	10-20	1	2-5
Insulin Lispro	10-20	1	2-5
Long-acting analogues			
Insulin Detemir	60-120	-	20-30
Insulin Glargine	60-120	-	Max. 24
Premix insulins			
Human premix insulin	30-60	4-6	12-16
Analogue premix insulin	10-20	4-6	12-16

Data are for orientation. Onset, peaktime and duration depend on dose, site of administration, physical activity and temperature.

The use of most varied combinations is possible, although in many countries financial limitations hinder the use of some regimens. In other words, everything is possible, and this

optimizes the patient's glycemic control. Even so, there are some rules which can be relied upon. Table shows the most commonly used insulin regimens.

Table: The most commonly used insulin regimens

Name of the regimen	Description	Target population
Basal insulin supplemented oral treatment (BOT)	Non-insulin based treatment complemented by basal insulin therapy	Type 2 DM and any diabetic population (except type 1 DM)
Prandial insulin treatment	Short acting preprandial insulin therapy without basal insulin treatment	Type 2 DM and any diabetic population (except type 1 DM)
Intensified (intensive) conservative insulin therapy (ICT) or basal-bolus regimen	At least 3 preprandial insulin shots with at least 1 basal insulin shot.	Any diabetic population
Conventional insulin therapy	Premix insulin given BID (twice daily), mornings and evenings	Elderly, easy to control type 2 diabetic patients with regular lifestyle

Insulin management of Type 1 Diabetes mellitus (Intensive insulin treatment)

This is the treatment of choice in type 1 diabetic adult patients. It will only be truly effective if appropriate patient education precedes it and if regular glucose monitoring (see related chapter) and corresponding insulin dose adjustments are implemented by the patient. This regimen, in particular with the use of insulin analogues, is highly adaptable to individual lifestyles. The use of insulin analogues implies less risk of hypoglycemic episodes and euglycemia can therefore be achieved more easily. A motivated patient is essential to this regimen. Depending on the patient's daily activity, two different types of regimens are recommended. Figure illustrates the insulin regimen prescribed for patients who wake up and eat breakfast relatively late.

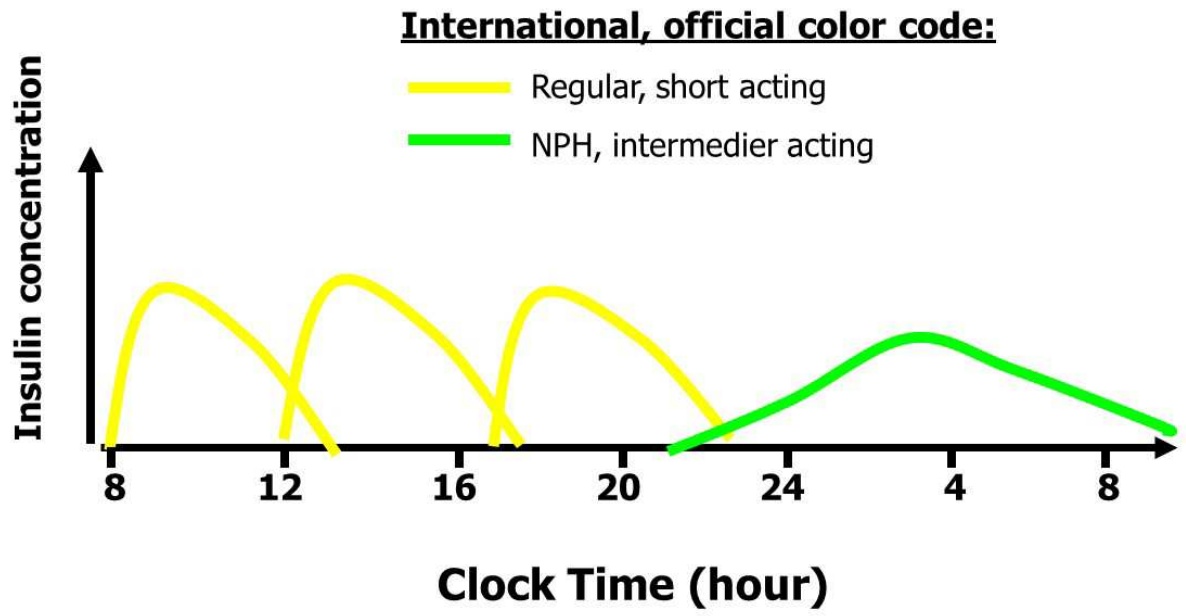

Figure: Human insulin regimen, recommended to patients who wake up later.

Figure shows one of the possible insulin regimens prescribed for patients who wake up, and eat breakfast early. Since prandial insulin before breakfast is given early, there is no appropriate overlap with the prandial insulin before lunch, thus intermediate insulin is also required in the morning. Another important difference is that because insulin treatment is started early, the evening's intermediate insulin requirements are modest. This regimen provides more freedom in the sense that lunch may be shifted within a certain time period.

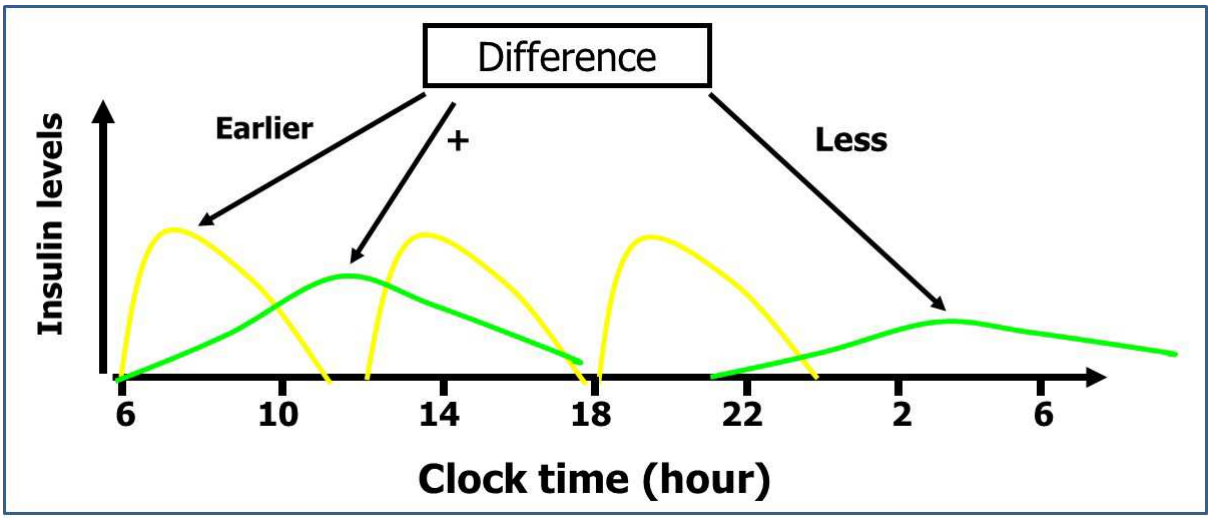

Figure: Human insulin regimen, recommended to patients who wake up early.

Human regular - short-acting (prandial) - insulin should be given 20 to 40 minutes prior to a meal, due to its relatively slow absorption. Intermediate (NPH) insulin can be administered

independently of meals although it is practical to give with the prandial one at least in the morning.

In human insulin regimens regular snacks at mid-morning, mid-afternoon, and usually mid-evening are necessary to prevent hypoglycaemic episodes.

Insulin regimens using rapid-acting analogues with intermediate insulin difficulty provide an appropriate basal insulin level; therefore use of a long-acting analogue (eg Detemir) will usually be desired. (Figure). The combination of intermediate insulin and rapid-acting insulin-analogue demands practically three times a day NPH administration (to maintain an adequate basal insulin level) which leads to interactions and hypoglycaemia, all of which has to be avoided.

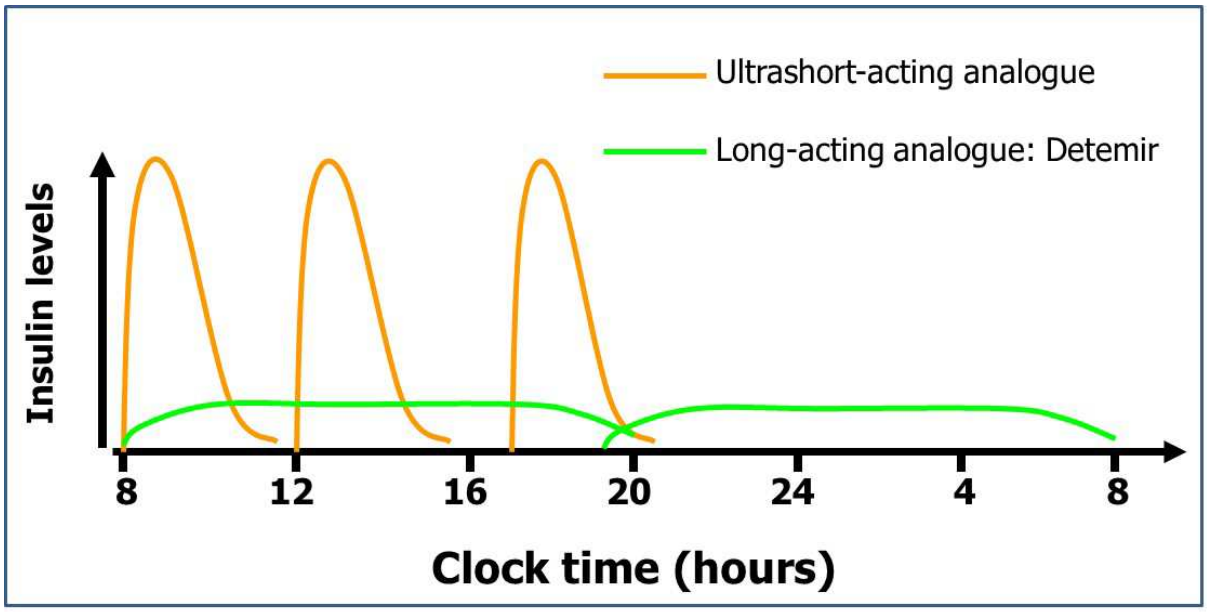

Figure: Rapid-acting and long-acting (Detemir) insulin analogue

Rapid-acting analogues can also be used in combination with long-acting analogue glargin (Figure). Glargin is administered once a day, but the timing varies from morning to bedtime according to the patient's needs.

A small dose of glargin is effective for a little under 24 hours, so the timing of its administration has to coincide with the duration of one of the rapid acting analogues to avoid basal insulin deficit prior to giving the glargin shots.

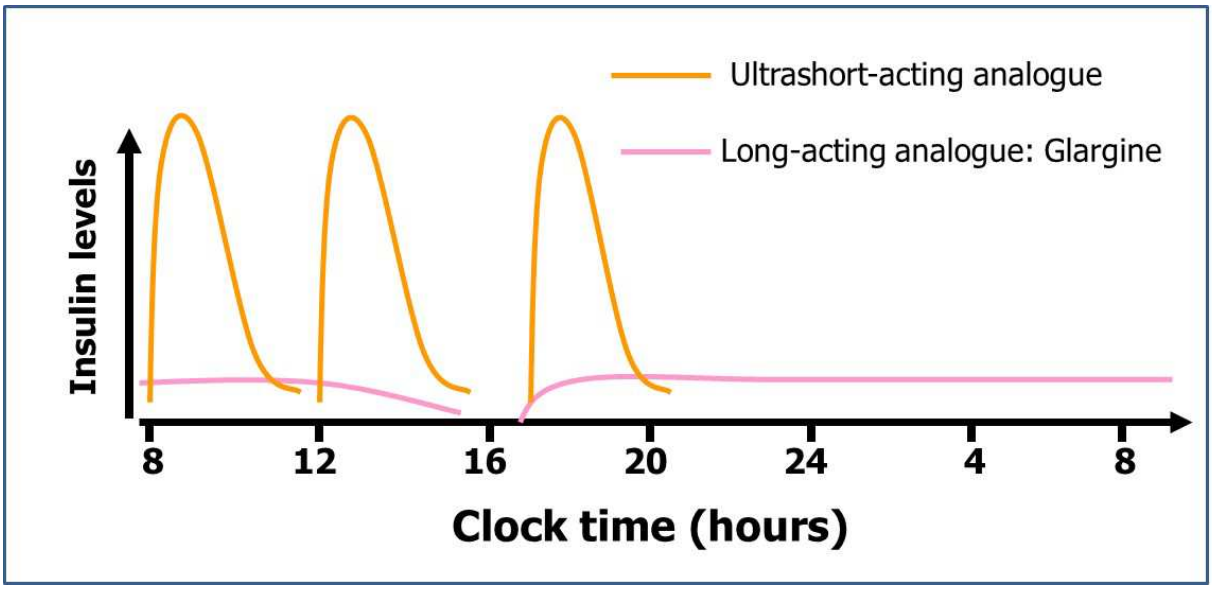

Figure: Rapid-acting insulin analogue in combination with glargin

If the preprandial blood sugar level is within the normal range, the rapid-acting analogue is given directly before meals. If the preprandial blood sugar is low, rapid-acting analogue have to be given either with or after meals. If the preprandial blood sugar is high, the patient has to wait 15 minutes after giving the rapid-acting insulin shot before starting to eat.

There is no need to have regular snacks in analogue insulin regimens. Whenever a patient insists upon these snacks, prandial low dose insulin analogue is recommended prior to snacks.

Insulin management of type 2 diabetes mellitus

The same insulin regimens can be administered as in type 1 diabetes mellitus.

Differences and special considerations are as follow:

1) When a newly diagnosed type 2 diabetic patient is in catabolic state, insulin treatment is obligatory.
2) A sustained asymptomatic period, possibly lasting for several years, can be achieved with temporary (over a period of a few weeks) use of aggressive insulin therapy at the disease onset of type 2 DM (so called “breakthrough”: see in Chapter 1. Introduction)
3) At initiation of BOT (Basal insulin supported oral therapy) the sulfonylurea dose has to be reduced in order to avoid hypoglycaemia.
4) BOT can only be temporary and insulin dosage in BOT must not be raised over 30-40 U/day. Prandial (bolus) insulin should be added to basal insulin whenever a larger dose is needed.

5) BOT is usually used for 3-4 years. It is not sufficient for maintaining adequate glycaemic control after that period.
6) In human ICT (Intensive Conservative Insulin Therapy) a single daily intermediate shot in the evening is usually sufficient, because endogenous insulin production is maintained at the early period of type 2 DM.
7) When detemir insulin is used in ICT, it is enough to be given once a day in the evening. In this case weight gain also usually decreases.
8) Metformin should be continued after the patient starts insulin therapy because it reduces cardiovascular- and cancer risk and is also associated with decreased weight gain and a lower insulin dosage.
9) The ideal dosage ratio between a rapid-acting (prandial) and long-acting insulin dose is approximately 50-50% in analogous regimens of type 2 diabetic patients
10) Analogue insulin treatment improves the quality of life and reduces the risk of hypoglycaemia.
11) PPT (Prandial Premix Insulin Therapy) might also be a therapeutic option when tight glycaemic control is aimed for, but for some reason ICT cannot be accomplished. In a PPT regimen a biphasic (premix) insulin analogue is given before breakfast, dinner and supper.

Chapter 8.
Insulin pump therapy
Dr. Gergő A. Molnár

With intensified insulin therapy, the insulin may be administered via a special insulin administering pen or via an insulin pump.

The insulin needs of our body can be divided into two larger parts. On the one hand one requires insulin to prevent blood glucose elevations resulting from meals, while on the other we also need insulin independent of meals, for instance to inhibit gluconeogenesis of the liver. The former is provided by bolus insulin, the latter by basal insulin.

The insulin pump system consists of several major parts: the pump itself, the subcutaneous inserted Teflon catheter and the infusion set connecting the two (Figure).

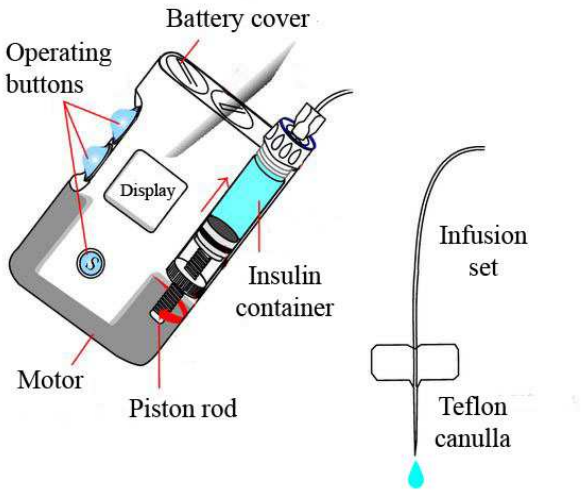

Figure: Shematic representation of the structure of the insulin pump. Modified after Valla et al, Experimental Diabetes Research (2010), Article ID 178372, 14 pages, doi:10.1155/2010/178372 (Copyright © 2010 Vasiliki Valla, Creative Commons Licence)

The insulin pump itself is a device that is able to provide continuous, slow infusion of insulin, in this way covering basal insulin need; it is also capable of administering the bolus insulin doses. For that, a rod driven by small electromotor pumps insulin out of the insulin-filled storage syringe inserted into the device.

Insertion devices may provide help in the setting of the canulla, by the help of which the needle can be inserted quickly and in a relative painless way. Upon filling and assembly of the system the most important thing is airtight sealing and avoidance of air bubbles.

The basal insulin is administered upon a pre-specified program, the setting enabling the speed of the pump to be altered every hour in 0.05-0.10 units/hour steps. Once the program is set, the device doses the basal insulin automatically, without external influence.

It is also possible to pre-program different basal profiles, e.g. for daytime and night-time shifts; for weekdays and weekends; for the period before or during menstruation or for days with and without exercise.

Moreover, it is also possible to change the basal rate temporarily, for couple of hours, e.g. to raise it transiently up by 100-120-130% or to decrease it to 90-80-70%... in cases of prolonged hypoglycaemia or for the periods of intense activity, such as sport.

The bolus doses have to be set by the patient upon the carbohydrates being consumed or prior to consumption, the time of the day, the type of meals etc. The pre-specified amount of bolus insulin is administered upon pressing a knob; that is, this also does not require a separate needle stitch.

The advantages of insulin pump therapy include the possibility of a very fine regulation of insulin doses, which has a special significance especially in cases where there is a very small insulin need, let's consider a small child with a daily insulin need of 10 units, which has to be divided into basal insulin and into bolus insulin administered alongside meals. This procedure can be carried out in a more even and a better regulable way. Besides that, because of the fine, hourly setting, the transient changes to the base amount, and the possibility of providing different basal profiles, the glucose excursions can be lowered more efficiently than with insulin administered via a pen.

Moreover, basal insulin administered by a pen will act even when it is not needed, so (e.g.) on occasions when unplanned physical activity takes place after the administration of a large dose of basal insulin even severe hypoglycaemia can develop. When using the pump, hypoglycaemia can be prevented by transiently decreasing or even stopping the administration of the basal insulin in such a case.

The insulin pump can also help in the prevention of the dawn phenomenon, meaning that high fasting blood glucose can be lowered.

A “carbohydrate-free day” can assist in setting the proper basal rate, as then the patient consumes only meals containing no or only a small amount of carbohydrates, and measures their blood glucose frequently (hourly - two hourly); using this technique the blood glucose-influencing effect of meals and bolus insulin can be ruled out, and we can really gain an hour-by-hour picture of whether and where the basal insulin rate should be increased or decreased.

The disadvantage of the therapy is that the patient is bound to a device, has to wear the pump constantly, and due to the nature of the device there is the chance of a technical failure.

Based on the abovementioned, it is obvious that the pump therapy is recommended mainly to diabetic patients who are well educated, is familiar with the disease, aware of carbohydrate counting, insulin kinetics, the signs and proper correction of hypoglycaemia etc. In cases of patients with bad glycaemic control and poor compliance the insulin pump would not provide a good result. Conversely, in cases where the patient has been carefully selected and in the presence of proper indications, the number of hypo- and hyperglycemias can decrease, and carbohydrate metabolism, e.g. the value of HbA_{1c} can be expected to decrease.

The current direction in insulin pump development is that the device should be able to communicate with a continuous glucose sensor and to dose insulin automatically upon the actual and previous glucose values, with minimal or no external influence. These devices, functioning in part on a negative feedback are called 'closed loop' insulin pumps. A “bionic pancreas” also exists, where two pumps can dose insulin and (to prevent hypoglycaemia) glucagon independently of each other. These devices are currently in the phase of clinical development.

Real indications of insulin therapy in type 1 diabetes in adults are:

- diabetes duration of at least 3 years
- a repeated HbA_{1c} value of >7.0%
- in cases of praeconceptional therapy >6.5%, or
- large glucose variability (>=10.0 mmol/l), or
- dawn phenomenon which can be verified (fasting morning glucose repeatedly >8.0 mmol/l), or
- min. 3 times/month clinically overt hypoglycaemia, or
- documented hypoglycaemia-unawareness, or
- severe hypoglycaemia (blood glucose <3.0 mmol/l) developing min. once in 6 months

The insulin pump therapy is not recommended:

- in cases of severe disability (problems at sensing, absence of basic hand skills, coagulation disorders etc.),
- in cases of psychic resistance: denial of diabetes, inability or rejection of self-monitoring,
- poor or insufficient compliance between patient and the treatment team,
- in cases of accompanying severe psychiatric disorders,
- instability of social support (family, friends), in cases of illiteracy.

Chapter 9.
Pancreas-kidney transplantation
Dr. Tibor Kovács

In type 1 diabetes the replacement of destroyed beta cells can be managed by the **transplantation of the entire pancreas** (I) or isolated beta islet cells (II.). Although the latter method is still rather at the experimental stage, its results are not particularly impressive. In type 2 diabetes, beta cell exhaustion and destruction are secondary processes, and so **pancreas transplantation is not an option in 2DM.** In obese type 1 diabetic patients, the efficacy of pancreas transplantation is also problematic due to insulin resistance (especially if the daily insulin requirement exceeds 60 IU).

I. **Entire pancreas transplants** (from cadaver donors) are today used in 3 different ways (distribution of operations in US are indicated):
   1. With type 1 diabetic patients with end-stage kidney failure, 75 % of pancreas transplants are implanted at the same time as cadaver renal transplants (**simultaneous pancreas kidney – SPK**). The advantage here is that both entities will be implanted in one surgery, and foreign HLA antigens are identical. The one-year graft survival is 86% and the 10-years graft survival is 54%.
   2. 15% of pancreas transplants are implanted into patients with a renal transplant (**pancreas after kidney - PAK**). *Disadvantage:* 2 surgery; where there is a stable graft function the immunosuppressive treatment must be reintensified and the organism has to encounter two different alien HLA antigens. This method may be important for patients with a living donated renal transplant. The one-year graft survival is 79% and the ten-years graft survival is 29%
   3. Pancreas transplantation into patients with a proper renal function: it is indicated by recurring life-threatening hypoglycaemic episodes and is applied in Brittle diabetes (**pancreas transplantation alone - PTA**) *Disadvantage:* requires immunosuppressive therapy. One-year graft survival of 80% and the 10-years graft survival is 27%.

Pancreas transplantation (PAK, PTA) is not yet available in Hungary for the latter two reasons.

Based on literature data, the survival rate of transplanted pancreases is highest in cases of simultaneous pancreas-kidney transplantation. In other countries, SPK is the most commonly carried out method of pancreas transplantation.

Benefits of pancreas-kidney transplantation performed in type 1 diabetic patients with chronic renal failure:

1. improvement to quality of life
2. termination of exogenous insulin therapy claims
3. normalization of carbohydrate metabolism, HbA_{1c}
4. dietary freedom
5. With late diabetic complications, stabilization or possible improvement, but established retinopathy /blindness or severe neuropathy are already irreversible processes. The progression of these alterations slows down or may stop.

In successful pancreas-kidney transplantations – due to the normalization of carbohydrate metabolism – the repeated development of diabetic nephropathy rarely occurs as compared to those who have only undergone kidney transplant. In the latter cases, diabetic nephropathy is expected to re-occur after 5-10 years after transplantation in the transplanted kidney. There are data about the cardioprotective role of the normoglycaemic state in patients with SPK. The decrease in the left ventricular mass and slowdown of coronary calcification are more significant in patients with SPK compared to that in diabetic patients with a kidney graft only.

A description of the surgical implantation of the pancreas exceeds the scope of this note, but it should not be ignored that the exocrine secretion of the transplanted organ can also be provided (flow of pancreatic juice into intestine).

The immunosuppressive treatment of patients with a pancreas graft is no different from patients who have undergone only kidney transplantation.

II. **Isolated pancreatic cell transplantation** could be beneficial in that it places a much smaller surgical strain on the patient and there is no need to provide the exocrine pancreatic function. The islet cells are isolated from the cadaver pancreas using special techniques for tissue digestion. The islet cells are infused into the recipients after the puncture of the portal vein transhepatically using the micro-invasive technique. Up to now the efficiency of this method has been poor, more than 90% of the patients treated in this way needing insulin therapy a year after the procedure.

Chapter 10.
Diabetes care and education
Dr. Gábor Fülöp

Since diabetes is a chronic disease which, if glycaemic state is uncontrolled, may lead to serious complications such as early disability and death, continuous medical care and education for individuals with diabetes is fundamental.

Regular care and therapy revision or modification is necessary in both type 1 and type 2 diabetes. Type 1 diabetes requires this either because intensive insulin therapy is used or because absolute insulin deficiency may lead to unstable glucose control, while in type 2 diabetes ongoing worsening blood glucose is anticipated due to the progressive nature of the disease. Individuals with diabetes need continuous and complex medical care. Between the medical visits continuous patient self management is required.

A chronic care model in diabetes as a complex process includes prevention, screening and diagnostic actions, classification, therapy, regular controls, education and rehabilitation.

There is a coordinated partnership between health care systems and patients in diabetes care, each having their rights and responsibilities. High-quality care is based on evidence-based clinical guidelines but it requires an individual adaptation to the patient.

The chronic care model includes 6 core components: (www.improvingchroniccare.org):

1. Delivery system design (moving to proactive care where planned visits are coordinated)
2. Self management support
3. Decision support
4. Clinical information systems
5. Community resources and policies (to support healthy lifestyle or smoking cessation programs)
6. Health systems (to create quality oriented culture)

There has been a steady improvement in the proportion of diabetic patients achieving recommended HbA_{1c}, blood pressure and LDL-cholesterol in the last 10 years.

The average HbA_{1c} was 7. 6% in 1999-2002 whereas it declined to 7. 2% in 2007-2010. (9).

However, 33-49% of diabetic patients do not meet target levels for HbA_{1c}, blood pressure or cholesterol and only 14% of them achieve all three targets and non-smoking status.

Diabetes self-management education (DSME) is an integral element of diabetes care since diabetes management is primarily accomplished by the patients (or their family members), and depends upon how their blood glucose is self-monitored, their meals, physical activity and living conditions under the guidance of heath care professionals. Patients with diabetes need regular education and practice to achieve and maintain this knowledge and related skills. Motivation of patients can be maintained or raised by achieving previously-set goals or by providing psychosocial support.

Basic education includes principles of lifestyle therapy (diet and physical activity), use of diabetic equipment and supplies (insulin pens, blood glucose monitors, insulin pump) and recognition, prevention and treatment of possible complications (especially hypoglycaemia).

Diabetes care is teamwork. Essentially, most patients with diabetes should be treated by the primary care physician and a specialist consultant is needed only in case of therapy modifications, complications, or other emerging problems. Patients with type 1 diabetes or type 2 diabetes with complications should rather be cared by specialist in collaboration with primary care physician.

A collaborative multidisciplinary integrated team may include a diabetologist and physicians from related specialities such as ophthalmology, angiology, vascular surgery, neurology, cardiology, and nephrology, in addition to nurses, physician assistants, dietitians, diabetes educators, mental health professionals, podiatrists and so on.

Recommendations for diabetes care and patient education are provided by the National Diabetes Education Study Group (www.betterdiabetescare.nih.gov), in the US and by the Diabetes Education Study Group (DESG) (www.desg.org) of EASD in Europe.

High-quality education (Diabetes self-management education, DSME) has been shown to improve patient self management, satisfaction and glucose control.

Taking the holistic view, the management of patients with diabetes includes not only glucose control but also the prevention and recognition of cardiovascular risk factors and other comorbid conditions.

Diabetes management concludes possible maintenance of adequate glucose control performed by proactive care. This can be achieved by regular monitoring, and it is recommended that HbA_{1C} is determined quarterly. Target goals should be defined individually, but within the ranges of 6-8%. Blood lipid controls are recommended yearly, although more frequent controls may be necessary in patients with dyslipidaemia or on atilipaemic treatment.

Patient Education

Education is the cornerstone of diabetes care and prevention for patients with diabetes as well as for health care professionals and even the population at large.

Unless adequate education is provided, patients with diabetes and their family members cannot cope with the burden of the disease and with the essential changes in life style.

Acquisition of the essential knowledge related to one's disease is the right and obligation of all individuals with diabetes.

Therapeutic patient education as an "added value" associated with patient education can be laid out as follows:

- As a result of ongoing education and study integrated in the health care system the patient will be able to manage his or her disease in an optimal way.
- The patient-oriented education approach includes screening of individuals with diabetes, provision of adequate information, learning of self-monitoring, psychosocial support, medical guidelines and organizing hospital and out-patient care. It also provides information about health-and-illness behaviour and outlines the possible prospects of rehabilitation.

Successful patient education requires ongoing self-instruction together with retraining from the instructors.

The most effective diabetes education is delivered either individually or in small groups.

Education which is matched to the patient's current knowledge and experience is interactive and involves both verbal and visual means (pictures, brochures, video films, even educational learning games - for instance, how to choose an appropriate diet). For further comprehension other written materials such as dietary booklets, brochures about foot care, diet- or hypoglycaemia diaries or web pages, prints and books can be recommended. Repetition and asking for confirmation ("loop technique) are fundamental in patient education.

An adequate adaptation of lifestyle interventions is an essential element of well controlled diabetes. Adequate lifestyle interventions include medical nutrition therapy and regular (in many cases also controlled) physical activity, which have to be coordinated with each other and also with diabetic pharmacotherapy. All this knowledge and accompanying skills have to be learned during the process of therapeutic patient education. Ideally, therapeutic patient education should be based on healthy literacy which has already begun to

be acquired at school. One of the important missions of the health care system is related to this: namely, to provide information and health education to a wide range of populations.

Chapter 11.
Self-monitoring of blood glucose, continuous glucose monitoring

Dr. Gergő A. Molnár

We also have to evaluate the efficacy of treatment of patients suffering from diabetes mellitus (DM). For that, there are a variety of options, for example laboratory tests such as the haemoglobin A_{1c} (HbA_{1c}) or fructosamine level, where the former provides information on average blood glucose levels of the last 3 months, the latter about the last 2 weeks. HbA_{1c} indicates glycation of haemoglobin of red blood cells, while fructosamine indicates glycation of plasma proteins (mainly albumin).

Each method requires blood drawing and a laboratory background, and has its own problems: the HbA_{1c} value is dependant both on the average blood glucose value and on e.g. the lifespan of the red blood cells, and thus may be influenced by anaemia, blood transfusion, or bone marrow disease. Similarly, in the case of fructosamine, the turnover time of plasma proteins may be a disturbing factor, and so the obtained value may underestimate the average blood glucose level in cases of marked proteinuria or hyperthyroidism.

The combined evaluation of HbA_{1c} and fructosamine may provide information on the temporal changes of blood glucose values, as we find out what the average blood glucose value was in the preceding 3 months, and within that period, in the last 2 weeks. A less elevated fructosamine besides a high HbA_{1c} may therefore indicate that the patient's recent glycaemic control was inferior to what it had been in the past. On the other hand, a high fructosamine value with an acceptable HbA_{1c} may signify that the patient has experienced worse glycaemic control in recent weeks or days, due perhaps to a current, severe infection.

When evaluating HbA_{1c} and fructosamine in combination, a discrepancy between the results may also draw our attention to the possibility that a confounding factor (e.g. anaemia, proteinuria, hyperthyroidism) should be sought.

A further problem with HbA_{1c} and fructosamine is that they only show the average blood glucose level, not the fluctuations. Thus, a patient with a completely properly controlled diabetes can have an HbA_{1c} value similar to that of a patient under bad control and experiencing both high blood glucose values and frequent hypoglycaemias.

The self-monitoring of blood glucose may have an important role in detecting blood glucose fluctuations. When taking the case history of a patient, whether in the outpatient unit or on the ward, one also has to establish if the patient has a glucometer at home, and if he

regularly controls his blood glucose values. If so, how frequently and at what times of day does he measure his blood sugar?

Multiple daily blood glucose measurement is also a useful tool in finding the right way to control a patient on multiple daily insulin injection therapy. In our practice, we usually suggest pairwise measurements, prior to and after meals, where the postprandial value is measured 1.5 hours after the meals; for this, target values are provided by guidelines. We usually also ask for daily profiles of six or more measurement points. For example, if the aim is to differentiate Somogyi effect from dawn phenomenon resulting from high morning fasting glucose values, night-time measurement is also suggested (depending on the time of administration of intermediate insulin, at midnight or at 3 a.m. Clinical studies have also verified that HbA_{1c} can change in a more beneficial way in patients who perform self-monitoring in combination with insulin dose adjustments.

Patients can keep the recorded values in the form of a glucose 'diary', but with many glucometers it is now possible to upload the values onto a computer or via a computer onto the internet, where we may obtain, besides tendencies, statistical evaluation (mean, standard deviation).

If we desire a more detailed daily glucose profile, there is also the possibility of continuous glucose monitoring (CGM). CGM systems usually comprise a sensor, a transmitting system and a monitoring device. Sensors may be minimally invasive, obtaining a signal from the interstitium, for instance via implantable glucose electrodes, using sensors based on microdialysis or microperfusion. A non-invasive measurement is enabled by sensors based on microporation, or transdermal or optical sensors.

As regards the transmission of the signal, besides wired devices, increasingly frequently today wireless devices are also available, and the miniaturisation of monitors enables devices to be directly connected to the sensor (mounted on the sensor).

The monitor is able to store the signals, and in some cases already converts them into glucose values. Some monitor systems are able to work in real-time mode, thus displaying actual values, graphs and trends to the patient. Another type of system does not provide results during monitoring, the information only being given to the patient and doctor after downloading the measurements onto a computer.

A major advantage of glucose monitors is that they show glucose fluctuations in a more sensitive way than do values obtained from the self-monitoring of blood glucose (SMBG, see Figure):

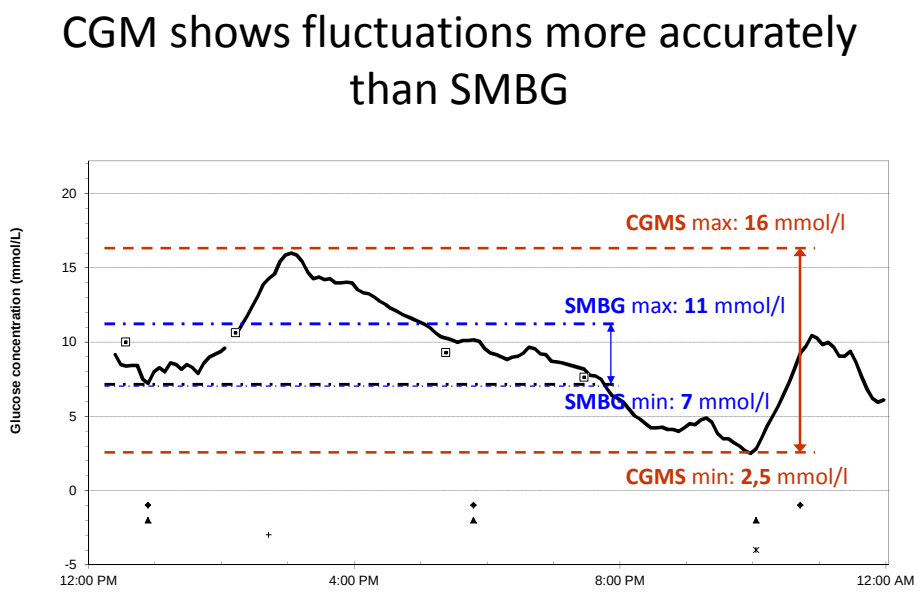

Figure: Blood glucose fluctuations on a continuous glucose monitor (CGM) and self-monitoring of blood glucose (SMBG). The small boxes represent SMBG values during monitoring, while the continuous line shows the result of the CGM. The dashed line (- - - - - - -) shows the range of CGM values, the dotted-dashed line (- · - · - · - · -) indicates the range of SMBG values.

Besides, they can provide an aid in detecting hypoglycaemias, mainly nocturnal hypoglycaemias, and in the detection of Somogyi effects. Besides that, they can be used as educational tools.

A further option is the use of sensory pumps, where the pump is able to communicate with the CGM sensor, thereby also working as a real-time CGM. Theoretically, this feature and the 'plain' real-time CGM systems could provide an aid in patient self-management; however, the price of CGM systems and sensors sets a limit to that.

Chapter 12.
Acute complications of diabetes mellitus and its management
Dr. István Wittmann

Hypoglycaemia and its treatment

Hypoglycaemia is characterised by abnormally low blood glucose concentration. The threshold glucose level is usually 3 mmol/l but the glucose level at which an individual becomes symptomatic is highly variable. Symptoms of hypoglycaemia can typically occur with a plasma glucose concentration of greater than 3 mmol/l, or can be absent with lower plasma glucose concentrations (especially after long-term diabetes and in diabetic neuropathy).

Hypoglycaemia can be mild, moderate or severe (if the patient requires assistance of another person). The symptoms and signs of hypoglycaemia are as follow (Table):

Table: Signs and symptoms of hypoglycemia

Autonomic	**Neuroglycopenic**	**General**
Sweating	Confusion	Nausea
Palpitations	Difficulty in speaking	Headache
Trembling	Dizziness Lack of coordination	
Hunger	Atypical behaviour	
	Vision changes	
	Perioral paraesthesia	

Causes of hypoglycaemia (common):

1) Insulin treatment
2) Oral antidiabetic agents:
    i) Sulphonylurea
    ii) Glinides (prandial glucose regulators)
    iii) Incretin therapy (seldom)
3) Advanced age (>75 years)
4) Alcohol
5) Kidney failure
6) Liver disease

7) Vigorous physical activity (without adjusting medications and diet)
8) Drug interactions (at the level of albumin binding and metabolism)
9) Drugs that mask symptoms and signs of hypoglycaemia and which inhibit counterregulation (e.g. beta blockers)
10) Inadequate diet
11) Lack of knowledge on the part of the patient (inappropriate patient education)

Mild and moderate hypoglycaemia can be treated by the patient. Ingestion of quick-acting carbohydrates (simple carbohydrates or 15-20 g glucose, either in liquid or in granulated form) is recommended, followed by the intake of long-acting complex carbohydrates. After 15 minutes, it is recommended that blood glucose is measured. If hypoglycaemia continues, the treatment should be repeated.

Hypoglycaemia may be extremely frightening to some patients with diabetes. These patients ingest glucose after the detection of the mildest hypoglycaemia, causing reactive hyperglycaemia. When the possibility of this reactive hyperglycaemia is not taken into account, the consequence may be an increase in insulin (or other antidiabetic) dosage and a "vicious circle" of hypoglycaemias and hyperglycemias may develop. Careful assessment of SMBG data is required in order to recognise and avoid this.

In severe hypoglycaemia, oral glucose intake has to be avoided due to the risk of aspiration. Intravenous glucose administration is required and hospitalisation may also be necessary. After relatively long-lasting hypoglycaemia, elderly patients may only regain their consciousness slowly, even with administration i.v. glucose infusion, thus frequent blood sugar measurements are required.

Glucagon should be prescribed for patients with type 1 diabetes and family members of these individuals should be instructed on its administration.

If hypoglycaemia is caused by sulfonylurea, especially in patients with renal impairment, prolonged or recurrent hypoglycaemia can be expected and so at least 48-72 hours of observation/hospitalisation and ongoing glucose infusion may be required. This scenario usually occurs in elderly patients treated with sulfonylurea and suffering from acute prerenal kidney injury and thus GFR decline due to intercurrent infections (diarrhoea, fever e.t.c) and/or inadequate fluid intake.

It is important to remember that a relatively significant number of hypoglycaemias, especially the nocturnal ones, remain asymptomatic and thus unrecognised. Another important point is that the recurrence rate is high after a severe hypoglycaemia, hence patients

may benefit from more permissive glycemic targets for a few weeks. Hypoglycemia in patients on alfa-glucosidase inhibitor therapy can be treated only with glucose, since this type of treatment inhibits degradation of di- and polysaccharides.

Diabetic ketoacidosis (DKA), and Hyperosmolar Hyperglycemic State (HHS) and their treatment

DKA happens predominantly in patients with type 1 diabetes. It may occur in milder form combined with hyperosmolar hyperglycaemic state in patients with type 2 diabetes, especially after long-lasting diabetes when endogen insulin secretion is significantly decreased. The clinical picture of both acute metabolic complications is dominated by dehydration and complicated by ion disturbances. Complaints and signs of patients are polyuria, polydipsia hypotension, tachycardia, prerenal acut kidney injury, muscle cramps and abnormal mental status. Signs and symptoms of possible underlying intercurrent infection or thromboembolic complications are also common. Patients with DKA often develop Kussmaul's breathing, and abdominal pain can also occur.

Both of these metabolic derangements are serious, life threatening conditions requiring hospitalisation.

The most common precipitating factors are as follows:

1) Infections
2) Cardiovascular events
    i) Myocardial infarction
    ii) Stroke
3) Gastrointestinal diseases
    i) Vomiting
    ii) Diarrhoea
4) Iatrogen factors, Drugs
    i) Diuretic abuse
    ii) Corticosteroids
5) Poor- or non-compliance on the part of the patient
    i) Inadequate diet
    ii) Discontinuation of or inadequate insulin /oral antidiabetic therapy

Basic laboratory studies and imaging tests for diagnostic workup also dealing with the detection of possible precipitating factors are as follows (not uncommonly more diagnostic tests are required):

1) Serum glucose levels
2) Arterial blood gas analysis (ABG)
3) CBC count
4) Urinanalysis (Urine dipstick)
5) BUN and creatinine levels
6) Serum electrolyte levels
7) ECG
8) Chest radiography
9) Microbiological cultures

To make a diagnosis accurate, the customary history taking and physical examination as well as correct evaluation of laboratory and imaging studies are required.
Table shows the differences between diabetic ketoacidosis and hyerglycaemic hyperosmolar state.

Table: Laboratory features of diabetic ketoacidosis (DKA) and hyperglycaemic hyperosmolar state (HHS).

	DKA	**HHS**
Glucose (mmol/l)	> 13,9	>> 33,3
Urine ketone	+++	-/+
pH	< 7,3	> 7,3
Serum bicarbonate (mmol/l)	< 10	> 15
Effective serum osmolality (mosmol/kg)	Variable	> 320

Treatment of DKA and HHS

Because of the dehydration, intravenous fluid replacement is indicated as first line therapy. 1-1.5 l isotonic saline solution (0.9% NaCl) or Ringer solution is infused during the first hour. The former is given when hyperkalaemia is present or when the result of serum potassium is pending, otherwise Ringer is recommended, except in the rare cases when serious hypovolaemic shock requires a plasma expander.

Intravenous treatment should be continued until the hyperglycaemic crisis is resolved and the patient's condition stabilises.

In severe mental status alteration or coma airway management, intravenous access, bladder catheterisation, initiation of antibiotic and antithrombotic medications are required; and admission to an intensive care unit is necessary.

Insulin therapy should be initiated after the first hour of treatment because early insulin administration may be associated with hypoglycaemia after circulation is restored due to the sudden rise in the insulin level. The insulin infusion dose has to be adjusted to the actual blood glucose level. It is usually recommended that an insulin pump be used (at a rate of 0.1 U/kg/h), but a mixture of short–acting insulin and isotonic sodium chloride solution mixture can also be used.

In DKA, blood glucose concentration should be maintained between 8-11 mmol/l, although it has been recommended by some that a higher level up to 14 mmol/l may also be reasonable as "ketone bodies burn in the fire of carbohydrates".

Intravenous insulin treatment is typically associated with a decrease in potassium concentration, thus potassium should be rigorously monitored and replaced if necessary.

A successful treatment requires correction of electrolyte imbalances along with rehydration therapy. Potassium correction has to be initiated in the first hour of the treatment, followed by management of magnesium and phosphate disturbances.

The following laboratory parameters should be monitored every 2-4 hours, depending on the patient's condition and the severity of laboratory disturbance.

1) Serum elecrolytes (Na^+, K^+)
2) Serum glucose
3) Arterial blood gas analysis (ABG)
4) Urine ketone
5) Serum creatinine

Bicarbonate is only infused if severe, life-threatening acidosis, where pH<7.0, is present; and after initiated it is only indicated until the pH is 7.0-7.1. Bicarbonate treatment has been correlated with cerebral edema; thus, if the pH is 7.0 or higher, no bicarbonate therapy is recommended. During bicarbonate infusion strict potassium control is required because bicarbonate administration leads to hypokalaemia.

Following the resolution to the hyperglycemic crisis and successful elimination of the predisposing factor (such as infection), transition to previous antidiabetic therapy can be initiated with an overlap of 4-8 hours of parenteral therapy.

Chapter 13.
Cardiovascular complications in diabetes mellitus

Dr. Gergő A. Molnár

Diabetes mellitus (DM) is a population disease, which exerts a heavy financial load on developed societies, not only directly through treatment of the disease itself, but also through treatment of its complications. Of the latter, cardiovascular (CV) diseases are of special importance. While a couple of decades ago, diabetes-related death was mainly in connection with acute complications, nowadays it is rather related to long-term macrovascular (mainly CV) and microvascular complications and malignancies. In DM, on the one hand diabetes itself, while on the other hand, other accompanying factors (e.g. hypertension, dyslipidaemia, obesity, renal failure) represent a risk factor for the development of CV diseases. In diabetes, the function and/or structure of the blood vessel wall can be damaged among other ways via hyperglycaemia, the polyol pathway, advanced glycation end-products, inflammatory cytokines and free radicals.

In characterizing diabetes we frequently regard the CV-risk as a high risk, as if the patient had already suffered a myocardial infarct. Accordingly, the CV-risk of patients with diabetes is approx. 2-4 times as high as in the non-diabetic population.

The effect of the treatment of diabetes mellitus on CV risk in general

On planning the therapy of a patient, one has to consider differences between patients with type 1 and type 2 diabetes mellitus. Other risk factors, found in type 2 diabetes mellitus and accompanying the disease, also have to be taken into consideration. We believe that glycaemic control is of fundamental importance; however, its significance is different in type 1 or type 2 diabetes. Based on data from the literature on large studies, such as the DCCT trial, a milestone study dealing with type 1 diabetic patients, in the original observation period of 10 years, the reduction of macrovascular risk was not significant, although during the extension of the study to a further 20 years of follow-up, the DCCT-EDIC trial showed a clear advantage of prior intensive treatment with regard to CV risk. It also raised the possibility of a 'metabolic memory'. This would mean that prolonged good or bad glycaemic control may have an impact on CV risk even years later, i.e. the body 'remembers' its state of 10 years earlier.

In patients with type 2 diabetes, in the 15 years of observation in the classical UKPDS study, with regard to macrovascular endpoints no overall significant difference could be

observed between patients treated in an intensive and in a non-intensive manner, although tendencies seemed to favour intensive therapy. The extended, 25-year follow-up of the UKPDS has however shown a significantly better survival rate regarding macrovascular complications with the original intensive treatment. Based on that, we believe that glycaemic control is important in decreasing CV risk.

Several large studies over recent years have raised the possibility that too tight a glycaemic control may lead not to a decrease, but rather an increase in CV risk, mainly in elder patients. Taking this into consideration, today we do not recommend a uniform HbA_{1c} target value, but rather a target range tailored individually to age and accompanying diseases for the treatment.

We believe that complex therapy of the patients is important, i.e. lifestyle changes, application of glycaemic control and treatment of other accompanying risk factors.

„Silent ischemia”

We should not forget about a special characteristic of patients suffering from diabetes and coronary heart disease (CHD), namely the 'silent ischemia', where patients may not be aware of pain related to ischemia as a consequence of neuropathy. Because of that, screening of high risk, asymptomatic patients may be important above the age of 50 or in the presence of other risk factors. A part of the assessment of cardiovascular risk is blood pressure measurement on each visit by the patient, added to which an ECG, lipid-control measurement of the ankle-brachial index should be performed at least annually.

Types of antidiabetics and cardiovascular risk

Besides the target range of antidiabetic treatment, the choice of antidiabetic type to be used also influences CV risk. Let us observe that in greater detail:

Sulphonylureas

When antidiabetics, i.e. sulphonylureas, are used for the longest time one important consideration is pancreas selectivity, as sulphonylurea receptors can be found not only in beta-cells of the pancreas, but also on cardiomyocytes and cells of the blood vessel walls. For this reason, non-cardioselective sulphonylureas may for instance worsen ischemic preconditioning, thereby increasing the likelihood of mortality. They may moreover also worsen CV risk via hypoglycaemia-triggered arrythmias. Therefore, on a theoretical basis it is important that we should choose a cardioselective sulphonylurea that leads to less

hypoglycaemia, and which has a more stable effect. Upon meta-analysis, sulphonylureas have been associated with higher CV risk as compared to metformin, the only exception being gliclazide in patients with a previous CV-event, as well as in patients without a prior CV event. Taking the abovementioned into consideration, a differentiated sulphonylurea therapy is preferable where medication is selected on the basis of its favourable and non-favourable properties.

Metformin

In the extension of UKPDS, metformin has been more efficacious than conventional therapy as regards CV risk. The results of meta-analyses are not entirely consistent: the data from many studies have shown metformin to be more effective than other antidiabetics, but a smaller portion of the studies has been unable verify this (although disadvantageous effects could not be observed here, either).

Acarbose

In a study carried out using acarbose, the use of acarbose has led to significantly lower CV risk than placebo, however, due to the small number of CVevents, the result is of restricted value. The result of one meta-analysis indicated that acarbose was CV-protective; here the statistical power was already appropriate.

Thiazolidine-diones (glitazones)

The CV safety of antidiabetics is of especial interest, since in 2007, according to the data from a meta-analysis, the long marketed rosiglitazon was shown to increase CV risk. The meta-analysis was highly criticized by many; however, precisely because of this potential CV risk, the marketing of the substance was limited in many countries, while in others its use was temporarily cancelled. As a result, drug authorities have set tight CV safety criteria. However, data concerning rosiglitazone are not unambiguous; and so we do not consider its use as safe. According to several studies, pioglitazon is safer than rosiglitazon, something underlined by prospective double-blind studies, as well as by meta-analyses.

Glinides (postprandial glucose regulators)

According to studies and retrospective analyses, this group of medications can be regarded as neutral from the aspect of CV.

DPP-4 inhibitors

Results of for the most part retrospective analyses of non-CV-endpoint designed, efficacy studies now suggest a CV safety regarding both the group and the individual substances. In the study carried out using saxagliptin, saxagliptin turned out to be neutral in general; however, it increased the risk of heart failure. The study carried out using alogliptin provided a neutral result. We await new results of these agents and also results of CV-targeted studies from other agents from this group. Sitagliptin proved to be CV-neutral.

GLP-1-receptor agonists

For GLP-1 receptor agonists, results of both retrospective analyses and retrospective meta-analyses of non-cardiovascular designed studies are available, based upon which this group can be regarded as cardiovascularly safe. Results of prospective, targeted CV studies are also awaited for this group.

SGLT-2 inhibitors (gliflozins)

Few data are also available regarding gliflozins, as they have only been marketed and appearing in clinical studies for a short time. Given the CV safety data needed for their approval, these agents can be regarded as safe overall from the CV aspect, and they have not led to any statistically significant increase in risk of individual complications. Moreover, empagliflozin decreased the risk for CV-death.

Insulin

In a Swedish registry study related to insulin, insulin – mainly in combination with sulphonylureas – led to an increase in CV risk that could be attenuated by the addition of metformin. According to a Danish meta-analysis, in the comparison of insulin monotherapy vs. insulin + metformin, a non-significant increase in CV-risk was found; however, the statistical value of this study can be strongly called into questiondue to the low number (2 vs. 4) of events.

In conclusion, we can say that correct glycemic control is protective, but overtight metabolic control may be risky, especially in the case of patients of higher age and established vascular disease. For this reason, a target range, and within that an individual target value based on age and co-morbidities is recommended. Of the antidiabetics, metformin and empagliflozin can be regarded as safe from a CV point of view, and may be beneficial not only in lowering insulin-relaetd increased risk of malignancies, but also in lowering potential

insulin-related CV risk. Therefore, in type 2 diabetes mellitus – unless contraindicated because of accompanying diseases – we may recommend the furthre use of metformin in combination with insulin therapy. The sulphonylureas are not beneficial from the aspect of CV, and a differentiated use may be suggested. Acarbose seems to be cardiovascularly protective from the CV point of view. Of the thiazolidine-diones, the CV safety factor of roziglitazon is at the least questionable, while pioglitazon seems to be CV-safe. The data on glinides show that they can be administered safely. According to data related to DPP-4 inhibitors, GLP-1-receptor agonists and SGLT-2 inhibitors, no CV-risk has been demonstrated, thus they may be regarded as safe.

Chapter 14.
Cardiological issues in diabetes
Dr. Attila Cziráki

Type 2 diabetes is a metabolic disease of civilisation which develops insidiously over the years and is associated with several cardiovascular complications.

The term “cardiometabolic syndrome” is often used in medical literature to refer to the mutual pathophysiological nature of two diseases, such as endothelial dysfunction, vascular remodelling, oxidative stress and vascular inflammation.

Diabetes Mellitus and Coronary Artery Disease Patients with diabetes are 2-5 times more likely to experience myocardial infarction moreover mortality rate is higher after acute coronary syndrome and infarction. Symptoms of angina and angina equivalents like dyspnoea have to be carefully searched for in diabetic patients. Pain sensation is often impaired due to autonomic neuropathy which results in silent or painless angina.

ST and T alterations may not be detected on a standard 12-lead ECG, and so it is necessary to use 24-hour ECG recording (Holter) and/or ambulatory ECG monitoring with an event-loop recording (ELR) device over several weeks.

To detect myocardial ischemia, stress tests have to be performed in good time. The Bruce protocol treadmill exercise test, dipyridamole and dobutamine echocardiography (stress echocardiography), and isotope myocardial perfusion scintigraphy (SPECT) are the tests of choice.

The combined use of SPECT and PET examinations could represent a major advancement in detecting the presence of cardiovascular autonomic neuropathy.

CT coronary angiography or coronarography demonstrates diffuse coronary artery disease (significant stenosis of more than one, and usually all three coronaries) and the serious involvement of small vessels, all characteristic of epicardial vessel alterations of diabetic patients

Therapeutic options and success rates of percutaneous transluminal coronary angioplasty (PTCA) or coronary bypass procedures (CABG) might be diminished due to such alternatives.

When stenting has been decided upon, drug eluting stents (DES) are usually recommended. In a complex three-vessel disease CABG is the treatment of choice. Medical therapy after revascularisation does not differ from therapeutic options used in the non-diabetic population.

Diabetes and Heart Failure According to the Framingham Heart Study, type 2 diabetes is a major and independent risk factor in heart failure. There is a significant increase in patients above 60 years of age. Some studies have found left ventricular systolic dysfunction in 26% and diastolic relaxation disturbances in 25% of this population, respectively.

2 D echocardiography can help detect left ventricular dilatation or regional wall motion abnormalities also associated with normal cavity sizes in the majority of diabetic patients.

Doppler echocardiography allows identification of diastolic dysfunction, which is usually isolated, indicating a functional disturbance caused by a metabolic disorder. (Evaluation of Mitral Inflow signal)

The Echocardiographic patterns of diabetic myocardial disease also supported by histological abnormalities (diabetic cardiomyopathy) are as follows: Diastolic (relaxation or compliance-abnormalities decreased coronary reserve) and systolic (wall motion abnormalities, abnormal circumferential fibre shortening, decreased ejection fraction) dysfunctions not associated with other conditions.

Currently tissue Doppler imaging (TDI) echocardiography allows us to detect the condition of the differently oriented left ventricular myocardial fibres

In this patient population severe left ventricular asynchrony is common, and treated with a specialized type of pacemaker therapy (cardiac resynchronization therapy, CRT) in addition to medical therapy (RAS inhibitors, beta receptor blockers, mineralocorticoid antagonists).

Diabetes and Cardiac Arrhythmias Reduced heart-rate variability associated with a significant rise in cardiovascular risk is well known in diabetes mellitus.

The electrical activity and conduction pathways of the heart are often damaged, leading to supraventricular arrhythmias. Atrial fibrillation occurs in about 13% of diabetic patients, which along with the previously described structural alterations results in a significantly high risk of a stroke. For this reason it is of major importance that arrhythmias are detected and treated in this patient population. Invasive electrophysiological studies, catheter ablation therapy of rhythm disturbances and pacemaker implantations are commonly used procedures.

Diabetes and Sudden Death Sudden death is the most common death cause in diabetes mellitus. Predisposing factors are as follows: microvascular disease, autonomic neuropathy, myocardial fibrosis, serious plasma glucose fluctuations and ion disturbances. Arrhythmias must be detected using 24-hour Holter recording or ambulatory ECG monitoring with an event-loop recording (ELR). When antiarrhythmic drugs are proven to be unsuccessful, implantable cardioverter defibrillator (ICD) therapy is indicated.

Chapter 15.
Diabetic neuropathy
Dr. Richard Halmai

Neuropathy is one of the microvascular late complications of diabetes mellitus or impaired glucose tolerance (IGT). Diabetic neuropathy represents either a functional or a structural impairment of the peripherial and/or autonomic nerve system, pathophysiologic processes are both demyelination and axon injury.

In the patomechanism there are two main processes: first the not well-controlled carbohydrate status leads to hyperglycemia, which provokes metabolic changes – first of all oxidative stress –, that directly harm the nerves, on the other hand the injury of the „vasa nervorum" i.e. the microvasculature of the nerves – which is practically the own blood supply of the nerves – causes an indirect nerve injury. The most important link between these two components is probably the endothelial dysfunction.

There are also other factors that significantly contribute to the initiation and progression of neuropathy: smoking, nephropathy, components of the metabolic syndrome, e.g. obesity, pathologic lipid metabolism and arterial hypertension.

On the basis of epidemiological studies the prevalence of neuropathy is app. 10-50%, the different types of diabetes and the different manifestations of neuropathies influence mainly the statistics.

In diabetes either the symmetric or asymmetric injury of the autonomic-, sensory-, or motor nerves can occur, and the beginning is either slow or rapid, furthermore it can be both painful but also painless. The different types of neuropathy are summarized in a separate table.

Table: Types of diabetic neuropathy

autonomic neuropathy (AN)	**sensory neuropathy**	**motor neuropathy**	**less common types of neuropathy**
1.cardiovascular AN	„positive symptoms"	muscle atrophy, muscle weakness	acute painful neuropathy
2.orthostatic hypotension	„negative symptoms"	hammer toe; clumsiness of the hands	mononeuropathy; mononeuropathy multiplex
3.hypoglycemia unawareness		uncertain walk, mobility-impairment	diabetic amyotrophy
4.erectile dysfunction			radiculopathy
5.gastrointestinal AN			
6.urinary retention			
7.sudomotor dysfunction			

Types of autonomic neuropathy

Autonomic neuropathy (AN) affect the most organs and it leads to the most various and partly also to the most severe complications.

First the parasympathic then the sympathic nerves are damaged, the former is responsible for the *tachycardia at rest,* which augments the risk of *atrial fibrillation* and that of cardiovascular events. The damage of the innervation of the heart can lead to *diastolic and systolic left ventricular dysfunction*, to *left ventricular hypertrophy*, to *long QT-syndrome*, to *diminished heart rate variability,* to *malignant arrhytmias*, to the so called *silent angina*, and to *silent myocardial infarction,* or also to *sudden cardiac death*.

With the pathologic innervation of the vessels the normal daily rhythm of blood pressure disappears (so called *non-dipper profile*), because of damage of the sympathic nerve system an *orthostatic hypotension will develop*, but in a lying position and by effort a pathologic *hypertension* can emerge.

Due to AN a *hypoglycemia unawareness* and a reduced counter regulation to hypoglycemia can develop, which can lead to *more frequent* and *more severe hypoglycemia*.

E*rectile dysfunction* is a type of AN. It causes a sexual dysfunction, furthermore it is also a prognostic factor of macrovascular complications, like myocardial infarction. Erectile dysfunction raises *per se* the risk of cardiovascular mortality, and worsens also the depression of these patients with chronic metabolic disease.

All parts of the gastrointestinal tract can be involved in neuropathy: esophageal dysmotility and dysfunction of the esophageal sphincter muscle lead to *gastroesophageal reflux*; „gastroparesis diabeticorum" causes *rapid bloatedness after meals, nausea, vomiting* and the prolonged absorption of carbohydrates can be partly responsible for the *frequent hypoglycemias*; the modified motor and secretory function of the gastrointestinal system can lead to *obstipation* or *diarrhoea and even to fecal incontinence*.

The diminished motility and contraction of the gall bladder favours the formation of *gall stones.* Disturbances in the innervation of the urinary bladder will lead to enlargement of the bladder, less frequent emptying of the bladder, later on also to „ischuria paradoxa", and also because of the later developed residuum in the urinary bladder *more frequent urinary tract infections* will be present. *Nota bene* the inflammatory sign-, and symptom-unawareness – because of AN – will increase the possibility of the development of more severe infections even the occurrence of sepsis.

The damage of the sympathic innervation of the sweat glands begins *on the foot*, through the lack of fluid the *skin will be dry* and also *fissures* will emerge. In contrast, *on the upper body* a *compensatory hyperhydrosis*, i.e. unpleasing overperspiration will develop.

Sensory and motor neuropathy and less common types of neuropathy

The sensory polyneuropathy leads to the so called classic symptoms of diabetic neuropathy. On the one hand pathological sensations develop (*„positive symptoms"*): because of the longer nerve fibers, *first* the *distal parts of the lower extremities* are *symmetrical in „stocking-glove" pattern* affected. Mainly during the night, at rest suffers the patient of paresthesia (*tingling, crawling*).

„Allodynia" means, that a typically painless stimulus (e.g. contact with the blanket) provokes a *burning, keen, or cramping pain*.

On the other hand, the loss of certain sensation properties, like: touch, proprioception, cold-, or warm sensation, sensation of vibration or pain will be summarized as *„negative symptoms"*: therefore the *patient will not feel the ground* properly, consequently *pathologic pressure points and callosities will develop on the sole of the foot*. *Perception of traumatic injuries will fail, painless ulcera* develop, the *walk will be uncertain* and the *risk of fall will rise*.

On the lower extremities - because of the inequal innervation - the motor neuropathy leads to dominance of the flexor muscles, and e.g. a *hammer toe* can develop. The *muscle atrophy* and the *diminished reflexes* cause *deformity of the foot*, *disturbed walk* and in more severe cases even *mobility-impairment*. The atrophy of the smalle muscles of the hand can also end in *clumsiness of the hands*. The classic types of the sensory and autonomic neuropathy are progressive, they develop slowly during many years, on both extremities and in both gender equally, and the progression depends on the (failure of the) control of the carbohydrate state. In most of cases other late complications of diabetes are also present.

The *less common types of neuropathy* are rather *for men typical*, they *can develop acutely, and also earlier already at the beginning of the „diabetes career"*. Typically there is *no connection between the degree of severity of neuropathy and the (success of) control of the carbohydrate state*, and these types *react* in general *better to the adequate therapies*. The sudden beginning of the „positive symptoms" of the upper detailed classical sensory neuropathy is typical for the *acute painful neuropathy*. *Mononeuropathy and mononeuropathy multiplex* mean the painful damage of one or more – of each other far apart localized – peripherial or cranial nerves. In case of *diabetic amyotrophy* components of the motor

neuropathy can be seen: muscle atrophy, pain, muscle twitching or even cachexia. *Radiculopathy* refers to a one-sided segmental pain, typically by older patients, besides peripheral neuropathy is also present.

Internal diagnostic procedure of diabetic neuropathy

The diagnosis of neuropathy will be confirmed with the help of *patient's history*, *physical examination* and by autonomic and sensory forms partly also *with instrumental examinations*.

For the screening of **AN** there are two simple test available: on the one hand *neuropad* (a blue teststrip wich contains cobalt, that will be placed on the plantar surface and the sweat will change the colour to pink if the sudomotor function is normal), on the other hand the presence of the *respiratory arrhythmia* (with naked eye clearly visible change *on the ECG* during a deep inspiration) make a severe AN unlikely. The *Ewing-tests, as the cardiovascular reflex tests,* give numerical results of parasympathic and sympathic neuropathies by the registration of changes in heart frequency and blood pressure due to different stimuli (respiration maneuvers, change in body position, stretch of the hand muscles), therefore these are suitable also for the follow-up of the therapeutic success. The latter investigations are not informative or contraindicated if arrhytmias (atrial fibrillation, frequent extrasystoles), uncontrolled hypertension, acute respiratory-, or heart failure, or even severe retinopathy are present.

The *Rydel-Seiffer graduated tuning fork* and the *Semmes-Weinstein monofilment* are suitable for the screening of the **sensory neuropathy**. By the former investigation the vibration sensation of the nerve fibers will be tested: the striked tuning fork is placed on the end of the big toe, on the inner ancle and on the extensor surface of the tarsometatarsal joint of the second toe; vibration sensation $\leq 5/8$ means a clearly pathological sensation. With the help of the Semmes-Weinstin monofilament the protection-sensation is tested: the curved monofilament – which gives a constant pressure – is placed on different points of the sole and the patient gives a sign if he perceives the pressure. The invasive and the electrophysiologic investigations are performed by the neurologists.

Differential diagnosis of diabetic neuropathy

Neuropathy can originate from many causes: most of the causes are parts of the internal medicine, other diseases, toxic harms, etc. The most frequent causes are listed in.

Table: Most frequent causes of neuropathy

Internal medicine	Other causes
diabetes mellitus	chronic alcohol consume
hyper-/hypothyreoidism	paraneoplastic syndrome
chronic alcoholic and non-alcoholic (e.g.: chronic hepatitis C virus infection) liver diseases	intoxications – heavy metals; carbone monoxide; medications e.g.: sulfonamid, metronidazol, gentamycin, etc.
chronic kidney disease, uraemia	infections (e.g.: lyme-disease, HIV, varicella zoster, sepsis, etc.)
hematological diseases, porphyria	direct harm of the peripheral nerves (e.g.: tuberculosis)
chronic inflammatory bowel diseases, malabsorption – vitamin B deficiency / folic acid deficiency	allergies (e.g.: after tetanus vaccination, medicines, etc.)
systemic autoimmune diseases (e.g.: SLE, vasculitis)	genetic causes

In Hungary the most frequent cause of polyneuropathy is definitely diabetes mellitus. The painful form of neuropathy has to be differentiated first of all from the *obliterative peripheral arterial disease* – e.g. from a macroangiopathic complication of diabetes. For diabetic neuropathy the following features are typical: pain at rest, disturbed sensation, diminished tendon reflex, warm and dry foot with trophic disorders on the pressure points, well palpable pulse and positive tests for sensory/motor/sudomotor dysfunction. In contrast, in case of macroangiopathy: the foot is cold, the pulse is not palpable, the pain becomes worse during walking, the neuropathic test results are negative, and necrosis develops rather on the top of the toes/fingers. Neuropathy and obliterative peripheral arterial disease are often parallel present, therefore it is no surprise that also in our homeland the *diabetic foot* is the most frequent cause of the non-traumatic amputations.

Therapy of the diabetic neuropathy

In the therapeutic plan of all types of diabetic neuropathy the following **primary aspects** have to be considered: **well controlled carbohydrate metabolism,** and the **therapy of other factors, that have a main influence on the progression**.

Both by **AN** and also by **sensomotor neuropathy** the *non-pharmacological therapy* is of great importance: by orthostatic hypotension the use of compression stockings, enough fluid intake, avoidance of the rapid change in body position, stop taking peripheral vasodilator drugs and diuretics (because they aggravate hypotension); by dry and insensible foot moisturize the limbs, avoid traumatic foot lesion and regular self-control of the feet is

necessary; training for perception of hypoglycemia and thereby augmentation of the hypoglycemia-perception threshold is also very important!

For the **AN** and also for the **sensomotor neuropathy** there are basically 2 different therapeutic forms available: on the one hand *a causal pharamacological therapy*, which means, that these drugs intervene on different parts of the pathomechanism and they slow down the progression of this complication; on the other hand a *symptomatic pharmacological therapy*, that ameliorates the symptoms of the patients. The application of these medications (parenteral / oral; sequential therapy, etc.) can be adapted to the severity of the disease and to the different patient groups (**Table**). The causal and the symptomatic treatments can be combined with each other, and also a combination within the medication groups is possible (causal/symptomatic therapy).

The alpha lipoic acid acts mainly as an antioxidant, on the other hand benfotiamine inhibits the hyperglycemia-induced pathological metabolic pathways.

Pregabalin and gabapentin act as antiepileptic drugs, and they also inhibit the release of transmitter in nerve endings, where the experience of pain will be transferred. Duloxetin has two effects: it acts antidepressant and it increases the effect of the painkiller–acting descending nerve pathes in the spinal cord. The use of NSAIDs in the treatment of neuropathy is a mistake, because it is not adequate for the treatment of neuropathy, furthermore the potential severe side effects can harm the patient.

There are several other drugs for the symptomatic treatment of **AN,** e.g. by orthostasis, diarrhoea, or obstipation, furthermore by the treatment of the erectile dysfunction the use of phosphodiesterase-5-inhibitors can ameliorate also the endothelial dysfunction (see patomechanismus!).

Table: The most important medications for causal and symptomatic therapy of diabetic neuropathy

causal therapy	**symptomatic treatment**
alpha lipoic acid	pregabalin
benfotiamine	gabapentin
	duloxetin

If the diagnosis of diabetic neuropathy is made at the right time and the treatment is also adequate, than both the quality of life and the life expectancy of these diabetic patients can be considerably improved.

Chapter 16.
Diabetic nephropathy
Dr. István Wittmann

Definition

Those diabetic patients should be regarded as having diabetic nephropathy, in whom there is an acceleration of loss of renal function, and parallel to that they show either stage of proteinuria (microalbuminuria, macroalbuminuria, proteinuria, nephritic syndrome); or they show a decline in renal function, in the presence of normalbuminuria if the patient is on a prolonged and effective renin-angiotensin-aldosterone system (RAAS) inhibition therapy and another renal disease is not suspected; or if the renal histological examination verified signs indicating diabetic nephropathy.

Epidemiology

Approximately 20-40% of diabetic patients have diabetic nephropathy, and in countries with a western style of living, diabetic nephropathy is the most common cause of end-stage renal disease.

Pathogenesis

Pathogenesis: Genetic predisposition: It seems that polymorphisms of the RAAS may play a role in the development and progression of diabetic nephropathy. Those diabetic patients, that concomitantly carry certain variants of aldose reductase and GLUT1, have a 9-times elevated risk regarding diabetic nephropathy. Expression of eNOS variants may promote the development of diabetic nephropathy, which effect may be independent of blood pressure. According to human studies, a certain polymorphism of eNOS, in interaction with a polymorphism of methylene tetrahydropholate reductase, may increase risk of microalbuminuria. Latter polymorphism is related to homocystein metabolism, which is related to the field of oxidative stress. According to a currently published meta-analysis one of the polymorphisms of SOD2 decreases the risk of diabetic nephropathy by 20%. Carriers of apoliprotein E4 have a 2.25-fold risk as compared to other E alleles.

Pathogenesis: Epigenetic approach: In the background of epigenetic changes, acetylation/deacetylation of the lysine amino acid residue, or methylation/demethylation of arginin may be found. Both directions (acetylation/deacetylation and methylation/demethylation) of both processes (acetylation and methylation) are catalyzed by

different enzymes. Methylation is a modification that lasts longer and is more stable, but both acetylation and methylation result in activation of affected genes. Not only histone, but also DNA may be methylated, and in diabetes and chronic kidney disease there is a hypomethylation of the DNA. Hyperglycaemia may lead to epigenetic changes through 'metabolic memory' to the development of diabetic complications among them to diabetic nephropathy.

Pathogenesis: Hemodynamic aspects: The evaluation of the most important factor of the hemodynamic approach, namely hyperfiltration is impaired by methodologic problems, mainly uncertainties in the determination of the GFR. The relative kinetics of renal enlargement and hyperfiltration is uncertain, but both are characteristic for the renal affection in diabetes. Possible causes of hyperfiltration include oxidative stress, an increased secretion of VEGF, the effect of insulin and an increased expression of SGLT2. As we do not have a clinical study that would be long enough, large enough, and well enough documenting GFR on the outcomes of GFR or albuminuria, at the moment no specific therapy is required to hyperfiltration. It may be assumed that this is also beneficially influenced by RAAS inhibition, such as in case of albuminuria, but further studies are needed to be able to say this.

Pathogenesis: Metabolic aspects: One important component of the metabolic dysfunction in diabetes, hyperglycaemia is able to evoke intracellular glucotoxicity, which on the one hand directly damages the cells, and on the other hand is able to induce insulin resistance. Insulin resistance is able to alter the function of the podocytes (that play an important role as a filtration barrier) in a way that many alterations that are well-known in diabetes and are characteristic for diabetic nephropathy, may be be related to it. However, also the possibility rises that the podocyte-effect of insulin resistance may play a role in other pathologies not considered as diabetic nephropathy (e.g. obesity-related renal damages, maybe secondary focal segmental glomerulosclerosis), or the worsening of other renal diseases (eg. progression of IgA nephropathy).

Pathogenesis: Oxidative stress approach: All types of cells are affected by free radical damage and the injury of redox regulation. It may launch different pathologic processes, depending on the regenerating effect of the given cell. Diabetes mellitus is a typical example for disorders in redox regulations, in the background of which we can mainly find the reducing property of glucose, by which an unpaired spin electron can be transferred to various molecules, thereby increasing their reactivity to an extreme value and this way damaging cells. Free radical-derived and other effects can lead in diabetes to a tubulointerstitial hypoxia in the kidney, thereby leading to early vitamin D and erythropoietin deficiency. Activation of

the RAAS, effects of cytokines and AGEs, all lead to free radical processes on a subcellular level. Therefore, inhibition of the RAAS, the aim to achieve a good glycaemic control does not mean anything else at a subcellular level then normalizing the redox balance.

Pathogenesis: Non-enzymatic glycation: The non-enzymatic glycation leads to abnormal proteinuria and a decline in GFR by damaging all parts of the kidney. This is one of the leading pathophysiological factors of the development of diabetic nephropathy. Unfortunately, at the moment there are no real tools to its direct inhibition that could be used in clinical practice.

Pathogenesis: Cytokines: An increased production of pro-inflammatory cytokines can be observed in the background of subclinical inflammation. Most important roles are played in diabetic nephropathy by TNF-alpha and the profibrotic TGF-beta.

Pathogenesis: Renin-angiotensin-aldosterone system: At the organ-tissue level the pathogenesis of diabetic nephropathy is dominated by the activation of RAAS. In the background of insulin resistance, oxidative stress, non-enzymatic glycation, hypoxia, hyperfiltration, cytokine effects, the activation of RAAS can always be found. Hyperglycaemia and AGEs are able to activate the RAAS by themselves.

Histology

No renal biopsy is carried out in the likelihood of diabetic nephropathy, the diagnosis must be set clinically. Glomerular damages related to diabetic nephropathy are thickening of the GBM, mesangial expansion, the Kimmelstiel-Wilson-type nodular glomerulosclerotic lesion and a marked glomerulosclerosis. This may be complemented by tubulointerstitial and vascular lesions.

Diagnosis

The diagnosis of diabetic nephropathy is based on three pillars: detection of diabetes mellitus, microalbuminuria/proteinuria and GFR-loss. As provided in the definition, in the absence of histology, a rule-out diagnosis will be set. As it shall be highlighted at the detailed description of clinical course, the absence of microalbuminuria/proteinuria does not exclude today the diagnosis of diabetic nephropathy. The diagnosis may be underlined by (but its absence does not exclude the diagnosis) if we are able to observe hyperfiltration or with an ultrasonography enlargement of the kidneys in a diabetic patient.

Differential diagnosis

Besides the general consideration, carrying out a renal biopsy is suggested in diabetes mellitus (especially in type 2 diabetes), if the patient presents with glomerular-type hematuria, or has no or only slight diabetic retinopathy (as compared to the level of renal damage), or an early onset (within 5 years of diagnosis of diabetes) a sever (nephrotic range) proteinuria is present, or if we see an early onset and fast decline in kidney function. Haematuria may be caused by frequently coinciding urinary tract infection, malignancy, arterial or venous thrombosis/embolism and papillary necrosis. In these cases, however, a haematuria with normal morphology of the red blood cells is observed in the urine sediment, and no renal biopsy is needed.

Clinical presentation, stages and prognosis

Table: Stages of DNP

DNP stage	**European staging**	**GFR-based staging (ml/min/1,73m^2)**
Stage 1.	Normoalbuminuria, hyperfiltration	>90
Stage 2.	Normoalbuminuria, decreasing filtration	60-89
Stage 3.	Abnormal (30-300 mg/day) albuminuria, decreasing filtration	30-59
Stage 4.	Abnormal (>300 mg/day) albuminuria, decreasing filtration	15-29
Stage 5.	End-stage renal disease	<15

New phenomena in the clinical course of diabetic nephropathy: The threshold of hyperfiltration (125, 130, 135 ml/min) should be corrected because of the approx. 1 ml/min/1.73m2/year decline in the GFR above 40 years as: 125(130,135) - (age - 40).

Currently we have no data on the prognosis of patients who are normalbuminuric due to RAAS-inhibition and statin therapy but with impaired or normal renal function. Although this question is always of higher clinical relevance, as though we earlier meant that there can be no nephropathy in diabetics without abnormal albumin- and proteinuria, now we can observe that this condition is always becoming more frequent due to the wide use of RAAS-inhibitors and statins.

Screening for abnormal albuminuria: One measurement of albuminuria is not enough, as the intraindividual variability is large, therefore, we can talk about an abnormal albuminuria, if 2 out of 3 measurements are positive. There are also causes for transient positivity, the diagnosis of abnormal albuminuria can only be set or declined, after these are ruled out. If the diabetic patient has no abnormal albuminuria, annual control is suggested. In patients with type 1 diabetes, 5 years after the diagnosis of diabetes, in type 2 immediately at the diagnosis a screening for albuminuria is suggested. Normoalbuminuria means an albumin amount < 30 mg in the 24-hour collected urine, or if the albumin/creatinine ratio in a non-collected urine specimen is < 3.0 mg/mmol. If the patient performs no urine collection, the albumin/creatinine ratio should be used.

Development of abnormal proteinuria and albuminuria: Structures in the kidney that should prevent protein loss are endothelium, the glomerular basement membrane, the podocyte, and the slit membrane that is stretched between the foot processes of the podocytes. Protein can only get into the urine, if the reabsorptive capacity of proximal tubular cells are exhausted.

Significance of abnormal proteinuria and albuminuria: In case of a patient with abonormal albuminuria, besides renal disease also dyslipidaemia, obesity, hypertension, micro- and macrovascular complications should be screened.

Measurment of albuminuria: Nowadays albuminuria is detected using routine immunological methods, such widespread methods are immunonephelometry and immunoturbidimetry.

Factors influencing albuminuria measurement: Positional that is postural, so-called orthostatic proteinuria can occur. The clinical significance of this entity is debated. Clinically overt urinary tract infections, most inflammatory diseases, acute febrile states, physical exercise, heart failure, dietary protein load may induce transient proteinuria. In case of stored urine samples – even at -80°C storage – we have to face the possibility of obtaining a lower result.

Factors determining progression of albuminuria: Higher albuminuria, higher HbA_{1c}, the mean arterial pressure (MAP) value, cardiovascular disease in the family history, hypertension, smoking, body mass and treatment of the patient seen to be predominant in terms of determining progression of albuminuria.

Connection between blood pressure and diabetic nephropathy: While earlier guidelines set the target of less than 130/80 mmHg in case of a proteinuria < 1 g/day, and suggested the range below 125/75 mmHg in case of a proteinuria > 1g/day, now more permissive are

declared targets (< 140/90 mmHg is suggested)in the absence of data. Maybe it is more correct if we talk about a target blood pressure range, knowing that a too large decrease in systolic and diastolic blood pressure can increase mortality. Thus the systolic blood pressure should not be lower than 100 mmHg, and the diastolic should not go below 60 mmHg. Probably here, as in all fields of medicine, an individualized therapy should be emphasized, and the target blood pressure should be determined by taking into account co-morbidities, age, gender, the way of living, life expectancies of the patients. In order to reach the target, in general 2-4 antihypertensive medications need to be combined.

Recurrence of diabetic nephropathy after transplantation: If the diabetic nephropathy recurs in the transplanted graft kidney, then less time is needed to develop the mild damage than in case of the native kidney. .

Connections between albuminuria and cardiovascular diseases: Renal disease and cardiovascular disease progress together in diabetic patients. The explanation of this may be the following: the same risk factors (smoking, components of the metabolic syndrome) lead to an abnormal albuminuria and renal damage, as to the development of cardiovascular diseases.

Common evaluation of GFR and albuminuria: To elaborate the risk of cardiovascular mortality and development of renal failure, albuminuria and the GFR value should be used in combination. This method has a high predictive value, is widely available and cheap.

The therapy of diabetic nephropathy

The glycaemic control of diabetes: A common statement of guidelines is that the intention to reach normoglycaemia can delay development of abnormal albuminuria in both type 1 diabetic and type 2 diabetic patients. It seems that in an established nephropathy the gylcemic control may not be as effective to slow down the progression. While intenting euglycaemia, we should not forget that an ideal HbA_{1c} range can be set up for mortality, as mortality increases both above and underneath this range. We have to try to reach values in the lower part of this range in order to decrease the risk of diabetic nephropathy.

The use of oral antidiabetic medications should be tailored individually to the GFR, while we know about gliquidone, pioglitazone, gliptins and insulin can be given at any stage of renal disease.

Inhibition of the renin-angiotensin-aldosterone system (RAAS): According to guidelines, diabetic patients with albuminuria (in females excluding time of pregnancy) an ACEI or ARB is recommended. In case of patients with type 1 diabetes mellitus ACE may be preferred, while in patients with type 2 diabetes, hypertension and abnormal albuminuria,

ACEI and ARB may be equally good. If these patients also exhibit a decline in GFR, ARB therapy is preferred. In case of intolerance to ACEI or ARB, an agent from the other class should be chosen. After starting ACEI and ARB therapy, serum creatinine and potassium measurements are eligible. Normalization of proteinuria is an important consideration in the therapy of a diabetic patient. The RAAS-inhibitor therapy should not be discontinued when the renal function becomes impaired, as it is further needed to prevent cardiovascular damage in these diabetic patients.

The order of use of antihypertensive drugs in diabetic nephropathy: The following order may be set up between antihypertensive drugs in diabetic nephropathy (numbers indicate order of choice):

1. RAAS inhibitors
2. Diuretics and/or calcium channel blockers
3. Beta-blockers (cardio selective, metabolic neutral, neutral to peripheric arterial disease; if myocardial infarct or heart failure is found in the past medical history, then use with RAAS inhibitors in the first line)
4. Central nervous system-acting or $alpha_1$-blocker
5. Direct vasodilator

Lipid-lowering therapy: Statins (except for rosuvastatin) may decrease albuminuria, proteinuria, some studies even described a beneficial effect in GFR-decline. Fenofibrate may significantly decrease albuminuria both in micro- and macroalbuminuria, this effect is most evident among patients with hypertriglyceridaemia, and fenofibrate also lead to a slowing down of progression of albuminuria. Moreover, it seems favourable concerning GFR loss.

The role of diet: In CKD stages 1-4, sodium intake should be below 2.3 g/day, total fat intake less than 30% of the total energy intake, saturated fatty acids less than 10% of total calory intake, cholesterol intake should be below 200 mg/day, carbohydrate intake should cover 50-60% of total energy intake. Protein intake in CKD 1-4 stages should be 0.8 g/day.

The role of weight loss: Weight loss could lead to a decrease in proteinuria in obese diabetic and non-diabetic patients, meanwhile the GFR decreased (if they were hyperfiltering) or remained constant.

Cessation of smoking: Although no randomized, controlled study was carried out because of ethical reasons, the available data suggest that cessation of smoking may provide significant benefit in regards of the development and progression of the diabetic nephropathy.

New treatment modalities verified as effective by human studies: From vitamin D and its analogues, paricalcitol proved to decrease the rate of albuminuria and does not cause significant adverse effects. In a meta-analysis, glitazones have shown to decrease

albuminuria. In randomized, controlled trials, pentoxyphyllin lead to a significant decrease of albuminuria in patients with abnormal albuminuria (>300mg/day) (9 studies), but proves inefficient in case of slighter (30-300 mg/day) albuminuria (4 studies). Aldose reductase inhibitors are known and studied for 40 years, however their effect on albuminuria was only studied oin one clinical study in patients with type 1 diabetes and abnormal albuminuria, there a significant improvement was observed. Endothelin-inhibitors, given on top of RAAS-inhibitors are able to decrease proteinuria, unfortunately they increase the chance of oedema formation and one of them may lead to higher rate of heart failure. Further studies are required to weigh risks and benefits.

Chapter 17.

Microvascular complications of diabetes: diabetic eye problems

Dr. Zsolt Biró

Ocular complications of diabetes is not synonymous with diabetic retinopathy, for practically all structures of the eye can be affected by the disease. Ocular complications can be divided into extraocular and intraocular complications. Extraocular complications include inflammation of the eyelid (blepharitis), yellowish deposits of fat underneath the skin (xanthelasma) extraocular muscle palsy, especially involving the III (oculomotor nerve) and VI (abducense nerve) cranial nerves, and microaneurysms of the conjunctiva. To the ocular complications belongs reduced corneal sensitivity resulting in recurrent corneal epithelial damage, glaucoma and disturbed visual function. Among the ocular complications mention must be made of alterations of lens leading to myopia and early development of cataracts, as well as diabetic retinopathy and anterior ischemic optic neuropathy (AION).

Let us look at this in greater detail.

Conjunctival bacterial infections occur in 80-90 % of patients with diabetes, resulting in a decreased number of goblet cells which may lead to keratosis. Microaneurysms in the bulbar conjunctiva are more common in diabetic individuals. There is a change in tear film composition, leading to reduced corneal sensation, which results in increased risk of corneal damage.

Tear break up time, which is a minimum of 20 seconds in healthy individuals, significantly diminishes as a result of damage to tear film disposition and stability in the **corneal** surface.

Superficial corneal inflammation (punctate keratitis) and recurrent corneal erosions have also been linked to decreased corneal sensitivity and poor adhesion between epithelial cells and the basal membrane.

Diabetic individuals may find it difficult to use contact lenses, as the cornea may become oedematous and epithel damage may occur.

One of the most serious complications of diabetes is the neovascularisation of the **iris.** This alteration is usually first observed at the pupillary margin but it can involve the entire iris surface and filtration angle. Neovascularisation arises from hypoxia caused by retinal capillary damage. It is reported up to 60 % of proliferative retinopathies.

In diabetic patients the **pupils** may be more narrow (miotic) and may have weaker reaction to topical mydriatics originating in diminished innervations of pupil dilatator muscle due to diabetic neuropathy.

The occurrence of **Uveitis** (inflammation of the iris or ciliary body) is also more common in diabetes.

Neovascularisation of the iris results in neovascular glaucoma. The newly growing vessels block the drainage of aqueous fluid through the anterior chamber angle, causing elevation of intraocular pressure. The pupil may become irregularly shaped; the eyes become red and painful leading to loss of visual acuity if not treated (e.g. by normalising intraocular pressure).

Refractive changes are common in diabetes because significant plasma glucose fluctuations (in uncontrolled diabetes) induce shifts in glucose concentration of aqueous humour which leads to swelling of the lens. Glycosylation of lens proteins results in a decrease in the lens's transparency.

Patients with diabetes have a 2 to 4 times greater risk of developing cataracts than do non-diabetic people. Cataracts typically tend to develop earlier and the risk increases with age, duration of diabetes, uncontrolled diabetes (high HbA1c) and kidney disease. The only effective treatment of a matured cataract is surgery.

Macular edema, which is actually the swelling or thickening of the central retina, is often (in 7%) found while examining diabetic patients. Epidemiological data indicate that it is the major cause of vision loss in diabetic individuals. Treatment of diabetic macular edema includes Argon laser photocoagulation of the fundus, as well as the proper management of systemic risk factors such as hyperglycaemia, hypertension and hyperlipidaemia.

Extensive laser photocoagulation may result in complications like central and paracentral scotoma (visual field loss), colour vision changes or loss, or occasionally secondary retinal neovascularisation. In these cases anti VEGF treatments are recommended, such as intravitreal administration of bevacizumab, ranibizumab, pegaptanib, or aflibercept. Attempts have been made to administer glucocorticosteroids. Triamcinolon, fluocinolone and dexamethasone can be used intravitreally for the treatment of diabetic macular edema.

Diabetic retinopathy (DR)

The risk factors for DR are as follow: duration of diabetes, younger age, high HbA_{1C}, hypertension, smoking, alcohol consumption, life style and pregnancy.

There are different stages in diabetic retinopathy: There is no fundus alteration in preretinopathy. The characteristic lesions of mild (background) and moderate retinopathy are micoaneurisms, haemorrhages, soft exudates (cotton wool spots) and hard exudates, all visible on the retina or on the retinal vessels. Edema may also occur. As the ischemia progresses the number and extensions of lesions increase. Proliferative retinopathy develops, characterised by abnormal new vessel growth from the papillary area or from the retinal surface (neovascularization). Preretinal or vitreous haemorrhages and traction retinal detachment may also occur.

Regular care and follow-up of diabetic patients is of utmost importance. In pre- and background retinopathy annual controls are usually recommended, while patients with proliferative retinopathy should be re-examined as frequently as 2-4 month intervals. Women with diabetes who become pregnant should undergo an eye examination in the first trimester and regular follow-ups are needed throughout their pregnancy.

Chapter 18.
Hypertension and diabetes mellitus
Dr. István Wittmann

Hypertension in type 1 diabetes mellitus

Hypertension in young (<30-40 years), people with type 1 diabetes is usually related to diabetic nephropathy. When a young type 1 diabetic patient develops hypertension, especially resistant hypertension without albuminuria or GFR reduction, secondary hypertension (other than underlying diabetic nephropathy) should be considered.

High blood pressure occurring in older (>40-50 years) patients with type 1 diabetes is frequently a primary (essential) hypertension, especially when it is associated with obesity or metabolic syndrome.

Newly developed hypertension in a pregnant, type 1 diabetic woman may be a sign of early nephropathy or preeclampsia.

Hypertension in type 2 diabetes mellitus

Because type 2 diabetes and pre-diabetic states (IGT, IFG) often occur as components of metabolic syndrome, and as hypertension is a metabolic syndrome-component as well, unsurprisingly primary hypertension usually precedes or develops together with diabetes.

It is also not uncommon that hypertension emerges only after type 2 diabetes has already been developed. In this case nephropathy should be considered (alike in type 1 diabetes) and measurement of albuminuria and determination of GFR is indicated. Primary hyperaldosteronism and obstructive sleep apnea syndrome (causes metabolic syndrome-like clinical picture) are also to be ruled out.

Hypertension in other specific types of diabetes mellitus

Hypertension, which occurs in diabetes associated either with endocrinopathies (primary hyperaldosteronism, hyperthyreosis, diseases caused by excessive amount of cortisol, growth hormone or epinephrine etc.) or with iatrogenic factors (drug-or chemical-induced diabetes) is well known. Iatrogenic diabetes and concomitant hypertension have to be discussed in more detail because their occurrence is relatively common and usually avoidable. Corticosteroids lead simultaneously to rise of blood pressure and blood glucose, thus in the treatment of autoimmune diseases the aim should be to use the minimum dose required to achieve a therapeutic effect.

In middle aged, hypertensive, non-diabetic patients with high doses (25-50 mg) of thiazides and non-cardioselective beta blockers, treatment occurs much more frequently. This combination is associated with a more than twofold risk of developing diabetes.

We have also been able to observe in the clinic that some patients develop diabetes after having received 50 mg thiazide and beta blockers for years. The reversibility of diabetes depends on the duration of drug exposure. It is also important to remember that this drug combination can cause dyslipidaemia and may be associated with a decline of renal function.

Unfavourable metabolic effects can be avoided through the use of low dose (1.5-2.5 mg) thiazid-like diuretics and third-generation beta-blockers (carvedilol, nebivolol).

Screening for hypertension in diabetes

Blood pressure should be measured at every routine visit. Home blood pressure self-monitoring and 24-h ambulatory blood pressure monitoring is often required to provide an accurate diagnosis.

The absence of dipping or rising in nocturnal blood pressure is often associated with obstructive sleep apnoea and diabetes.

Treatment goals are constantly revised. According to recent guidelines, people with diabetes and hypertension should be treated with an aim to achieving a blood pressure of <140/90 mmHg. Lower blood pressure targets such as <130/80 mmHg may be appropriate for certain individuals, such as young patients with proteinuria. In this regard individual target goals seem to be more appropriate but there is as yet a lack of clear-cut recommendations (as in the case of glycemic targets).

Treatment of hypertension in people with diabetes

Patients with blood pressure >120/80 mmHg should be advised on lifestyle changes (weight loss, physical activity, cessation of smoking, diet, salt restriction, moderation of alcohol intake) to reduce blood pressure. Patients with confirmed blood pressure higher than 140/80 mmHg in office should, in addition to lifestyle therapy, have initiation in pharmacological therapy.

To understand the pharmacological treatment of diabetes it is important to know that advanced glycation end products formed in high doses in diabetes activate the renin-angiotensin aldosteron system. Glycation end products also cause nephron loss and consequently GFR-reduction, directly or indirectly, by triggering proteinura. Because kidneys play a major important role in the elimination of AGE products, the reduction of GFR leads to

further increase in the level of glycated end products. Glycation end products are not only nephrotoxic but also vasculotoxic, resulting in early atherosclerosis and leading by this to increased cardiovascular morbidity and mortality in diabetes and especially in diabetic nephropathy.

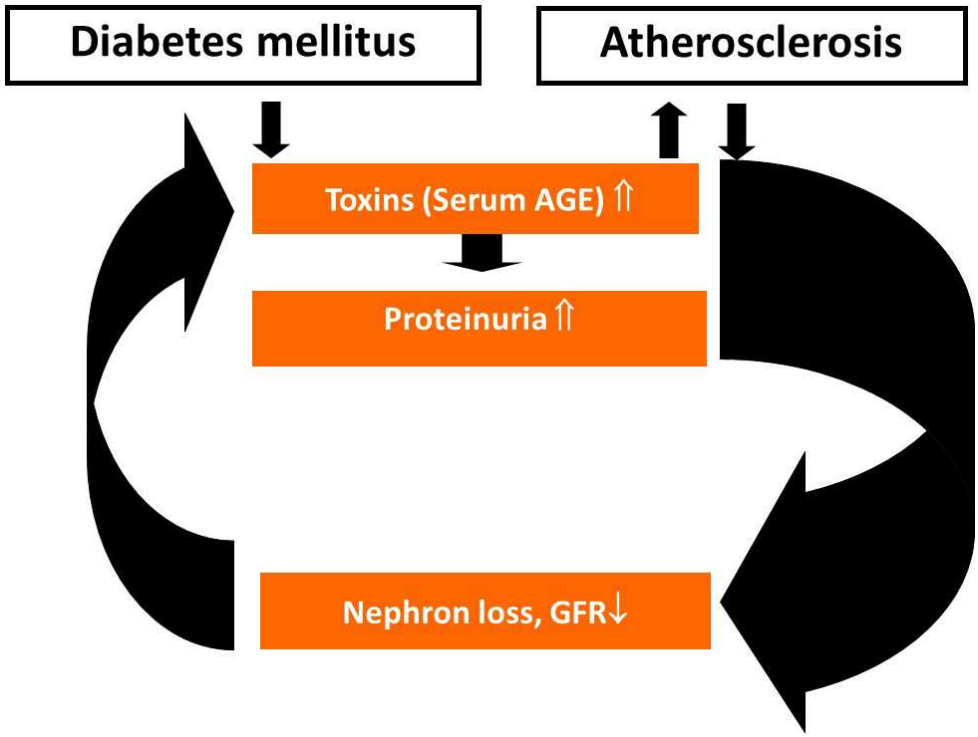

Figure: Correlation between non-enzymatic glycation, proteinuria, nephron loss (GFR reduction) and cardiovascular morbidity

It follows from the above that RAAS inhibitors should be used as first-line hypertension therapy in people with diabetes and even more so with diabetic nephropathy. An ACE inhibitor should be the first drug of choice, titrating up to the highest tolerable dose.

When despite a maximal dose ACE inhibitor treatment proteinura remains and GFR is > 60 ml/min, the addition of a mineralocorticoid receptor antagonist or angiotensin receptor blocker to the ACEI inhibitor based regimen may provide additional benefits regarding high renal risk. Claims that combination therapy lacks cardiovascular benefits or may harm the kidneys are not sufficiently substantiated. When GFR is <60 ml/min initiation of combination RAS blockade (i.e. ACE+ARB or ACE + spironolacton e.t.c) is not recommended, but combination therapy that has already begun can be maintained. A combined blockade of the RAS system is recommended to reduce proteinuria without further reduction of blood pressure. It is also important to mention that this therapy requires experience and strict controls; serum creatinin, eGFR and serum potassium levels should be monitored.

If ACE inhibitor intolerance occurs ARBs should be substituted.

Mineralocorticoid receptor blocker therapy plays a favourable role in the antihypertensive treatment of obese patient with type 2 diabetes. The reason for this is that visceral fat cells in abdominal obesity produce not only cytokines but also aldosterone releasing factors contributing to an even higher aldosterone level. Therefore mineralocorticoid receptor antagonists induce not only blood pressure reduction but may also improve glucose control and reduce target organ damage in this population. In obese type 2 diabetic patients (without underlying primary hyperaldosteronism) serum potassium levels that are slightly low or at the low end of the normal range and mild or compensated metabolic alkalosis may predict the efficacy of mineralocorticoid antagonist therapy.

Resistant hypertension is common in patients with metabolic syndrome, obstructive sleep apnoea and diabetes mellitus with nephropathy. Thus multiple-drug therapy (minimum 3-4 agents at maximal doses) is usually required to achieve blood pressure goals.

Because an increased aldosteron level may lead to salt-sensitive hypertension in diabetes, low dose diuretics are recommended as second- or third-line therapy. Low dose thiazide-like diuretics may compensate the potassium sparing effect of RAAS inhibitors.

The next agents of choice are the metabolically neutral calcium channel blockers. In patients with a previous history of myocardial infarction, treatment should be complemented with β-blockers. Patients with diabetes and a history of myocardial infarction or stroke probably suffer from peripheral artery disease. In this regard nevibolol or carvediolol may be a more favourable β-blocker of choice.

Even more antihypertensive agents may be necessary to achieve blood pressure targets, especially in patients with impaired kidney function. Thus the addition of further blood pressure medication over and above those previously mentioned should be made, such as alfa-blockers or central nervous system acting drugs or even sometimes direct vasodilatators (e.g.: dihydralazine)

In patients with serious kidney impairment (<GFR 30 ml/ min) loop diuretics should usually be prescribed for further blood pressure reduction due to volume retention. A loop diuretic is not recommended for blood pressure reduction in patients whose renal function is normal due to its short duration of action.

The sequence of antihypertensive agents usually recommended for use on patients with diabetes and hypertension is as follows:

1. RAS-inhibitors (ACE inhibitors or ARBs)
2. Low-dose thiazide-like diuretic and/or mineralocorticoid receptor antagonist

3. Dihydropyridin calcium channel blockers
4. Beta-blockers
5. Alfa- receptor-blockers or CNS-drug
6. Direct vasodilator

Chapter 19.
Management of dyslipidaemia in diabetes mellitus

Dr. Gábor Fülöp

Diabetes, metabolic syndrome and even prediabetes are associated with a typical pattern of dyslipidaemia leading to increased risk of cardiovascular morbidity and mortality.

In type 1 diabetes typical lipid disorder occurs primarily when carbohydrate metabolism is poorly controlled or disturbed. Prevalence of dyslipidaemia in well controlled (normoglycaemic) type 1 diabetic patients corresponds to that in the non-diabetic population.

Lipid disorder occurs in more than 80 % of patients with type 2 diabetes.

These lipid disorders include not only quantitative but also qualitative abnormalities of lipoproteins.

This typical dyslipidaemic pattern is as follows:

1. Increased triglycerides
2. Low HDL- cholesterol
3. Small dense LDL particles
4. Postprandial lipemia
5. Near-normal LDL cholesterol

These changes are caused by insulin resistance/hyperinsulinemia. Because this lipid abnormality promotes atherosclerosis it is called atherogenic dyslipidemia. Small dense LDL particles are more susceptible to oxidative modification. These modified particles have decreased binding to the LDL receptor, hence they spend more time in circulation, incorporate into the endothelium and are eliminated only via alternative scavenger receptors.

Before treating diabetic dyslipidemia, assessing the patient's cardiovascular risk using **SCORE** (Systemic Coronary Risk Evaluation) risk charts is elemental. These charts are based on gender, age, total cholesterol, systolic blood pressure and smoking status and estimate risk for fatal cardiovascular disease events over a ten-year period. A score higher than 5 % indicates high risk, while a score over 10 % indicates very high risk for fatal cardiovascular events.

Type 1 and type 2 diabetes denote per se high risk, whereas diabetes associated with 2 or more risk factors and/or organ damage (cardiovascular disease) implies very high risk for fatal cardiovascular events.

Table shows treatment goals for lipid therapy in different cardiovascular risk categories.The principle of treatment is known as treat to target therapy.

Table: Target lipid levels in different cardiovascular risk categories

Target lipid leves (mmol/l)	
Very high risk	High risk
*Cholesterol: < 3.5 LDL-cholesterol: <1.8 **Non-HDL-cholesterol: <2.6 * In acute coronary syndrome, stroke and critical limb ischemia highly efficacious statin therapy in maximal tolerable dose is recommended irrespectively of target values	Cholesterol: <4.5 LDL-cholesterol: <2.5 Triglycerid: <1.7 HDL-cholestreol: >1.0 (men) >1.3 (women) **Non-HDL-cholesterol: <3.3

[**]Non-HDL-cholesterol is identified as a secondary lipid target. Target values are 0.8 mmol/l higher than those for LDL-C values in the corresponding cardiovascular risk category.

Regarding the linear correlation between LDL-Cholesterol and cardiovascular events confirmed by major clinical studies, the primary target of antilipemic therapy is the reduction of LDL-cholesterol levels.

The latest epidemiologic and clinical data indicate that apo B and non-HDL-cholesterol may be a slightly better predictor of cardiovascular risk than LDL-C. Raising HDL cholesterol and lower triglycerid levels are proposed as a secondary target.

Target levels are as follows: HDL-C ≥1.3 mmol/l in women and ≥1.1 mmol/l in men respectively, whereas triglyceride ≤1.7 mmol/l.

Diabetic dyslipidemia is not typically associated with LDL-C abnormalities, thus in diabetes non-HDL-C is a better indicator of underlying adverse lipid abnormalities and predicts cardiovascular risk more reliably.

Calculation of **non-HDL cholesterol:** Total Cholesterol – HDL cholesterol. LDL-C concentrations can be directly measured in laboratories or can be estimated from the quantitative measurements of total cholesterol, HDL cholesterol and plasma triglycerides, using the **Friedwald equation**: LDL-C=Total cholesterin – HDL-cholesterin – plasma triglycerids/2.2 (mmol/l).

The limitations of the Friedwald formula are as follows: plasma triglycerid concentration exceeds 4.5 mmol/l, presence of chylomicronaemia or dysbetalipoproteinaemia (Fredrickson type III hyperlipoproteinaemia).

In atherogenic dyslipidaemia statin therapy combined with fibrates has resulted in additional reduction in fatal and non-fatal cardiovascular events. This is called residual risk reduction.

Lifestyle modification, including increased physical activity and appropriate diet is a cornerstone in the treatment of lipid abnormalities.

The improvement of glycaemic control is an important first step in managing diabetic dyslipdaemia.

Despite achieving an almost normoglycemic state, lipid abnormalities may remain and so additional antilipemic therapy is usually required.

Because the majority of patients are overweight calorie restriction is commonly recommended. For every 1-kg decrease in body weight, non-HDL cholesterol decreased by 0.06 mmol/l while increased physical activity resulted in a 4-5% decrease in non HDL cholesterol. The cessation of smoking is essential.

Dietary therapy: The diet focuses on the reduction of consumption of cholesterol, saturated and trans-fatty acids. The total dietary cholesterol intake should not exceed 200 g, and limitation of saturated fat to less than 7 % of total calories is recommended.

Consumption of simple, rapidly absorbed carbohydrates and (even moderate) alcohol should be avoided because they adversely influence glucose control and contribute to high triglyceride levels.

A diet containing complex carbohydrates and rich in vegetables and omega-3 fatty acids (e.g fish) which also limits the daily intake of saturated fat is recommended.

A daily intake of 1.5-6 g of fish oil as a nutrition supplement may be advocated although its high energy content should be taken into consideration.

Pharmacologic therapy Lifestyle modification may be sufficient as long as initial LDL-C is between 2.6-3.3 mmol/l and no cardiovascular disease is present. When LDL-C exceeds 3.4 mmol/l or CVD is present, pharmacologic therapy accompanied with lifestyle changes is recommended

HMG-CoA reductase inhibitors (statin) are the drug of first choice for lowering LDL cholesterol. The use of statin results in a 30-50 % decrease in LDL cholesterol levels. It is necessary to achieve treatment goals (e.g. a decrease of LDL cholesterol by at least 50 % from baseline in high risk patients) in order to attain favourable cardiovascular outcomes. Statins also moderately raise HDL cholesterol and lower triglyceride and exert many vascular protective, pleiotropic effects.

For initiation therapy moderate intensity statins (simvastatin 40 mg, atorvastatin 20 mg, rosuvastatin 10 mg) are recommended due to their pleiotropic effect.

By doubling the statin dose there is an approximate 6% increase in LDL cholesterol-lowering efficacy (the 6 percent rule).

If there is an inadequate response to statins, treatment may be complemented with ezetimib, a selective cholesterol absorption inhibitor which provides an additional 20-25 % reduction of LDL cholesterol. Ezetimib used as monotherapy is also beneficial in patients who are unable to tolerate statins. Bile acid sequestrants might also be a further drug choice in cases of poor therapeutic response.

When HDL cholesterol levels are proven to be low, lifestyle interventions with weight loss, smoking cessation and increased physical activity along with PPAR-α agonist fibrates or nicotinic acids are recommended.

When triglycerides are >2.3 mmol/l and LDL cholesterol is <2.5 mmol/l, fibrate therapy might be initiated. Life style modification should be a first line treatment when triglycerides are above target level, but under 4.5 mmol/l. When triglyedrides go above 4.5 mmol/l, pharmacological therapy associated with lifestyle changes is recommended. Fibrates and nicotinic acid derivatives are the most effective agents in lowering triglyceride. Fenofibrate also decreases the risk of microvascular complications.

In cases of severe hypertriglyceridaemia, when the triglycerid level is above 10 mmol/l, urgent treatment such as severe fat restriction (daily fat intake is reduced to less than 10 % of total energy intake) in addition to fibrate or nicotinic acid therapy is necessary to reduce the risk of pancreatitis.

Combination therapy. Statin combined with ezetimib is considered a useful way to reduce LDL cholesterol, whereas in atherogenic dyslipidaemia statin accompanied with fibrates (or Ω-3 fatty acid) is regarded as being an efficacious combination. Combination therapy is safe when used with caution and adherence to a summary of product characteristics, although regular follow ups (control of liver function and creatinin kinase) are recommended.
Possible future treatment options include cholesterylester transfer protein (CETP) inhibitors and proprotein convertase subtilisin /kexin type 9 (PCSK9) inhibitors.

Chapter 20.
Rehabilitation in diabetes mellitus
Dr. Gábor Fülöp

During the process of medical rehabilitation the health care system provides help and support for disabled people who, by developing their extant capabilities or using an assistive technology device, become able to partially or completely regain independence and to participate in the activities of a normal life. The first steps of rehabilitation include the evaluation of current impairment level and the assessment of existent functions and capacity for work, followed by improvements of conditions, development and maintenance in individual functions.

Individuals who have diabetes are among those regarded as disabled people. Diabetes leads to a substantial change in lifestyle: medical therapy, and particularly insulin treatment, requires strict schedule. The risk of hypoglycaemia in insulin treated diabetics may restrict access to some professions such as pilot, bus- and engine driver or work at heights or near a high voltage power line. Night or shift work activities or jobs accompanied by extremely varied physical activity might also not be recommended because fluctuant or high blood glucose level and poor glucose control are expected. All these factors have to be considered in the career choice process.

Chronic complications of diabetes further deteriorate the capacity to work and quality of life (loss of vision, lower limb amputation, stroke, coronary heart disease, renal replacement therapy).

People with diabetes often develop multiple, complex disabilities which require comprehensive team work (e.g. care of a blind person, one with an amputated leg or on renal replacement therapy).

Diabetes care includes rehabilitation. The foremost goals are the reduction of cardiovascular risk and the optimal treatment of co-morbidities along with the maintenance of adequate glycemic control in order to prevent late complications and slower progression.

If complications develop, strict control and timely interventions are required to avoid more serious conditions and further health damage (e.g. laser therapy to prevent retinal bleeding, retinal detachment and visual loss due to diabetic retinopathy).

Type 2 diabetes has been associated with increased risk of falls, fractures, depression, and cognitive impairment.

In a diabetic group aged over 70 years and living in a community, difficulties in performing daily activities were seen in 53%, urinary incontinence in 27%, fecal incontinence in 11%, depression in 14%, and dementia in 15%. Only 36% of them were free from such problems.

Risk factors include strokes, peripheral artery disease, depression, smoking, and rare physical exercise, but the strongest independent risk factor was mobility limitation at baseline.

The process toward disability is complex and involves social-, economic- and lifestyle-related factors (e.g. poor diet, obesity, smoking, sedentary habits), psychological factors (personality type, coping strategies), psychiatric condition (mood disorders, changes in cognition) and a range of disabling medical conditions (arthritis, cardiopulmonary disease, cancer, stroke). Most factors contributing to disability are also significant in the development of type 2 diabetes and its complications. A third of patients develop some degree of mobility limitation after 5 years of diabetes, peripheral neuropathy, arthritis and history of stroke being the most frequent contributing factors.

Mobility impairment is often an early step in the progression to future disability, thus it may be a useful early marker for preventative and rehabilitation efforts in diabetes.

Rehabilitation is based on health care system underlying clinical evidence personalised by a cooperative multidisciplinary team. After all, psychosocial support and involvement of the community and society are inevitable. Comprehensive assessment of the patient and an optimal treatment plan are also necessary for appropriate rehabilitation.

More careful diabetes care accompanied by frequent therapy modifications is usually required. Treatment goals often have to be revised according to the condition and prognosis of the patient. For example, an elderly patient with cognitive impairment and severe coronary heart disease requires a more permissive glycemic control (HbA_{1c} level could be kept in a higher range), because strict glucose control is associated with a high risk of hypoglycaemia, which is dangerous in this case.

Exercise is a cornerstone of treatment for type 2 diabetes. There is a variety of literature data about the favourable effects of exercise on blood sugar levels and cardiovascular risk; however, evidence is missing regarding how to treat or prevent disability in diabetic patients.

A physiotherapist-supervised group training program has proved to be effective and resulted in improved balance and reduced fear of falling in patients with neuropathy.

Although the rehabilitation of diabetic patients has aroused intense recent interest in literature, so far there has been little clinical evidence in this field.

Chapter 21.
Perioperative management of patients with diabetes mellitus
Dr. Botond Csiky

Diabetic patients have increased perioperative risk compared with their non-diabetic counterparts. This risk is further increased in patients with inadequate glycemic ontrol. The neurohumoral changes induced by surgery may lead to an imbalance of carbohydrate metabolism, even in patients who have adequate glycemic control.

Diabetes should be properly under control prior to elective surgery. Surgery for patients with diabetes should ideally be performed in the morning.

Biguanid therapy should be stopped 48 hours before the surgery and long-acting oral hypoglycemic medications (sulphonylureas, basal insulin) should be witheld.

During the surgery and in the perioperative period blood glucose should be monitored regularly.

We can distinguish minor or major surgical procedures from the diabetic point of view.

Minor surgical procedure: this is short (general duration <30 min), it is performed under local anesthesia and does not involve the opening of the pleural or abdominal cavity.

Major surgical procedure: this is longer, performed under general anesthesia and the abdominal or pleural cavities have to be opened. Oral nutrition cannot be recommenced immediately after the surgery.

Minor surgical procedure

In patients with properly controlled diabetes treated either solely through diet or through a combination of diet and oral antidiabetic drugs minor surgical procedures can be performed without any significant change in the therapy. Long-acting oral hypoglycemic medication and metformin should be witheld as mentioned above. The patient should fast prior to the operation, so the oral antidiabetic drugs should not be given to the patient before the operation; they should be given before the first permitted meal.

Major surgical procedure

On the day of the operation, an insulin-glucose-potassium (GIK) infusion should be used to maintain normoglycaemia (short-acting insulin in the infusion). The amount of

glucose, potassium and insulin administered to the patient should be set and modified according to the results of frequent laboratory controls.

The infusion can be stopped as soon as the patient's oral nutrition can be restarted and the patient can resume the previous antidiabetic therapy. It is important to have an overlap of at least 4 hours between the parenteral and oral nutrition. The final antidiabetic therapy can be set following the stabilization of the patient.

If acute major surgical procedure is needed, the above mentioned insulin-glucose-potassium infusion therapy can be used if the patient has satisfactory glycemic control; if not, then the GIK infusion can be administered only after correction of the glucose control.