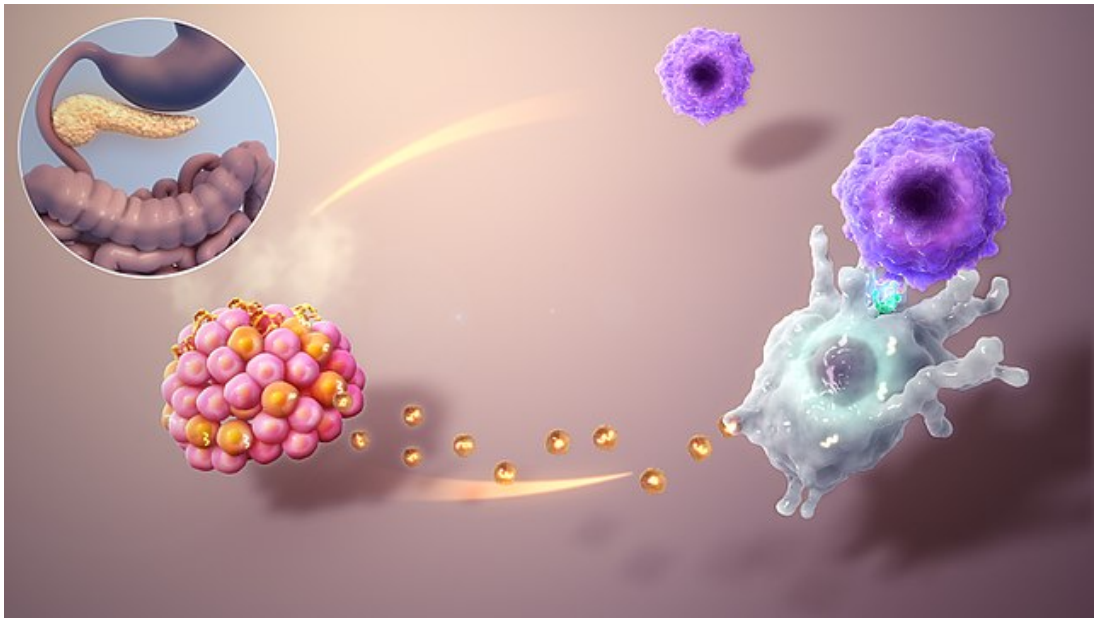
Diabetes Mellitus — Types, Complications and Treatment

See online here

Diabetes mellitus is a metabolic disease in which chronic hyperglycemia can lead to a number of different early and late complications. The high prevalence of the disease with its heterogenic variety of symptoms demands interdisciplinary care including many specialties. Therapy options can be very successful here. Therefore, good knowledge of the clinical picture is absolutely relevant for up-and-coming physicians as contact with diabetics is part of the daily routine.



Definition

Diabetes mellitus describes a heterogenic group of metabolic diseases whose basic characteristic is chronic hyperglycemia with subsequently elevated sugar in the urine. This is where the term diabetes mellitus comes from, referring to the historic term ‘honey-sweet flow’.

Forms of Diabetes Mellitus

Insulin is at the center of this metabolic disease. This hormone is produced in the beta cells of the pancreas and ensures the absorption (as well as the storage) of glucose in different cells of the body. The insulin receptor involved in this process, a transmembrane protein with tyrosine kinase activity, causes the translocation of the glucose transporting protein **GLUT4** to the surface of the cell so that glucose can increasingly be transported from the capillary bed to the intracellular compartment. The glucose level in the blood

decreases. In people with diabetes mellitus, this mechanism is disrupted at different levels.

Here, we differentiate between different forms of diabetes mellitus based on their etiology:

Diabetes mellitus type 1

Due to the destruction of beta cells, an absolute insulin deficiency is created. This destruction occurs due to either idiopathic (rarer) or immunological processes.

Genetic factors play a predisposing role. A special type of this immunological form of diabetes is **LADA** (**L**ate **a**utoimmune **d**iabetes in **a**dults), in which the diabetogenic metabolic condition does not occur until adulthood (> 25 years). **Pathological hyperglycemia** usually occurs from a beta cell loss of approximately 80%. In the diagnosis of autoimmune conditions, one frequently finds antibodies against cytoplasmic islet cells, anti-glutamic acid decarboxylase (anti-GAD) antibodies, insulin autoantibodies, and anti-2A tyrosine phosphate antibodies.

Diabetes mellitus type 2

In 90% of diabetes cases, a pronounced triad consisting of insulin resistance of the target tissue, a secretory defect, or **progressive apoptosis** of beta cells is present. This constellation often develops in combination with metabolic syndrome, which is frequently found in our affluent society.

Caused by overeating, excess weight, and a simultaneous lack of exercise, permanently high insulin levels occur, which decrease the sensitivity of the insulin receptors and lead to subsequent down-regulation. This causes the insulin level to increase by way of a **vicious cycle**. At the same time, simultaneously progressing **atherosclerosis** develops via the **dyslipoproteinemia** in connection with diabetes mellitus type 2, with numerous late complications.

Note: Regarding hereditary tendencies, diabetes mellitus type 1 and 2 are distributed as follows: diabetes mellitus type 2 more frequently affects first-degree relatives than diabetes mellitus type 1. Child with an affected parent has a 50% likelihood to suffer from the same disease during their lifetime, whereas only 10% of affected individuals suffering from diabetes mellitus type 1 have a positive family history.

Gestational diabetes

Gestational diabetes is any disruption of carbohydrate metabolism during pregnancy. In most cases, the diabetic metabolic tendency resolves after the pregnancy but with an increased risk of a later manifestation of diabetes mellitus. **Gestational diabetes** can increase the risk of **preeclampsia, hydramnios,** and urinary tract infections.

The pathological metabolic condition of the mother creates certain peripartum health risks for the child as well. Therefore, respiratory distress syndrome and postpartum (reactive) hypoglycemia are observed frequently.

Genetic defects of beta cells

Several genetic defects can cause hereditary diabetes mellitus, which affects approximately 1% of all diabetic patients, with most of them being affected by the

disease at a very young age. This form of diabetes is referred to as **M**aturity **o**nset **d**iabetes of the **y**oung (**MODY**) which has different genetic causes. The most frequent MODY forms include (important exam question):

- **MODY2**: 15% of all cases. The affected gene is glucokinase. MODY2 is characterized by mild progression, mostly without any late complications
- **MODY3**: 65% of all cases. The affected gene is HNF-1-alpha

Rare causes of diabetes mellitus

Less frequent causes of diabetes mellitus include a disorder of the exocrine pancreas, endocrinopathy, medications (glucocorticoids, oral contraceptives, etc.), infections, cystic fibrosis, and hemochromatosis. Obviously, a diabetic metabolic condition frequently occurs after pancreatic surgery. Should diabetes mellitus occur as a result of the destruction of pancreatic tissue in general, it is referred to as **pancreoprivic diabetes.**

This form of diabetes is notably difficult to treat as not ‘only’ the beta cells are destroyed but the production of glucagon and somatostatin is inhibited as well.

Symptoms of Diabetes Mellitus

Initially, diabetes mellitus manifests as unspecified general symptoms such as fatigue, exhaustion, or weakness.

Hyperglycemia classically causes **polyuria with polydipsia** along with weight loss. In addition, this will cause electrolytes to fluctuate resulting in many patients reporting leg cramps or vision problems.

Frequently, diabetes can also be recognized in the skin. Typically, there is a reddening of the face (**rubeosis diabetica**) or skin infections due to a weakened immunological barrier. Further, erectile dysfunction has been reported.

As a matter of principle, one should remember that diabetes mellitus type 1 becomes symptomatic rather early on, whereas diabetes mellitus type 2 can remain undetected for a long period of time. Acute symptoms of diabetes mellitus could include hyperglycemia or hypoglycemia, and these are described in more detail below.

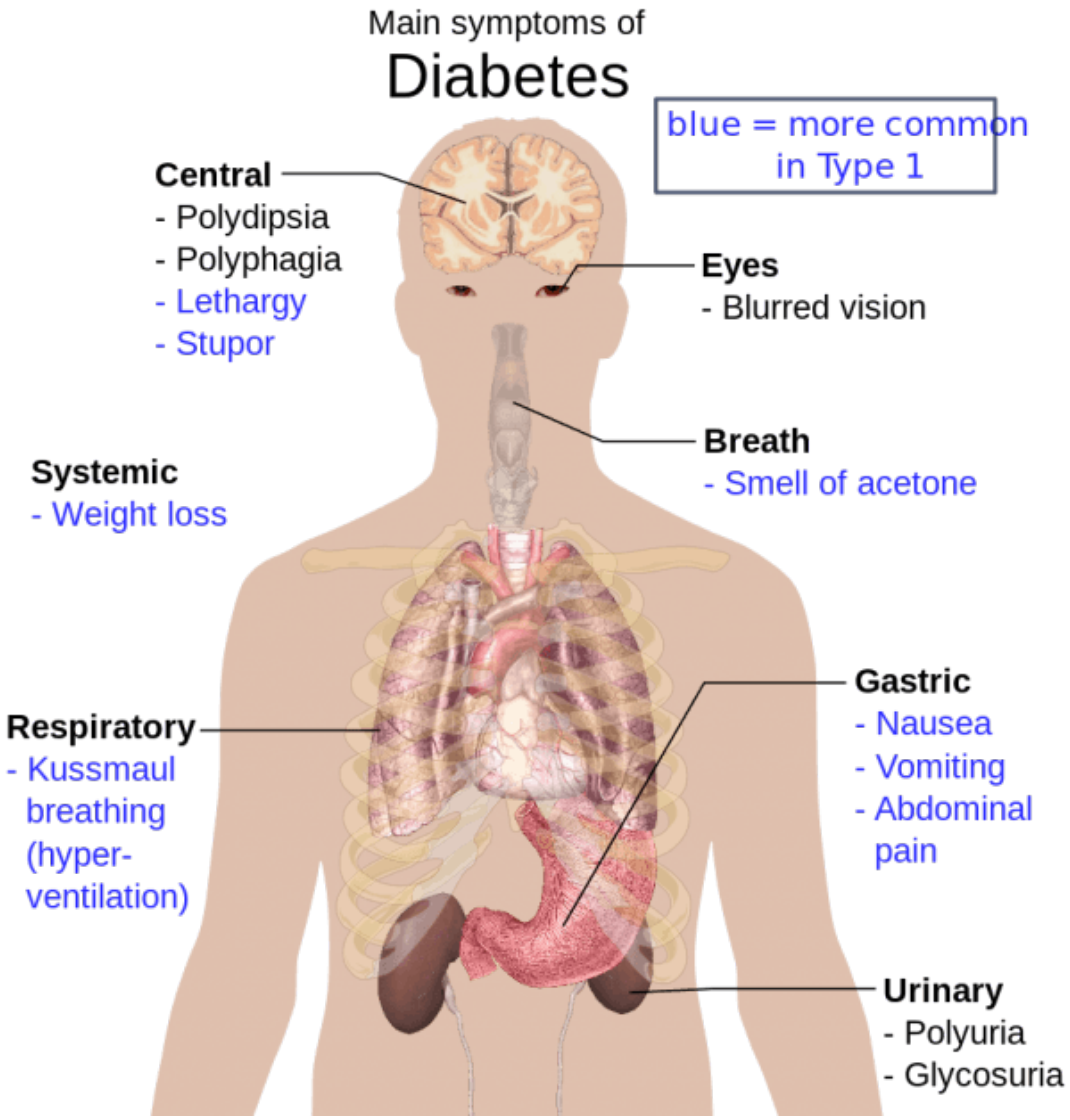


Image: “Overview of the most significant possible symptoms of diabetes”. License: Public Domain

Complications of diabetes mellitus

The extent of the disease only becomes apparent when considering the long-term effects of chronic hyperglycemia.

Elevated blood sugar levels are present throughout the whole body, meaning diabetes mellitus is comparable to a systemic disease with its corresponding pronounced spectrum of complications. The walls of large and small vessels, in particular, are damaged over time.

Physicians distinguish between macroangiopathic damage, with arteriosclerosis, and microangiopathic damage, through the glycosylation of proteins of the basal membrane.

Macroangiopathic damage in diabetes mellitus

The distribution pattern of the macroangiopathic damage is usually nonspecific. Approximately half of all diabetics die of a heart attack.

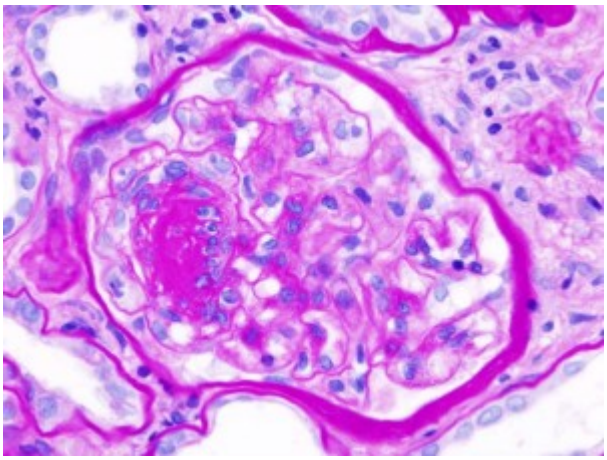
Aside from the coronary arteries, peripheral arterial occlusive disease and arteriosclerosis of the cerebral arteries with subsequent cerebral infarction frequently occur.

Tip for the clinical routine: In coronary heart disease in diabetics, microangiopathic damage (see below) frequently causes symptoms of silent angina pectoris with pain-free infarctions meaning that in case of a suspected myocardial infarction, the medical history of the diabetic patient cannot be relied on!

Microangiopathic damage caused by diabetes mellitus

Dysfunction at the capillary level particularly affects the kidney, retina, nervous system, as well as the intramural smaller coronary arteries.

Diabetic nephropathy



Diabetic glomerulosclerosis

While type 1 diabetes tends towards **glomerulosclerosis** (**Kimmelstiel-Wilson type**), type 2 diabetes has an unspecified pattern of damage in the kidney. Hyperglycemia causes the activation of growth hormones resulting in renal hypertrophy along with the thickening of the basal membrane and, in turn, increased **glomerular permeability**. Fibrotic transitional processes thus lead to kidney insufficiency.

Diabetic retinopathy

Here, the result is microangiopathy with microaneurysms, vascular caliber fluctuations as well as intraretinal bleedings. If angiogenic growth factors are produced as a result, proliferative retinopathy can occur aside from the non-proliferative form along with the formation of new vessels on the pupil.

Diabetic neuropathy

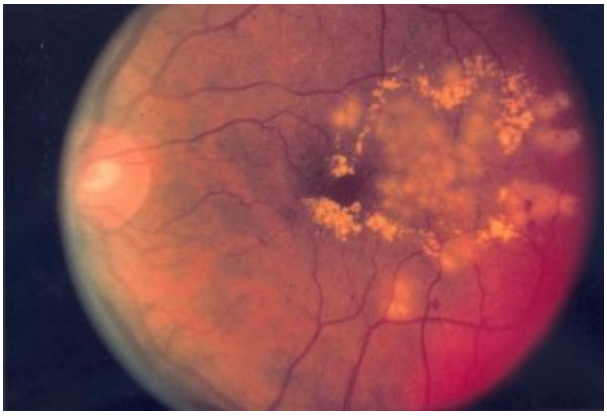


Image: “Diabetic retinopathy after focal laser treatment”.
License: Public Domain

One assumes a microcirculation disturbance of the **vasa nervorum** in connection with the glycosylation of different neuronal proteins. This classically causes a peripheral sensorimotor neuropathy with distal, symmetrical characteristics. During a neurological examination, **areflexia** and **hypoesthesia** are apparent in addition to a trophic disorder of the lower legs and feet. The affected patients often report paresthesia (‘**burning feet syndrome’**) and could ultimately experience paresis.

In addition to this type of distribution, there is also diabetic polyneuropathy, peripheral facial paresis, or diabetic radiculopathy. Furthermore, neuropathy of the autonomic nervous system may frequently occur, whereby both the sympathetic and parasympathetic innervations are affected. Here, the symptoms are as varied as the autonomous nervous system. Differences exist between cardiovascular forms and autonomous diabetic neuropathies of the gastrointestinal tract, urogenital system, neuroendocrine system, or thermoregulation.

Tip for the clinical routine: Diabetic patients often have warm and dry feet. This obviously does not apply in cases of simultaneous peripheral arterial occlusive disease.

Diabetic foot syndrome

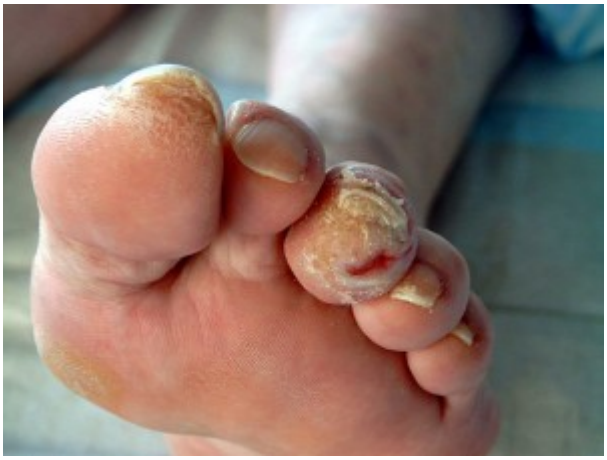


Image: “The diabetic foot syndrome” by PhilippN. License: CC BY-SA 3.0

Many diabetics complain about injuries to the foot as combined macro and microangiopathic long-term complications. Diabetic foot syndrome represents the most frequent complication.

Different forms of diabetic foot syndrome include:

Neuropathic diabetic foot is typically warm and dry. Sensitivity is impaired, while perfusion is good. The affected patients frequently wear the wrong footwear or do not notice small injuries resulting in **ulcerating but almost painless ulcers**.

Ischemic foot with peripheral occlusive disease, on the other hand, is cool to the touch and pale due to the lack of perfusion. Necrosis or gangrene is painful.

Particularly unfavorable are **combined forms,** which exist in 35% of diabetic feet. In these cases, surgical amputations are more frequent than with the other forms.

Other complications of diabetes mellitus

Apart from micro and macroangiopathic damage, **diabetic cardiomyopathy** can occur, which is an immunological decrease in resistance resulting in an increased tendency toward infections and lipid metabolism disorders, finally causing **hepatic steatosis**.

Diagnosis of Diabetes Mellitus

Diagnosis can be made based on clinical symptoms of manifested diabetes mellitus in combination with a spontaneous blood glucose level of > 200 mg/dL. Even without other symptoms, spontaneous blood glucose levels of > 200 mg/dL severally measured could lead to the diagnosis.

Furthermore, glucose tolerance and diabetes mellitus can be diagnosed via fasting blood glucose or an oral glucose tolerance test. Therefore, pregnant women should have their blood glucose closely monitored. If a high risk for diabetes is suspected, an oral glucose tolerance test is recommended.

Diagnosing diabetes mellitus is relatively easy. Due to its high prevalence and grave (and economical) long-term complications, diabetes screening is recommended for anyone over the age of 45. In case of risk factors, screening should take place even earlier.

Once the diagnosis has been made, other clinical tests are available depending on the long-term complications, especially because many of these tests can be performed easily without complicated equipment. With a thorough medical history, further (cardio) vascular risk factors must be assessed in order to be able to assess and treat angiopathic damages in time.

At least once a year, testing for **microalbuminuria** is necessary.

Therapy of Diabetes Mellitus

Diabetes mellitus diet

As a matter of principle, over the course of the day, several smaller meals are recommended in order to prevent greater fluctuations in the need for insulin. Alcohol inhibits gluconeogenesis, thereby increasing the risk of hypoglycemia during insulin therapy. If alcohol is consumed, carbohydrates should be consumed at the same time.

The opinion that diabetic patients should be on a ‘diet low in sugars’ is widespread but not advantageous. The need for glucose does not decrease because of the disease.

Instead, a balanced diet with slowly absorbable saccharides should be adhered to. In

connection with sufficient fibers, slow sugar absorption can be achieved, reducing spikes in blood glucose levels. Fructose is processed independent of insulin but leads to more dyslipoproteinemia and excess weight than other sugars.

With regard to dietary recommendations, one has to differentiate between the types of diabetes. Hereby, one can memorize the following principles:

- Normalizing weight is of the highest priority in type 2 diabetes. With this, a break from the aforementioned **vicious cycle** can be achieved and the tendency for insulin resistance can be normalized again.
- Type 1 diabetic patients are frequently normal-weight or underweight. In this case, their diet must aim for an optimal balance between glucose supply and insulin delivery in order to avoid both hypoglycemia and hyperglycemia.

Pharmacological therapy for diabetes mellitus

Diabetes mellitus type 1 essentially depends on insulin delivery due to its absolute insulin deficiency. With regard to diabetes mellitus type 2, a phase-specific step therapy consisting of weight normalization, oral antidiabetics, and insulin is implemented.

Oral antidiabetic drugs (OADs)

The high prevalence of diabetes mellitus has led to a wide variety of OADs. Here, insulinotropic and non-insulinotropic medications should be differentiated.

- **Non-insulinotropic pharmaceuticals** have a more peripheral effect on the target tissue of the insulin and improve the effect of insulin on these tissues. The risk for hypoglycemia is significantly lower here. They are used especially at the initial phase of the disease.
- **Insulinotropic pharmaceuticals** cause increased insulin secretion in the beta cells and can also be used at the later stages of the disease. There is, however, an increased risk for hypoglycemia.

Among the non-insulinotropic OADs are **biguanides (metformin), alpha-glucosidase inhibitors (acarbose, miglitol),** and **glitazones (pioglitazone, rosiglitazone)**.

Non-insulinotropic antidiabetic	Important characteristics
Biguanides (metformin)	First-choice OAD; minimal risk of hypoglycemia or weight gain. **Note:** Pause 48 hours before and after elective surgeries or exposure to contrast agents. Risk of lactate acidosis.
Alpha-glucosidase inhibitor (acarbose, miglitol)	Inhibits the splitting of disaccharides in the small intestine; minimal risk of hypoglycemia or weight gain; frequent gastrointestinal side effects; works almost exclusively on postprandial blood sugar levels.
Glitazones (pioglitazone, rosiglitazone)	Third-line therapy in combination with, for instance, metformin, sulfonylurea or glinides; minimal risk of hypoglycemia. Contraindications: heart insufficiency, liver dysfunction; efficacy only after 2–4 weeks.

Among the insulinotropic substances are sulfonylureas (**glibenclamide, glimepiride**), glinides (**repaglinide, nateglinide**), and glucagon-like peptide 1 (GLP1)-based therapy via dipeptidyl peptidase-4 (DPP4) inhibitors (**sitagliptin, vildagliptin, saxagliptin**) or incretin mimetics (**exenatide, liraglutide**).

GLP1 is a small intestinal hormone, which is released during meals, promoting insulin

secretion and the release of glucagon and inhibiting gastric emptying. Therefore, GLP1 primarily stimulates insulin secretion under hyperglycemic conditions, meaning that under normoglycemic conditions, GLP1 has a minimal effect.

Note: At the time of diagnosis, there is frequently a relatively elevated insulin level because of the metabolic syndrome. Although insulinotropic substances improve blood glucose levels through even higher insulin release, they reinforce the metabolic syndrome at the same time.

Insulinotropic antidiabetic	Important characteristics
Sulfonylureas (glimepiride, glibenclamide)	They stimulate endogenous insulin secretion. Sulfonylureas are commonly third-line therapy or used if metformin is contraindicated. There is a risk of hypoglycemia and weight gain! Start off with low doses and under observation!
Glinides (repaglinide, nateglinide)	Similar effect to sulfonylureas with a significantly shorter half-life which is why it is administered 3 times daily. Start off with low doses under observation!
DPP4 inhibitors (sitagliptin, vildagliptin, etc.)	DPP4 is a key enzyme in GLP1 breakdown; due to the pharmacodynamics (see above) there is no risk of hypoglycemia; weight-neutral
Incretin mimetics (exenatide, liraglutide)	Have a structure similar to GLP1 but possess a breakdown-resistant structure; subcutaneous application; no hypoglycemia; weight loss could occur

Insulin therapies

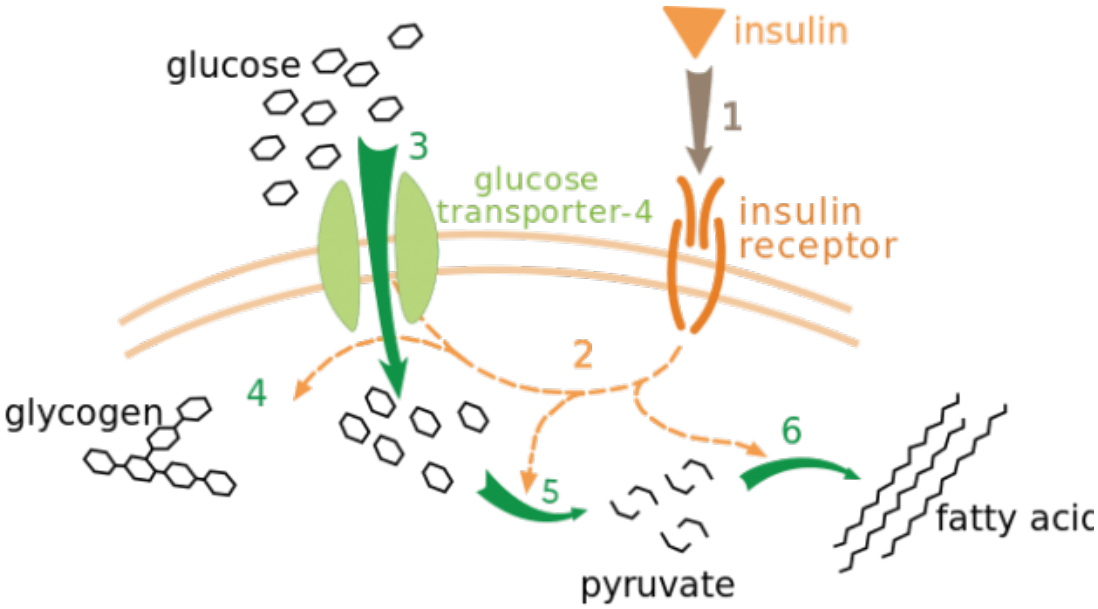


Image: “Effect of insulin on glucose uptake and metabolism. Insulin binds to its receptor (1), which in turn starts many protein activation cascades (2). These include translocation of Glut-4 transporter to the plasma membrane and influx of glucose (3), glycogen synthesis (4), glycolysis (5) and fatty acid synthesis (6). It works at other sizes, but sometimes truncates the text on the far right.” by Magnus Manske. License: Public Domain

Insulin is a polypeptide that causes glucose uptake in muscle and fat cells and supports anabolic metabolism. Hereby, insulin also ensures the intercellular transport of potassium.

Humans usually experience a permanent basal insulin release as well as a meal-dependent increased insulin release in order to manage the sudden surplus of sugar. If there is an absolute lack or relative deficit that can no longer be managed with OADs, insulin therapy is required, which should resemble as much as possible ‘natural’ insulin production.

In order to achieve this goal, different kinds of insulin with special pharmacokinetic characteristics are available:

Insulin characteristics	Insulin product

Rapid-acting insulin	Insulin lispro, insulin aspart, insulin glulisine; fast availability through a change in the amino acid sequence; efficacy after approximately 10 minutes; efficacy duration approximately 3.5 hours; no waiting between injection and meals is necessary.
Short-acting insulin	Regular insulin; first-generation insulin; efficacy after 30–60 minutes; efficacy lasts approximately 5 hours. If administered subcutaneously; a waiting period of approximately 20 minutes between injections and meals is necessary.
Intermediate-acting insulin	NPH (**Neutral protamine hagedorn**) insulin; efficacy after approximately 60 minutes; efficacy lasts approximately 9–18 hours
Long-acting insulin	Insulin detemir, insulin glargine; efficacy after 60 minutes; efficacy lasts up to 24 hours
Pre-mixed insulin	Mixes of short-acting and long-acting insulin with different mix ratios

In order to optimally cover the individual insulin need, there are different strategies that pay particular attention to the risks and options of patients:

1. **Basal supported oral therapy (BOT):** Here, oral antidiabetic therapy is supplemented with the administration of long-acting insulin.
2. **BOT plus therapy:** In addition to BOT, blood sugar spikes caused by intense meals are balanced with a short-acting insulin product.
3. **Conventional insulin therapy:** For patients with a regular daily routine and similar daily meals, pre-mixed insulin administered twice daily can be considered.

At breakfast and dinner time, a predetermined amount of insulin is administered, which covers the entire daily need. This concept is very easy to handle if the size of the meals remains constant. Problems can be caused by changes in daily routine (sports, alcohol, trips, etc.). This can cause dangerous hyperglycemia but also hypoglycemia.

4. **Intensified conventional insulin therapy:** Long-acting insulin is administered as a fixed basal insulin dose. The remaining daily insulin need is covered by additional doses depending on meals in case of blood sugar spikes. The amount of the necessary insulin must be determined individually which not only includes the pre-calculated meal size but also obtained fasting glucose values. This ensures the appropriate insulin delivery.

Absolute prerequisites for this therapy, apart from extensive diabetes training, are cooperative patients with the ability to therapeutically care for themselves with daily blood sugar self-monitoring in addition to care by a physician experienced in diabetes.

Note: This concept replaces physiological insulin production most successfully! This insulin concept, however, is not suitable for everyone.

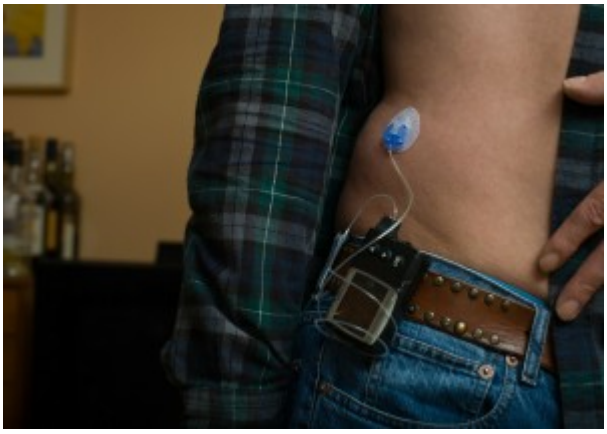


Image: “Insulin Pump and single malts” by Alden Chadwick.
License: CC BY 2.0

5. **Insulin pump therapy:** Regular insulin or a short-acting insulin analog may be administered subcutaneously via an external pump attached to a belt. The pump continuously delivers insulin at an hourly rate. At mealtimes, the user determines a calculated insulin bolus in accordance with the intensified conventional insulin therapy, which is ‘relayed’ to the pump so that the additional bolus is administered. This insulin pump is used, for instance, for pregnant women or in cases of a pronounced dawn phenomenon.

Treatment of acute blood sugar derailment

Acute hyperglycemia is part of the daily medical routine. Especially for emergency room situations, one should memorize a few useful basic thoughts:

- The administration of short-acting or long-acting insulin alone is not sufficient.
- Individual basal-bolus therapy should be calculated.
- For this, a basal insulin need of 0.5 E/kg body weight can be assumed without the risk of hypoglycemia becoming too great.
- Depending on the actual blood sugar status, this basal need will be increased, following a fixed correction scheme at first.
- Following this start of therapy, daily monitoring of the blood sugar situation with corresponding dose titration should be implemented.

A practical example of the determination of the starting dose: A patient weighing 80 kg needs 80 kg x 0.5 E/kg body weight = 40 E insulin per day. This is distributed over 40% of basal insulin and 60% of prandial blood sugar spikes at an assumed ratio of 2: 1: 1, meaning 12 E: 6 E: 6 E. Depending on the actual blood sugar level, this ratio is initially supplemented equally but the basal insulin amount remains the same.

The following table can be very helpful as a supplement and can be used in the clinical routine:

Measured pre-prandial blood sugar level	Additional insulin units in the morning	Additional insulin units at noon	Additional insulin units in the evening	Consistent basal insulin rate
below 100 mg/dL	-2	-2	-2	16
100–150 mg/dL	Starting dose	Starting dose	Starting dose	16
151–200 mg/dL	+2	+2	+2	16
20–250 mg/dL	+4	+4	+4	16

251–300 mg/dL	+6	+6	+6	16
> 300 mg/dL	+8	+8	+8	16

Hyperglycemia vs. Hypoglycemia–Symptoms and Emergency Medication

Acute derailments of blood glucose can be potentially life-threatening. Hyperglycemic and hypoglycemic conditions can lead to somnolence and coma. These metabolic conditions must be addressed quickly and correctly.

Hyperglycemia

Caused by insulin deficiency, hyperglycemia leads to hyperosmolar syndrome with intracellular dehydration.

Typical symptoms are:

- Loss of appetite
- Vomiting
- Thirst
- Polyuria
- Weakness
- Tachypnea
- Exsiccosis

At the same time (especially in type 1 diabetes), there is increased **lipolysis** which, through the accumulation of ketone bodies, leads to **metabolic acidosis (ketoacidosis)** with **pseudo-peritonitis** or **acidosis** (with the smell of acetone).

Therapy requires intensive medical measures. Need-oriented rehydration with the balancing of the **hyperosmolar syndrome** is crucial. Intravenous regular insulin at a low dose along with regular laboratory/chemical monitoring should achieve a mild decrease of the hyperglycemia. The acidosis can only be balanced with a significant pH change (< 7.1) with careful administration of bicarbonate.

Hypoglycemia

Different factors can cause hypoglycemia in diabetes: excessive insulin, alcohol, sports, or insufficient carbohydrates in the diet are the most frequent reasons.

Blood sugar levels of < 50 mg/dL are indicative of hypoglycemia. If the blood sugar level drops to the point that the assistance of third parties is needed, it is referred to as severe hypoglycemia.

Alert individuals can increase their low blood sugar with dextrose tablets or sugary drinks (**no sweeteners!!!**). Unconscious patients are administered highly concentrated glucose (20–60%) while regularly monitoring of their blood sugar levels. Quick recovery should occur within minutes. If this does not occur, another dose must be administered (while considering other reasons for the unconsciousness).

References

Allman, T. (2008). *Diabetes*. New York: Chelsea House Publishers.

Colwell, A. R. (1950). *Types of diabetes mellitus and their treatment*. Springfield, IL: C.C. Thomas.

Holt, R. I., & Wiley InterScience (Online service). (2010). *Textbook of diabetes*. Chichester, West Sussex: Wiley-Blackwell.

Ingram, W. W. (1943). *The diagnosis and treatment of diabetes*. Sydney: Angus & Robertson.

Keen, H., & Jarrett, J. (1982). *Complications of Diabetes*. London: E. Arnold.

Medfact, Inc. (1980). *Treatment of diabetes*. Massillon, OH: Medfact.

Saudek, C. D., Margolis, S., & Johns Hopkins Medicine. (2011). *Diabetes*. Baltimore, MD: Johns Hopkins Medicine.

Watkins, P. J. (2003). *ABC of diabetes*. London: BMJ Pub. Group.

Notes