Diabetes Mellitus — Types, Complications and Treatment

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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 of Diabetes Mellitus

Diabetes mellitus describes a heterogenic group of metabolic diseases whose basic characteristic is chronic hyperglycemia with subsequently elevated sugar contents 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 a 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 humans with diabetes mellitus, this mechanism is disrupted on different levels.

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

**Diabetes mellitus type 1**

Due to a destruction of beta cells, an absolute insulin deficiency is created. This destruction occurs due to either idiopathic (rarer) or immunological processes (approximately five percent of all diabetics in Germany).

Genetic factors play a predisposing role. A special type of this immunological form of diabetes is **LADA** (Late Autoimmune Diabetes in Adults), in which the diabetogenic metabolic condition will not occur until adulthood (> 25 years). **Pathological hyperglycemia** usually occurs from a beta cell loss of approximately 80%. In autoimmune diagnostics, one frequently finds antibodies against cytoplasmic islet cells, anti-GAD antibodies, insulin autoantibodies, and anti-2A tyrosine phosphate antibodies.

**Diabetes mellitus type 2**

In 90% of diabetes cases, a differently pronounced triad consisting of an insulin resistance of the target tissue, a secretory defect or a **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 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 **circulus vitiosus**. At the same time, a simultaneously progressing **atherosclerosis** develops via the **dislipoproteinemia** in connection with **diabetes mellitus type 2**, with numerous corresponding 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. A 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 the carbohydrate metabolism observed during pregnancy. In most cases, the diabetic metabolic tendency resolves after the end of pregnancy, however, with increased risk of a later manifestation of diabetes mellitus can occur. **Gestational diabetes** can increase the risk of **preeclampsia**, **hydramnion**, 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 were observed frequently.
Genetic defects of beta cells

There is a number of genetic defects causing hereditary diabetes mellitus. This affects approximately 1 % of all diabetics whereby most of them are affected by the disease at a very young age. This form of diabetes is referred to as Maturity Onset Diabetes of the Young (= MODY) which has different genetic causes. In order to shine during an exam, it would perhaps be prudent to memorize the most frequent MODY forms:

- **MODY2**: 15 % of all cases. The affected gene is glucokinase, 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 are, for instance, a disorder of the exocrine pancreas, endocrinopathy, medications (glucocorticoids, oral contraceptives, etc.), infections, cystic fibrosis, but also hemochromatosis. Obviously, a diabetic metabolic condition frequently occurs after pancreatic surgery as well. 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 extremely 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 itself through 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 affected patients to report leg cramps or vision problems.

Frequently, diabetes can be recognized in the skin as well. Typical is a reddening of the face (rubeosis diabeticca) or skin infections due to a weakened immunological barrier.

Furthermore, male patients report erectile dysfunction.

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 are, for instance, hyperglycemia or hypoglycemia, which is described in more detail below.
Complications of diabetes mellitus

The overall extent of the disease only becomes apparent, however, when considering the long-term effects which are created by chronic hyperglycemia.

The elevated blood sugar levels are present throughout the whole organism, 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, suffer certain damages over time.

Hereby, physicians distinguish between macroangiopathic damages with arteriosclerosis and microangiopathic damages through the glycosylation of proteins of the basal membrane.

Macroangiopathic damages caused by diabetes mellitus

As a matter of principle, the distribution pattern of the damages is unspecific. 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 damages (see below) frequently cause silent angina pectoris symptoms with pain-free infarctions meaning that in case of a suspected myocardial infarction, the medical history of the diabetic cannot be relied on!

Microangiopathic damages caused by diabetes mellitus

The dysfunction on the capillary level particularly affects the kidney, the retina, the nervous system as well as the intramural, smaller coronary arteries.

Diabetic nephropathy

While type 1 diabetes tends towards glomerulosclerosis (= Kimmelstiel-Wilson type), type 2 diabetes has an unspecified pattern of damage in the kidney. In Germany, diabetes mellitus is the most frequent reason to necessitate dialysis. 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
One assumes a microcirculation disturbance of the **vasa nervorum** in connection with the glycosylation of different neuronal proteins. This classically causes a peripheral sensomotoric neuropathy with distal, symmetrical characteristics. During the neurological examination, **areflexia** and **pallhypesthelia** are apparent aside from a trophic disorder of the lower legs and feet. The affected patients often report paresthesia (‘**burning feet syndrome**’) and finally experience paresis as well.

Aside from this distribution form, there is also diabetic polyneuropathy, a peripheral facial paresis or diabetic radiculopathy. Furthermore, neuropathy of the vegetative nervous system may frequently occur, whereby both the sympathetic and the parasympathetic may be damaged. Here, the symptoms are as varied as those of the autonomous nervous system. One differentiates between cardiovascular forms and autonomous diabetic neuropathies of the gastrointestinal tract, the urogenital system, the neuroendocrine system or thermoregulation.

**Tip for the clinical routine**: Diabetics often have warm and dry feet! This does obviously not apply in cases of simultaneous PAOD!

**The diabetic foot syndrome**

Many diabetics complain about injuries to the foot as a combined macro- and microangiopathic long-term complication. The diabetic foot syndrome represents the most frequent complication. One differentiates between different forms of diabetic foot syndrome:
The 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, almost painless ulcers.

The 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 that, unfortunately, exist in 35% of diabetic feet. In these cases, surgical amputations are more frequent than with the other forms.

Other complications of diabetes mellitus

Aside from micro- and macroangiopathic damages, diabetic cardiomyopathy can occur, which is an immunological decrease in resistance resulting in an increased tendency toward infections and lipid metabolism disorders, finally causing steatosis hepatis.

Diagnosis of Diabetes Mellitus

A diagnosis can be made on the basis of the 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 that were measured numerous times 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 high risk for diabetes is suspected, an oral glucose tolerance test is recommended.

Therefore, diagnosing diabetes mellitus is relatively easy. Due to the high prevalence as well as the 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 them can be performed easily and without any complicated equipment. With a thorough medical history, further (cardio)vascular risk factors must be inquired about 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 not provoke greater fluctuations in the need for insulin. Alcohol inhibits the glucogenesis, thereby increasing the risk of hypoglycemia during insulin therapy. If alcohol is consumed, carbohydrates should always be consumed at the same time.

The opinion that diabetics 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 for diabetics with type 2 diabetes. With this, a break from the aforementioned **circulus vitiosus** can be achieved and the tendency towards insulin resistance can be normalized again.
- Type 1 diabetics are frequently of 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 dangerous hypo- but also hyperglycemia.

The pharmacological therapy of diabetes mellitus

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

**Oral antidiabetics (OAD)**

The high prevalence of diabetes mellitus has motivated the industry, causing a wide variety of oral antidiabetic drugs to spread on the market. Here, differentiation should be made between insulinotropic and non-insulinotropic medications.

- **Non-insulinotropic pharmaceuticals** have a more peripheral efficacy on the target tissue of the insulin and improve its efficacy level. 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 on the beta cell and can also be used in the later stages of the disease. There is, however, an increased risk for relevant hypoglycemia.

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

<table>
<thead>
<tr>
<th>Non-insulinotropic antidiabetic</th>
<th>Important characteristics</th>
</tr>
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</table>
| Biguanides (metformin)          | OAD of the first choice, minimal risk for 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     | 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.  
(acarbose, miglitol)             |
| Glitazones (pioglitazone,       | 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.  
rosiglitazone)                  |
Among the insulinotropic substances are the group of the sulfonylureas (glibenclamide, glimepiride), the glinides (repaglinide, nateglinide) as well as the GLP1-based therapy via DPP4 inhibitors (sitagliptin, vildagliptin, saxagliptin) or incretin mimetics (exenatide, liraglutide).

GLP1 (= glucagon-like peptide 1) is a small intestine hormone, which is released during meals and promotes insulin secretion as well as the release of glucagon and inhibits gastric emptying. Therefore, GLP1 primarily stimulates the insulin secretion glucose-dependent and under hyperglycemia conditions, meaning that under normoglycemic conditions, there is a minimal effect of GLP1.

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

<table>
<thead>
<tr>
<th>Insulinotropic antidiabetic</th>
<th>Important characteristics</th>
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<tbody>
<tr>
<td>Sulfonylureas (glimepiride, glibenclamide)</td>
<td>They stimulate the endogenic insulin secretion, for third-line therapy or if contraindicated for metformin, risk of hypoglycemia and weight gain! Start off with low doses and under observation!</td>
</tr>
<tr>
<td>Glinides (repaglinide, nateglinide)</td>
<td>Similar effect to sulfonylureas with significantly shorter half-life which is why it is administered three times daily. Start off with low doses under observation!</td>
</tr>
<tr>
<td>DPP4 inhibitors (sitagliptin, vildagliptin, etc.)</td>
<td>DPP4 = Dipeptidyl peptidase-4 is a key enzyme in GLP1 breakdown, due to the pharmacodynamics (see above) no risk of hypoglycemia, weight neutral</td>
</tr>
<tr>
<td>Incretin mimetics (exenatide, liraglutide)</td>
<td>Pharmaceuticals with a structure similar to GLP1 but possess a breakdown-resistant structure, subcutaneous application, no hypoglycemia, weight loss</td>
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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 which causes the glucose uptake in muscle and fat cells and
supports the 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 a relative deficit, which can no longer be managed with oral antidiabetics, another therapy option with insulin must be found, which should come as close as possible to ‘natural’ insulin production.

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

<table>
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<tr>
<th>Insulin characteristics</th>
<th>Insulin product</th>
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<tbody>
<tr>
<td><strong>Rapid-acting insulin</strong></td>
<td>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 necessary.</td>
</tr>
<tr>
<td><strong>Short-acting insulin</strong></td>
<td>Regular insulin, first-generation insulin, efficacy after 30–60 minutes, efficacy duration approximately 5 hours. If administered subcutaneously, a waiting period of approximately 20 minutes between injection and meals is necessary.</td>
</tr>
<tr>
<td><strong>Intermediate-acting insulin</strong></td>
<td>NPH (Neutral Protamine Hagedorn) insulin, efficacy after approximately 60 minutes, efficacy duration approximately 9–18 hours</td>
</tr>
<tr>
<td><strong>Long-acting insulin</strong></td>
<td>Insulin detemir, insulin glargine, efficacy after 60 minutes, efficacy duration up to 24 hours</td>
</tr>
<tr>
<td><strong>Pre-mixed insulin</strong></td>
<td>Mixes of short-acting and long-acting insulin with different mix ratios</td>
</tr>
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</table>

In order to cover the individual insulin need optimally, 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, a pre-mixed insulin to be 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 easily handled if the size of the meals remains constant. Problems can be caused by changes in the daily routine (sports, alcohol, trips, etc.). This can cause dangerous hyper- but also hypoglycemia.

4. **Intensified conventional insulin therapy:** A long-acting insulin is administered as fixed basal insulin dose. The remaining daily insulin need is to be 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 the fasting glucose values at hand. This ensures the appropriate insulin delivery.

Absolute prerequisites for this therapy, aside from extensive diabetes training, are cooperative patients with the ability to therapeutically care for themselves with daily blood sugar self-monitoring as well as their care by a physician experienced in diabetes.
5. Insulin pump therapy: Regular insulin or a short-acting analog insulin may be administered subcutaneously via an external pump attached to a belt. The pump hereby continuously delivers insulin at an hourly rate. At meal times, 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 pronounced dawn phenomenon.

Treatment of acute blood sugar derailment

Acute hyperglycemic derailments are 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 insulins alone is not sufficient!
- An 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:

<table>
<thead>
<tr>
<th>Measured pre-prandial blood sugar level</th>
<th>Additional insulin units in the morning</th>
<th>Additional insulin units at noon</th>
<th>Additional insulin units in the evening</th>
<th>Consistent basal insulin rate</th>
</tr>
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<tbody>
<tr>
<td>below 100 mg/dL</td>
<td>-2</td>
<td>-2</td>
<td>-2</td>
<td>16</td>
</tr>
</tbody>
</table>
### Hyperglycemia vs. Hypoglycemia—Symptoms and Emergency Medication

Acute derailments of blood glucose can potentially take life-threatening turns. Hyper- as well as hypoglycemic conditions, can hereby take a somnolent but also a comatose turn. These metabolic conditions must be cared for quickly and correctly.

#### Hyperglycemic derailment

Caused by the insulin deficiency, the 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 diabetics), 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).

The therapy requires intensive medical measures. A need-oriented rehydration with balancing of the **hyperosmolar syndrome** should take place. Intravenous regular insulin at a low dose along with regular lab/chemical monitoring 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.

#### Hypoglycemic derailment

Different factors can cause hypoglycemia in diabetics: Too much insulin, alcohol, and sports or too little carbohydrates in their diet are the most frequent reasons.

From blood sugar levels of < 50 mg/dL on, one refers to a mild hypoglycemia. If the blood sugar level drops to the point that the assistance of third parties is needed, one refers to it as severe hypoglycemia.

Alert individuals can stop their blood sugar drop with dextrose tablets or sugary drinks (**no sweeteners!!!**). Unconscious patients are administered highly concentrated glucose (20–60 %) while regularly monitoring their blood sugar levels. Afterward, quick recovery should occur within minutes. Should this not be successful, another dose must be administered (as well as considering other reasons for the unconsciousness).
Review Questions

1. An 80-year old patient has had known diabetes mellitus for several decades. For the past several weeks, the patient has been suffering from bloating and pressure in the upper abdomen. What suspected diagnosis best fits these statements?

   A. Hyperglycemic ketoacidosis  
   B. Posterior myocardial infarction  
   C. Chronic pancreatitis  
   D. Gastroparesis  
   E. Boerhaave syndrome

2. For the etiology of diabetes mellitus type 1, genetic components play a role as well. Which statement is the most fitting here?

   A. As a rule, diabetes mellitus type 1 begins between the first and second year of life.  
   B. There is an underlying inherited, autosomal-dominant disorder of insulin release.  
   C. In diabetes mellitus type 1, one typically comes across more affected first-degree relatives than in diabetes mellitus type 2.  
   D. For the genetic predisposition for diabetes mellitus type 1, alleles in the HLA area play a role.  
   E. In diabetes mellitus type 1, physicians differentiate between monogenic inheritance with reduced penetration and the so-called Maturity Onset Diabetes of the Young (=MODY).

3. Insulin deficiency can lead to dehydration. Here, what is of most significance pathophysiologically?

   A. Osmotic diuresis  
   B. Pressure diuresis  
   C. Forced diuresis  
   D. Terminal glomerular kidney damage  
   E. Impaired urethral tonus of the Sphincter due to autonomous diabetic damages

4. A 57-year old woman, who has had known diabetes mellitus type 2 for the past three years, is coming to see you for the first time. You would like to examine the woman for possible complications. Which parameters do you use to best look for the first signs of diabetic nephropathy?

   A. Glycosuria  
   B. Testing becomes necessary only after at least five years  
   C. Microhematuria  
   D. Serum creatinine concentration  
   E. Microalbuminuria

References


**Correct answers:** 1D, 2D, 3A, 4E

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