Patients who have been suffering for years from high blood sugar concentration can expect serious consequences for their entire bodies.

Accurate knowledge of the complications that may arise in the course of the disease is important not only for the exam. Physicians may significantly contribute to the problem, so that amputations, blindness, kidney damage and cardiovascular disease can be avoided.

Introduction

The long-term diabetes mellitus (DM) causes damage to small and large blood vessels, resulting in microvascular and macrovascular complications, respectively, with subsequently increased mortality rates. The strict glycemic control is a cornerstone in the prevention of these complications, especially the microvascular ones such as retinopathy, nephropathy and neuropathy. Therefore, early diagnosis and early treatment measures to ensure euglycemia are crucial to increase the length and quality of life of diabetic patients.
Risk of Long-Term Complications

<table>
<thead>
<tr>
<th>Complications</th>
<th>Relative risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardial infarction</td>
<td>Men: 3.7</td>
</tr>
<tr>
<td></td>
<td>Women: 5.9</td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>Diagnosis before the age of 30: 9.1</td>
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<tr>
<td></td>
<td>Diagnose after the age of 30: 2.3</td>
</tr>
<tr>
<td>Apoplexy</td>
<td>2-4</td>
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<tr>
<td>Blindness</td>
<td>5.2</td>
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<tr>
<td>Renal failure in men</td>
<td>12.7</td>
</tr>
<tr>
<td>Lower-extremity amputations</td>
<td>22.2 to 45</td>
</tr>
<tr>
<td>Foot ulcers</td>
<td>Frequently</td>
</tr>
</tbody>
</table>

Macroangiopathy

Hyperglycemia increases the risk of atherosclerosis that leads to the stiffness and narrowing of the vessel walls. Even non-diabetics suffer from arteriosclerosis, but diabetes increases this risk multiple times. This is caused by the vascular endothelium dysfunction, which is favored by hyperglycemia.

Firstly, the dysfunction is caused by glycated LDL. These molecules penetrate the tunica intima and activate oxidative and inflammatory processes there, resulting in the typical plaques in the endothelium. Secondly, lipolysis is not inhibited by a lack of insulin. Resulting atherosclerosis and vessel narrowing present in a variety of conditions, such as:

- PAOD (peripheral arterial occlusive disease), intermittent claudication;
- CHD (coronary heart disease), myocardial infarction;
- Carotid stenosis (cerebrovascular sclerosis);
- Transient ischemic attack, stroke.

Myocardial infarction is particularly dangerous for the diabetics as it often occurs painlessly, unnoticed by the patients, due to the concurrent diabetic neuropathy. 60% of all diabetics die from cardiovascular disease.

Reducing the cardiovascular risk factors, in addition to the blood glucose monitoring, are essential preventive measures in diabetic patients. Such factors as obesity, lack of exercise, smoking and alcohol consumption contribute to the development of macroangiopathy and should be largely eliminated. Hypertension and hyperlipidemia are other risk factors that need to be appropriately managed. The administration of anticoagulants is also useful to prevent the formation of thrombi.

Microangiopathy

As previously mentioned, diabetes mellitus affects the small vessels (microangiopathy) in addition to large vessels (macroangiopathy). Hyperglycemia results in non-enzymatic glycosylation of proteins. These advanced glycosylated end products are accumulated in structural proteins and connective tissue within the capillary basement membranes and renal glomeruli. The result is vessel occlusion, ischemia, hypoxia and reduced glomerular filtration rate (GFR).

Microangiopathy is often symptomatically linked to the eye, kidney and nerves, but it can also affect other areas of the body.
Diabetic retinopathy is divided into non-proliferative retinopathy and proliferative retinopathy.

**Non-proliferative retinopathy**, also called **background retinopathy**, is the earliest stage of retinal involvement in diabetic patients. It is characterized by microaneurysms, dot hemorrhages, exudates and retinal edema.

**Proliferative retinopathy** presents with the formation of new blood vessels. Due to hypoxia, which is the consequence of hyperglycemia, growth factors are increasingly formed and new blood vessels appear (neovascularization). In this case, VEGF (vascular endothelial growth factor) plays a decisive role, which is detectable in blood and can be inhibited by drugs.

The new blood vessels can grow even in the vitreous humor. However, it is quite dangerous as they are very unstable and may cause bleeding in the eye. If the newly formed blood vessels do not lead to any vision problems, or only slight impairment is noticed, then we deal with non-proliferative retinopathy. If increased bleeding into the vitreous humor and the new blood vessels do cause problems, it is called proliferative retinopathy. The consequences range from blurred vision to retinal detachment, glaucoma and blindness.

**Diabetic macular edema** is defined as retinal thickening within the center of the macula, due to the plasma leakages. It can occur at any stage of diabetic retinopathy.

**Note:** Diabetes is the leading cause of acquired blindness in the developed countries.

**Treatment of diabetic retinopathy**

Diabetic retinopathy is primarily treated by **laser therapy**. It should be performed as soon as neovascularization or vitreous hemorrhage has occurred. The **intravitreal corticosteroids** (dexamethasone, triamcinolone and fluocinolone) positively affect a diabetic macular edema.

**Angiogenesis inhibitors** such as Pegaptanib and Bevacizumab directly block vessel growth-promoting substances (VEGF) in the eye that lead to swelling of the central retina. In many cases, they are repeatedly injected in the eye every few weeks.
Diabetic Nephropathy

Diabetic nephropathy is divided into five progressive stages which asymptomatically run at the beginning, being partially reversible. However, they eventually lead to irreversible damage. Depending on the stage, we may observe different symptoms; therefore, corresponding therapeutic measures are necessary to be taken. In the first place, however, **euglycemia** and **normotension** are the primary **treatment goals** in all the stages.

**Stage 1** is “high glomerular filtration stage.” This stage is reversible, asymptomatic and characterized by increased GFR. The hyperglycemia leads to enlarged kidneys and increased filtration capacity.

**Stage 2** is “normal albuminuria stage.” This stage is reversible, asymptomatic and characterized by normal albumin excretion in urine (< 30mg/24h). It usually begins after several years of diabetes. The basement membrane of the glomeruli is considerably thickened, the mesangial matrix is increased, and consequently, the filtration performance is already restricted.

**Stage 3** is “early stage diabetic nephropathy.” It is characterized by **microalbuminuria** (30 – 300mg/24h) and **hypertension**. The diffuse glomerular changes can be seen and glomeruli become more permeable to proteins. These symptoms usually occur only after 5 to 15 years of diabetes. They are a sign of the beginning of **renal failure**. The treatment of this stage with **angiotensin-converting enzyme inhibitors (ACEIs)** is recommended to protect the kidneys, lower the protein excretion and normalize blood pressure.

![Image: “Histopathological image of diabetic glomerulosclerosis with nephrotic syndrome,” by KGH. License: CC BY-SA 3.0](image)

**Stage 4** is “clinical diabetic nephropathy.” It is characterized by excretion of large amounts of albumin (> 500mg/24hour) and often occurs after 10 to 25 years of diabetes. The renal hypoperfusion, hypertension and reduced filtration performance is also seen. In addition to ACE inhibitors, diuretics, calcium channel blockers and beta-blockers may be used during this stage. Though the GFR continues to decline in this stage, the serum creatinine level may be normal.

**Stage 5** is “renal failure,” which is an irreversible stage. The filtration performance is dramatically reduced, and pathological creatinine values are detectable in the blood. Since the renal failure is irreversible, only dialysis and renal transplantation remain as therapeutic measures.
Diabetic Neuropathy

The persistent chronic hyperglycemia leads to neuropathy affecting the quality of life. The neurons are affected due to ischemia and insufficient oxygen supply because of angiopathy. Both the peripheral and the autonomic nerves may be affected.

The earliest symptoms of diabetic neuropathy often present as tingling, pain and numbness in the extremities. These symptoms are the warning signs and should not be ignored.

If not properly managed, the peripheral nerve fibers are progressively damaged in a glove-and-stocking distribution, resulting in reduced or complete loss of pain perception. The injuries will remain unnoticed by the patient and can spread in an unhindered way. A diabetic foot is an especially dangerous complication that can lead to the amputation of the limb.

Diabetics should necessarily obtain insured medical foot care for the prevention of a diabetic foot syndrome. In addition, attention should be paid to suitable footwear. Diabetic patients should check their feet daily for any injuries, abrasions or scratches. In the case of very painful neuropathies, tricyclic antidepressants, such as amitriptyline, may be of benefit. Furthermore, Gabapentin and Pregabalin are effective drugs against neuropathic pain.

If the autonomic nerves are damaged, it may cause multiple effects on the body. So, diabetics may suffer from the following afflictions:

- Erectile dysfunction;
- Dizziness, syncope (fainting);
- Diabetic gastroparesis, diarrhea, constipation;
- Diabetic cystopathy with frequent infections;
- Circulatory disorders of the skin;
- Heartburn, difficulty swallowing (dysphagia), gastroparesis;
- Related cancers.

Other Complications
Apart from typical long-term consequences, diabetes also causes other complications that are less well-known. These include stiff shoulder (frozen shoulder) or finger/hand changes (cheiropathy). Diabetic neuropathic osteoarthropathy (DNOAP), also called neuropathic arthropathy, is a disease which leads to a non-infectious, inflammatory destruction of bones and joints. It represents a special form of diabetic foot ulcers.

In diabetes mellitus type 1, there is increased prevalence of other autoimmune disorders such as Hashimoto’s thyroiditis, Addison’s disease, vitiligo and pernicious anemia.

Review Questions

The correct answers can be found below the references.

1. Which disease cannot be included in the list of macroangiopathic complications of diabetes mellitus?
   - A. Peripheral arterial occlusive disease
   - B. Coronary heart disease
   - C. Transient ischemic attack
   - D. Diabetic nephropathy
   - E. Carotid stenosis

2. Which medication is suitable for the treatment of diabetic retinopathy?
   - A. Anakinra
   - B. Adalimumab
   - C. Rituximab
   - D. Bevacizumab
   - E. Imatinib

3. Stage 3 of diabetic nephropathy is characterized by...
   - A. ...microalbuminuria and hypertension.
B. ...macroalbuminuria.
C. ...symptomlessness.
D. ...necessity of dialysis.
E. ...kKetonuria and basement membrane damage.

References


Correct answers: 1D, 2D, 3A

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