DIABETIC RETINOPATHY – RISK FACTORS, PATHOGENESIS, DIAGNOSIS AND TREATMENT
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ABSTRACT
Diabetic retinopathy (DR) or diabetic eye disease, is the major long-term complication of diabetes and main cause of vision impairment and vision loss. Major risk factors of the disease are the diabetes duration and glycemia (hyperglycemia and glycemic variations). One can also distinguish high blood-pressure, lipid disorders, pregnancy and puberty, age at diagnosis, ethnicity and genetic disorders among others. Diabetic retinopathy develops as a consequence of long-term accumulation of damage of retinal vessels. Its most advanced, proliferative stage leads to complications that are a direct cause of vision impairment or vision loss. The mechanism of this pathology includes macular oedema, vitreous hemorrhage, neovascular glaucoma and tractional retinal detachment by fibrovascular proliferations. Diabetic eye disease remains asymptomatic at the primary stages. In more advanced phases gradual vision acuity impairment is reported. In some cases, type 2 diabetes is diagnosed at the same moment as diabetic eye disease, which threatening with blindness. Running screening tests (fundus photography) allow to detect early, asymptomatic disease’s stages. Most frequently used diagnostics method to recognize DR ad hoc is direct ophthalmoscopy. Other useful methods are optical coherence tomography (OCT) and fluorescent angiography among others. Regular routine tests play a crucial role in DR diagnose. Pregnant women should be treated with special attention. The most substantial form of treatment and/or prevent from progress is intensification of metabolic control, minimalization of glucose fluctuations and achieve the normoglycemia. Laser coagulation and vitrectomy are also recommended, bearing in mind that their early performance gives better results. Intravitreal application of vascular endothelial growth factor (VEGF) antagonists and steroids has a positive impact on macular oedema.
Diabetic retinopathy (DR) is the major long-term complication of diabetes and is the main cause of vision impairment and vision loss [1]. DR is the leading cause of blindness worldwide [2]. According to WHO (World Health Organization) affects 2.6% of blind people [3]. Percentage of population older than 40 years in the United States suffer from DR (also known as diabetic eye disease) is reported from 28 to 40%. [4]. Rapid increase of diabetes incidence observed in recent years, from 108 million in 1980 to estimated 422 million in 2014, is mostly owed to lifestyle changes and the ageing of population. It would seem to lead to the increasing cases of chronic diabetic complications worldwide. On the other hand, DR is less and less common reason of vision loss, which is observed especially in developed countries [5].

**RISK FACTORS**

The major risk factor for developing diabetic eye disease is the duration of diabetes. In epidemiologic study of Wisconsin group, representative for white population, after 20 years of illness about 99% of people with type 1 diabetes and 60% with type 2 diabetes develop changes characteristic for retinopathy [6].

Another important factor is the self blood glucose monitoring. Diabetes Control and Complications Trial (DCCT) was a randomized, cutting-edge trial, which proved that intensive treatment and glycemic control can significantly diminish the risk of developing diabetic eye disease and slow down its progression, concerning insulin-dependent diabetes mellitus. As far as the primary prevention of the retinopathy is concerned, the prevalence was 76% lower and in case of secondary prevention it was 54% lower comparing with conventional therapy [7]. Tight blood pressure control may also limit the development and progression of the disease [8], however to a lesser degree than the glycemic control.

The dependency between the blood concentration of certain lipid fractions and the development of diabetic retinopathy is complex. [9] Paradoxically, lower levels of cholesterol were detected in patients suffering from DR. However, they were also taking more medication in order to reduce the lipid blood levels. More than double higher incidence of the illness was noted in patients treated with insulin compared with the subjects treated by oral antidiabetic drugs (53.6% versus 19.6%, respectively). Mikroalbuminuria also turned out to be an important parameter, since the process commonly occurs in patients with diabetic retinopathy [10]. Pregnancy and puberty should not be forgotten, due to the fact that they constitute independent risk factors of the DR.

Other risk factor is the age at diagnosis - when it is less than 30 years it is related with later developing advanced stages of the disease in comparison with those, who had the diabetes diagnosed at the age of 30 or older [11, 12]. Among genetic factors, which could contribute to the progression of the disease, genes that code agents responsible for the molecular pathogenesis are taken into account. These include angiotensin converting enzyme (ACE), nitric oxide synthase (NOS2A, NOS3), vascular endothelial growth factor (VEGF), protein kinase C-beta (PKC-beta) and receptors for advanced glycation end products among others. Diabetic eye disease incidence is also higher among Hispanics and African-Americans [13].

Moreover, no significant difference in incidence was discovered between men and women. Despite the assumptions, tobacco smoking, a history of cardiovascular incidents or waist-to-hip ratio have no influence on the development of the disease [10].

**Pathogenesis:**

This medical condition results from long-term accumulation of damage of retinal vessels. Chronic blood flow disorders and ischaemia lead to a certain reaction of capillaries, veins and arteries as well as the tissue of retina. The coexistence of blood-retinal barrier impairment, thickening of basal lamina and deficiency of pericytes results in microaneurysms, intraretinal ecchymosis and blood outpouring, ischaemic areas, intraretinal microvascular abnormalities and, in the last phase – proliferation of new vessels and fibers. The proliferative stage leads to the complications that are a direct cause of vision impairment or vision loss. The most important of these include vitreous hemorrhage, neovascular glaucoma and tractional retinal detachment by fibrovascular proliferations.

An essential phenomenon is also macular oedema, which may be diagnosed even at early, benign stages of the disease. It is the most common cause of vision loss, especially in noninsulin-dependent diabetes mellitus.

**Symptoms:**

Diabetic eye disease remains asymptomatic at the primary stages. It does not cause vision impairment nor pain afflictions. It may only be diagnosed during specific ophthalmological examination. In case of more advanced phases gradual vision impairment is reported. It manifests itself in impaired visual acuity, distorted images or spots floating in a visual field. Macular oedema can cause cloudy vision. In some patients sudden, painless vision loss may appear, which is caused usually by vitreous hemorrhage in proliferative diabetic retinopathy. In some cases, type 2 diabetes is diagnosed when diabetic eye disease, threatening with blindness. Those patients may suffer from diabetes for many years without being aware of it.

**Prevention & diagnosis:**

Running screening tests allow to detect early, asymptomatic disease’s stages and provide a possibility to initiate proper treatment. Diagnosis should be taken, early enough to prevent the progression to more advanced stages.

According to newest Polish Diabetes Association (PTD 2016) in case of patients with type 1 diabetes the first examination should be performed within first 5 years since symptoms have occurred. On the other hand, patients with diabetes type 2 ought to undergo proper tests in the same time or shortly after the diagnosis is confirmed. However, if patient is diagnosed during puberty, examination should be carried out immediately after identifying disease. It is also essential to follow up these patients. Frequency of medical check-ups depends on the severity of the disease.
on patients’ state of health and stage of observed changes in eye’s fundus. Pregnant women should be treated with special attention. They have to be followed-up during whole period of pregnancy, with check-ups every 1-3 months.

The most common method of screening tests are digital, colored images of eye’s fundus, which, however, cannot substitute a comprehensive ophthalmic examination. Another reason standing by these screening tests is their economical advantages for governments, which bear the costs of the care of blind people. An example in this case is Great Britain which pays approx. 7452 pounds per one blind. In contrast, the cost of one test is 29.99 pounds [14].

Most frequently used diagnostics method, especially by general practitioners, is direct ophthalmoscopy, because of zoomed images of retina’s details such as optic disk, retinal vessels and fovea. Despite the fact, that this examination is characterized by poor sensitivity and specificity, it is useful in detecting a diabetic retinopathy ad hoc.

Fluorescent angiography seems to be a crucial examination as well – an invasive dynamic test, which is able to expose such specific structures as individual retinal capillary vessels. None of presently available, fully objective, external systems of imaging, doesn’t give us such possibilities. During this examination we can observe progressively decreasing intensity of fluorescence. After 30-60 minutes only those molecules stay visible, which cause staining of inappropriate retinal structures and vessels.

Optical coherence tomography (OCT) test serves mainly for evaluation and monitoring of patients with macular oedema. Diagnostician receives high-resolution images, which can be used to examine retina’s thickness (previously possible only in postmortnal histopathological analysis). Ultrasound is particularly useful in evaluating density and expansion of vitreous haemorrhage and tractional retinal detachment.

TREATMENT

The most substantial form of treatment, particularly in initial phases of the disease, is intensification of insulin therapy. However, we should also beware of “early worsening” effect observed during the examination after 6 and/or 12 months, which most important risk factor is higher HbA1c (glycated haemoglobin) level in the screening examination and its rapid reduction during first 6 months [15]. Tight blood pressure control and lipid disorders treatment should not be ignored. What is more, cardioprotective doses of aspirin are not contraindicated in patients with DR, since they do not pose a threat of vitreous hemorrhage.

Another method of treatment is laser photoocoagulation of retina, which requires an unobscured view of the retinal tissue. It is important to remember that early conduction of the procedure suppresses the progression of diabetic retinopathy. Some contraindications to perform laser coagulation suggest carrying out cryotherapy. It does not reverse the damage of the retina but limits the process and prevent the progression.

Vitrectomy is a surgical intervention commonly used in order to remove the vitreous hemorrhage or macular involvement detachment. Also, early performance of the operation concerning less advanced stages of the disease leads to more satisfying therapeutic effects. Moreover, it causes postoperative vision acuity improvement. It is connected, though, with the risk of rarely occurring complications such as redetachment, iatrogenic retinal brakes, recurrent hemorrhages and neovascular glaucoma [16].

Severe stages of macular oedema require intravitreal application of VEGF antagonists: aflibercept, ranibizumab, bevacizumab, with the last one administered off-label [17]. Injections are a first-line therapy in any form of macular oedema involving central fovea. Studies showed that this treatment leads to significant improvement of visual acuity, central retinal thickness and patient-reported outcome 12 months after treatment start [18].

Macular oedema may also be treated by intravitreal or periocular application of steroids, having antiangiogenic and antiswelling effect, including triamcinolone or dexamethasone in an extended release system. Positive effects of this therapy on reducing macular oedema with concurrent lack of proceeding inflammation has also been documented [19]. Rehabilitation of blind people plays an important role if the irreversible vision loss appears.
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