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Expert group position statement on the use of sulodexide as adjunctive therapy in mild to moderate diabetic retinopathy

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DIABETIC RETINOPATHY – EPIDEMIOLOGY

Diabetic retinopathy (DR) remains the leading cause of vision loss in the working age population [1]. The number of patients with diabetes mellitus is growing exponentially, and the WHO has declared the disease a 21st century epidemic. Currently, an estimated 415 million people (8.8% of the population) – or one in 11 of the world's adults – are living with the disease. In Poland, according to the 2019 National Health Fund (NFZ) report, nearly 3 million people (9.1% of the population) have diabetes [2]. Approximately one in three people with the disease develop diabetic retinopathy. The incidence increases with the duration of the underlying disease. Factors elevating the risk of DR include metabolic decompensation of the underlying disease, abnormal lipid profile, as well as arterial hypertension. Unfortunately, some diabetic patients, despite normal parameters determined in the evaluations listed above, develop microangiopathy. Therefore, the

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role of partially identified genetic factors predisposing to the development of vascular complications of diabetes mellitus is being increasingly highlighted.

DIABETIC RETINOPATHY – CLASSIFICATION

Classification of the severity of diabetic retinopathy is based primarily on the analysis of ophthalmoscopy fundus images, as well as the results of retinal optical coherence tomography and fluorescein angiography (Table I) [1].

Typical signs of non-proliferative DR include microaneurysms, intraretinal hemorrhages, hard exudates (lipid and protein deposits), cotton wool spots (axoplasmic stasis in the ganglion cell layer secondary to retinal ischemia), venous dilation and beading, and intraretinal vascular abnormalities. **Hard exudates associated with DR reflect an increase in vascular permeability secondary to vascular injury. Their presence is indicative of current or prior diabetic macular edema.**

In the advanced stage of DR (proliferative diabetic retinopathy, PDR), the dominant feature of the disease is neovascularization. Changes of this type arise from the presence of large ischemic retinal areas secondary to the occlusion of damaged peripheral capillaries. Depending on its location, the observed neovascularization is divided into two types: new vessels on the disc (NVD) and new vessels elsewhere (NVE). Typically, NVE develops at the junction between normally perfused and ischemic retinal regions.

Diabetic macular edema (DME) is a distinct type of the discussed microangiopathy, occurring either in isolation, i.e. without accompanying changes typical of DR, or coexisting with non-proliferative/proliferative DR. The progression of DME is independent of the stage of DR. Ophthalmoscopic abnormalities typically identified in patients with diabetic macular edema include intraretinal hemorrhages, hard exudates, cotton wool spots, and an increase in central retinal thickness. The observed symptoms of DME result from the disruption of the blood-retinal barrier.

SULODEXIDE – MECHANISM OF ACTION

Endothelial cells line the inner surface of all blood vessels including the retinal capillary vasculature. Healthy endothelium contributes to the maintenance of intravascular homeostasis, thus ensuring blood fluidity, and regulates the rate of blood flow through the vessels. In addition, it provides a dynamic barrier allowing exchange between the intra- and extravascular space (a component of the blood-retinal barrier). The endothelial surface is coated with a mixture of glycoproteins and proteoglycans, i.e. membrane-bound protein cores linked to chains of polysaccharides (glycosaminoglycans, GAGs), glycolipids, and free polysaccharide chains. The layer, referred to as the glycocalyx, is characterized by antithrombotic properties. This negatively charged surface (GAGs are polyanions) provides electrostatic and mechanical protection of endothelial cells, determines their resistance to damage, maintains the integrity of the vascular wall, and mediates interactions between the blood flow and endothelial cells (mechanotransduction) [15].

In patients with diabetes mellitus, even before the morphological markers indicating disruption of endothelial continuity and function are visible on diagnostic/imaging examinations, the glycocalyx layer in the vascular bed, including retinal vessels, becomes thinner [9]. Impairment in the function of the described endothelial cells results in the loss of their antithrombotic, profibrinolytic, and vasodilatory properties. In addition, deterioration of the rheological properties of blood (elevated viscosity) caused by hyperglycemia and the most commonly coexisting lipid disorders slows down blood flow in the small retinal vessels and induces a local inflammatory response (facilitated leukocyte adhesion to the endothelium – leukostasis), which in combination with oxidative stress (secondary to hyperglycemia) causes retinal capillary damage typical of diabetic retinopathy. The use of antioxidant supplements in the early stages of diabetes improves metabolic status to some extent, but has no effect on the regeneration of the glycocalyx, resulting in its progressive thinning and impairment of function. Thus, identifying early changes indicative of diabetic retinopathy on ophthalmologic examination is not the "first alarm bell" to start therapy, but rather one of the final bells, if the progression of the disease, which has a damaging effect on the retinal vessels, is to be halted or slowed down.

Currently, means and methods are being sought to prevent the phenomena discussed above already at the early stages of diabetes. One of the agents known to have a protective effect on endothelial cells is sulodexide, which is a mixture of glycosaminoglycans naturally occurring in the body: a fast-moving heparin fraction (80%) and dermatan sulfate (20%) [3]. The drug's activity is based on its ability to inhibit the intravascular inflammatory reaction by reducing the blood concentration of proinflammatory cytokines and vascular endothelial growth factor (VEGF), and the protective effect on the endothelium which is exerted, among other processes, by lowering the susceptibility of cells to the cytotoxic effect of hyperglycemia, and suppressing intracellular oxidative stress and inflammation [4-6]. Another important effect is the ability of sulodexide to bring down the level of blood lipids through the activation of lipoprotein lipase, which reduces the cytotoxic effect of plasma on endothelial cells. Also, the profibrinolytic properties of the drug resulting in a reduction of fibrinogen levels decrease the viscosity of whole blood, improving rheological characteristics and blood flow in small blood vessels [12, 13]. A highly valuable property of sulodexide is that it contains naturally occurring glycosaminoglycan molecules which are present in the glycocalyx of endothelial cells. By binding to the surface of endothelial cells, sulodexide modifies the structure and properties of the glycocalyx, while affecting the function of these cells. The size and structure of the glycocalyx can become disrupted in various pathological conditions, such as ischemia/reperfusion or hypoxia, or under hyperglycemic circumstances [7, 8]. In diabetic patients,

Table I. Classification of the stage of diabetic retinopathy

Complication stage	Ophthalmoscopic findings
Diabetic retinopathy (DR)	
No apparent retinopathy	No abnormalities
Mild non-proliferative DR One- and five-year risk of developing proliferative retinopathy – 5% and 15%, respectively	Microaneurysms only
Moderate non-proliferative DR One- and five-year risk of developing proliferative retinopathy – 12-27% and 33%, respectively	Microaneurysms and other abnormalities (intraretinal hemorrhages, hard exudates, cotton wool spots) present but not meeting the criteria for the diagnosis of severe non-proliferative DR
Severe non-proliferative DR One- and five-year risk of developing proliferative retinopathy – 52% and 60%, respectively	Presence of any of the following symptoms: • intraretinal hemorrhages (≥ 20 in each quadrant) • venous narrowing (in two quadrants) • intraretinal vascular anomalies (in one quadrant) no signs of proliferative DR
Very severe non-proliferative DR One-year risk of developing proliferative retinopathy – 75%	More lesions listed above, multiple vascular occlusions, cotton wool spots, and particularly IRMA (intraretinal microvascular anomalies)
Early proliferative diabetic retinopathy	Severe non-proliferative DR and one or more of the following changes: • superficial retinal neovascularization • preretinal hemorrhage
Advanced proliferative diabetic retinopathy	As above, and additionally limited retinal detachment, neovascularization of the optic disc, vitreous hemorrhages
Diabetic macular edema (DME)	
No DME	No retinal thickening and hard exudates in the macular area
Presence of DME	Retinal thickening or **hard exudates** in the posterior pole
Mild DME	Retinal thickening or **hard exudates** in the posterior pole but outlying from the center of the macula (1000 µm in diameter)
Moderate DME	Retinal thickening or **hard exudates** approaching the center of the macula (1000 µm in diameter) but not involving the center of the macula
Severe DME	Retinal thickening or **hard exudates** involving the center of the macula
Classification based on DME location	
Non-central-involved DME	Retinal thickening in the macula not involving the central zone that is 1 mm in diameter
Central-involved DME	Retinal thickening in the macula involving the central zone that is 1 mm in diameter

thinning of the glycocalyx layer in the endothelium of blood vessels has been found, resulting in greater permeability of vascular walls to macromolecules [9]. Sulodexide used at a dose of 200 mg/day for a period of two months led to the thickening of the glycocalyx layer on the retinal vascular endothelial surface, with a concomitant decrease in its permeability [9, 10]. The authors also confirmed a decrease in plasma hyaluronidase activity after sulodexide treatment. These findings provide evidence that sulodexide has a protective effect on the glycocalyx which arises not only from providing a substrate for the regeneration of this structure, but also from blocking the activity of the enzymes that degrade it. Other clinically important characteristics of the drug include its effects on increasing HDL cholesterol levels during treatment and decreasing triglyceride levels, which is not to be underestimated in the treatment of diabetic patients [14].

DRESS (DIABETIC RETINOPATHY SULODEXIDE STUDY)

The efficacy and safety of sulodexide has been demonstrated in a number of randomized controlled clinical trials. Evidence for the beneficial effect of the drug in patients with

diabetic retinopathy was collected in a study by Ji Hun Song *et al.* [11]. The randomized, placebo-controlled, multicenter study involved patients with mild-to-moderate non-proliferative diabetic retinopathy secondary to type 1 and type 2 diabetes mellitus, and relatively good visual acuity (n = 130). The aim of the study was to evaluate the efficacy of sulodexide in the treatment of hard exudates in non-proliferative diabetic retinopathy. The study subjects were divided into a group receiving a placebo and a group treated with sulodexide at a dose of one 25 mg capsule twice daily (250 LSU) for 12 months. The endpoint of the study was to determine the proportion of patients who experienced an improvement at one-year follow-up, as measured by a decrease in the severity of hard exudates of at least 2 degrees on a 10-point severity scale (evaluated by color fundus photography). Classification of the severity of hard exudates (HE) was based on the size of the retinal area involved and the number of HE observed. Successful therapy was defined as an improvement in terms of severity/decrease in HE by at least two categories of severity in the adopted scale. Based on this definition, a reduction in hard exudates was observed in 39.0% of patients treated with sulodexide and 19.3% of patients in the placebo control group (p = 0.005). At the same time, a significant negative effect of high cholesterol and a significant positive effect of high HDL levels were demonstrated. Other variables analyzed in the study to determine their links to changes in HE severity (including blood glucose level, HbA_{1c}, LDL, and TG) were not found to be significant prognostic factors for treatment efficacy in this study.

The number of adverse events was similar in both study groups.

Similar findings to the DRESS study were obtained by a research team headed by Prof. Grabska-Liberek. A retrospective analysis of the efficacy of sulodexide (12 months) was conducted in a group of 190 patients with non-proliferative diabetic retinopathy. Visual acuity and the number of hard and soft exudates were evaluated at subsequent follow-up visits (set at 0, 3, 6, 9 and 12 months after enrolment). After one year of sulodexide treatment, there was a statistically significant improvement in visual acuity (from 0.5 to 0.58 based on Snellen charts, $p < 0.005$) and a statistically significant decrease in the number of hard exudates (from 21.9 to 13.1, $p < 0.001$). At the same time, there was a decrease (statistically insignificant) in the number of soft exudates.

Based on the data presented above, the Expert Group at the Polish Ophthalmological Society recommends sulodexide as adjunctive therapy in the treatment of mild and moderate diabetic retinopathy.

Recommended dosage regimen

One capsule (250 LSU) twice daily between meals.

Contraindications to the use of the drug

Hypersensitivity to the active substance or to any of the excipients, heparin or heparin-like drugs. Concomitant use of heparin or oral anticoagulants. Bleeding diathesis and hemorrhagic conditions.

Note:

The molecular structure of sulodexide is similar to heparin, so the drug may potentiate the effects of concomitantly administered heparin and oral anticoagulants.

Regular monitoring of blood clotting parameters is necessary during concomitant treatment with other anticoagulants.

Since the drug was first marketed (in 1974 in Italy), no hemorrhagic ocular complications have been reported in the regularly updated SPC of the medicinal product Vessel Due F (sulodexide).

CONCLUSIONS

Diabetes mellitus is a socially significant disease which affects a large proportion of the population. It leads to multiple organ complications including diabetic eye disease. The destructive effect of diabetes mellitus on the organ of vision is observed already at early stages of the disease, and structural changes in retinal vessels – including thinning of the protective layer of the glycocalyx – are frequently preceded by lesions typical of diabetic retinopathy which can be noted on fundoscopic examination. From its earliest stages, diabetic retinopathy involves progressive damage to the retinal vasculature, and any delay in the initiation of appropriate treatment makes the condition more challenging to treat. Sulodexide, with its unique contribution to the regeneration of the glycocalyx, and anti-inflammatory, anticoagulant, profibrinolytic, antioxidant and rheological characteristics, used as an adjunct to the primary treatment of diabetes mellitus, can inhibit and often reverse early retinal vascular changes. These effects were confirmed in studies based on experimental and clinical models, including the DRESS study. In addition, long availability on the pharmaceutical market and dozens of clinical trials evaluating the drug provided evidence for its safety.

DISCLOSURE

The authors declare no conflict of interest.

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