https://doi.org/10.5114/oku/199988 (Research Paper)

Received: 20.11.2024 Accepted: 16.12.2024

Treatment of the Early Stages of Diabetic Retinopathy

Jerzy Mackiewicz

Department of Vitreoretinal Surgery, Medical University of Lublin, Poland
Head: Professor Jerzy Mackiewicz, MD, PhD

Summary: Diabetes is considered an epidemic of the 21st century, and the most common microvascular complication, which affects every third patient, is diabetic retinopathy. In the course of retinopathy, the endothelial barrier of the retinal vessels is damaged, which begins with damage to the glycocalyx. Sulodexide rebuilds the glycocalyx and increases the tightness of the blood-retinal barrier, thereby protecting the retinal vessels against damage caused by hyperglycemia. Its multidirectional mechanism of action makes it an effective drug in the treatment of mild and moderately advanced non-proliferative diabetic retinopathy. It is recommended by many scientific societies in the treatment of vascular diseases. Clinical studies confirm its high effectiveness in the treatment of diabetic retinopathy, especially when this disease is accompanied by macular edema. Sulodexide is an effective and safe drug.

Key words: diabetes, diabetic retinopathy (DR), glycocalyx, sulodexide.

Epidemiology of diabetes and diabetic retinopathy

Diabetes is considered a disease of civilization. The incidence of diabetes in the world population is constantly increasing. Taking into account the aging of the population and demographic changes, epidemiological studies indicate that by 2045 the number of people with diabetes in the world will exceed 783 million, of which half of cases in the adult group will remain undiagnosed. In Poland, this problem affects approximately 9% of the adult population [1].

Diabetes is a globally prevalent metabolic disorder that can lead to serious health complications, including microangiopathy and macroangiopathy [2].

Microangiopathies such as diabetic retinopathy, nephropathy, and neuropathy constitute a significant health problem for diabetic patients worldwide. They can lead to permanent damage to the capillary system, which negatively affects the quality of life and increases the risk of death [3].

Diabetic retinopathy (DR) is the most common late complication of diabetes and the most common form of retinal damage of vascular origin. This complication, according to epidemiological studies, may occur in up to 30% of patients, and its incidence increases with the duration of diabetes. In the NHANES study, in patients with diabetes lasting over 15 years, signs of retinopathy were found in 36% of patients [4].

Pathophysiology of diabetic retinopathy

The pathogenesis of diabetic retinopathy is a complex process that involves many factors, including hyperglycemia, inflammation, and neurodegeneration. Damage to the blood-retinal barrier is considered a key mechanism leading to the development of DR [5]. Hyperglycemia leads to damage to the glycocalyx and retinal capillary endothelial cells as a result of ischemia, oxidative stress and the release of pro-inflammatory factors [6].

The glycocalyx, which is a delicate, negatively charged layer of glycoproteins and proteoglycans, covers the endothelial cells of blood vessels, including those of the retina. This structure plays key functions in regulating vascular permeability, angiogenesis and inflammatory processes. As a molecular barrier, the glycocalyx controls the flow of fluids and molecules through the vessel walls, protecting against excessive penetration of substances into the surrounding tissues. Components of the glycocalyx, including heparan sulfate, are involved in the regulation of angiogenesis. They interact with growth factors such as vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF) to promote or inhibit the formation of new blood vessels. Additionally, thanks to its negative charge, the glycocalyx prevents the adhesion of leukocytes to the endothelium, which minimizes the development of inflammation in the vessels [7].

Early symptoms of DR include loss of autoregulation in retinal cells and arteriovenous vasodilation. Arteriovenous vasodilation increases the hydrostatic pressure in the capillaries, which leads to tissue edema [6]. Damage to the blood-retinal barrier causes fluid and proteins to leak from the capillaries into the retina. This leads to macular edema, which is the main cause of vision deterioration in diabetic patients [8].

In the initial stages of the disease, microaneurysms, microhemorrhages and hard exudates appear on the fundus of the eye, i.e. leakage of proteins and lipids from blood vessels into the retina. The development of the disease associated with damage to the endothelium and its increased permeability may result in more serious changes, such as retinal bleeding, macular edema and vascular damage. In the later stages of DR, pathological angiogenesis, i.e. the formation of new blood vessels, develops. These new vessels are brittle and susceptible to rupture, which may lead to retinal hemorrhages [9].

The pathophysiology of diabetic macular edema (DME) is based on complex mechanisms leading to the accumulation of fluid in the macular region, which can cause significant deterioration of central vision. The main cause of macular edema is damage to the blood-retinal barrier. In a healthy retina, there are two main barriers that control fluid flow: the inner blood-retinal barrier (formed by tight junctions between the endothelial cells of the retinal vessels) and the outer blood–retinal barrier (formed by the retinal pigment epithelium). In DME, the permeability of these barriers increases, among other factors due to the action of VEGF, which leads to damage to the connections between endothelial cells, as well as increased transcytosis, i.e. the transport of fluids and proteins through cells. Loss of glycocalyx leads to increased vascular permeability. The lack of this protective barrier promotes fluid leakage and the formation of macular edema [10–12].

Retinopathy classification and treatment

Retinal damage may occur more frequently in patients with type 1 diabetes than in patients with type 2 diabetes [13].

The classification of diabetic retinopathy includes several stages:

- no signs of retinal damage,
- non-proliferative retinopathy (mild, moderate and severe) – retinopathy in the non-proliferative stage is characterized by the presence of petechiae, microaneurysms, hard exudates, and in the severe stage there are intraretinal microvascular abnormalities, the so-called IRMA (intraretinal microvascular abnormalities),
- proliferative retinopathy, consisting in the formation of new, pathological vessels and then the development of fibrovascular proliferation, which consequently threatens vision loss.

Additionally, in the course of diabetes, macular edema may develop, classified as mild, moderate or severe – depending on the location of the changes in relation to the center of the macula – which may also cause vision loss. It may occur as the only manifestation of microangiopathy in the eye or accompany retinopathy [14].

Treatment of diabetic retinopathy should be carried out in specialized centers and include efforts to achieve optimal glycemic control, good control of hypertension and a normal lipid profile – this is the task of the diabetologist [15].

Unfortunately, in some diabetic patients, despite normal parameters of the above-mentioned tests, microangiopathy will develop. Hence, attention is increasingly being paid to the importance of partially identified genetic conditions predisposing to the occurrence of vascular complications of diabetes [16].

The use of antioxidant supplements in the early stages of diabetes slightly improves the metabolic condition, but has no effect on the reconstruction of the glycocalyx structure, which results in its progressive thinning and impaired function. Therefore, the diagnosis of early changes in the nature of diabetic retinopathy during an ophthalmological examination is not the "first call" to start therapy, but rather one of the last steps to stop or slow down the progression of the disease, which is destructive to the retinal vessels [16].

Effectiveness of sulodexide in the treatment of diabetic retinopathy

Sulodexide rebuilds the structure of the glycocalyx and has many other beneficial properties, exerting anti-inflammatory and antioxidant effects, and reducing the expression of vascular growth factors [15].

Based on a clinical study conducted in patients with type 2 diabetes (range: 5.1–5.6 years from diagnosis), a 50% loss of endothelial glycocalyx in the retina was observed, which was partially restored by the use of sulodexide in the treatment [17].

Recommendations regarding the use of this drug in the early stages of diabetic retinopathy have been included for several years in the recommendations of the Polish Diabetes Association and in the Position of the Expert Group of the Polish Ophthalmological Society published in 2021 [15 16].

Sulodexide has antithrombotic, antiplatelet and anti-inflammatory effects. In animal studies and experimental models, sulodexide has shown the ability to inhibit clot formation, facilitate thrombolysis, prevent platelet aggregation and reduce the mass of formed clots. Additionally, the drug improves blood viscosity parameters and has an antioxidant effect [18].

Sulodexide appears to act through interactions with various components of the coagulation system, including antithrombin III and heparin cofactor II. The drug also affects the activity of enzymes and processes that regulate platelet aggregation. The drug promotes arterial dilation through a mechanism involving endothelium-dependent NO production by increasing, dilating, and decreasing vasoconstriction in vascular diseases [18].

Sulodexide, as shown by a meta-analysis, also effectively reduces blood pressure. Compared with the control group, sulodexide significantly reduced systolic (2.2 mmHg, $P = 0.02$) and diastolic (1.7 mmHg, $P = 0.004$) blood pressure. In patients with hypertension, the reduction in systolic and diastolic blood pressure was greater than in healthy subjects (10.2/5.4 mmHg, $P < 0.001$) [18].

Additionally, sulodexide appears to have a beneficial effect on endothelial function due to reducing the production of free radicals, chemoattractants and pro-inflammatory cytokines. In in vitro studies, sulodexide shows the ability to reduce the production of free oxygen radicals and other pro-inflammatory substances, which suggests its anti-inflammatory effect [18].

The drug also has the potential to improve blood viscosity parameters, which is important in the prevention of vascular diseases in patients with diabetes. Sulodexide has the ability to reduce the concentration of fibrinogen in the blood, which contributes to the reduction of blood viscosity [18].

Experimental studies have shown that administration of sulodexide into the peritoneal cavity significantly reduces retinal neovascularization in mice subjected to hypoxia. Moreover, they showed that the drug inhibits the expression of vascular VEGF, a protein that plays a key role in neoangiogenesis [19].

It is worth emphasizing that sulodexide does not have pro-hemorrhagic effects or negatively affect blood coagulation processes. This is important, especially in the case of treatment of diabetic patients, who are susceptible to vascular complications [18].

The study by Gericke et al. aimed to assess the impact of high glucose concentration on the aging of human retinal endothelial cells and the modulation of this process with sulodexide. The results showed that sulodexide reduced β-galactosidase activity, intracellular oxidative stress, p53 gene expression, IL-6 and VEGF-A secretion, and increased endothelial resistance (tightness of the blood–retinal barrier) [20].

A study by Broekhuizen et al. showed that in people with type 2 diabetes, glycocalyx thickness is reduced in 2 different vascular beds: sublingual and retinal. Similarly, blood vessel permeability was found to be increased in people with diabetes. The study participants were administered sulodexide, which is a glycocalyx precursor. After 2 months of treatment, the thickness of the glycocalyx increased and vascular permeability decreased [17].

The DRESS study was the pivotal study evaluating the effectiveness of sulodexide in the treatment of ischemic diabetic retinopathy. It involved 130 patients, half of whom received 50 mg of sulodexide daily and the other half received placebo for 12 months. The main measure of effectiveness was the hard effusion score, defined as a reduction in severity of effusions by at least 2 grades on a 10-point scale. There was a significantly greater improvement in the severity of hard effusions in the sulodexide group compared to the placebo group (39.0% vs. 19.3%). Logistic regression analysis showed an odds ratio of 2.79 for the effect of sulodexide treatment. This drug proved to be safe and no significant side effects were reported. The conclusions of the study suggest that oral therapy with sulodexide for 12 months is an effective and safe method of treating hard effusions in patients with diabetic ischemic retinopathy [21].

In another study involving 43 patients with type 2 diabetes and overweight, the effect of sulodexide on the course of diabetic retinopathy was examined for 6 months. The study showed that this treatment improved visual acuity by an average of 0.25. The number of hemorrhages ranged from 3 to 84, and the average was

41.27 (±3.2). After 6 months of treatment with sulodexide, the number of hemorrhages decreased in all eyes that were examined. The number of hemorrhages ranged from 1 to 54, and the average was 23.8 (±2.0) ($p< 0.001$). The number of microaneurysms ranged from 7 to 15, and the average was 7.6 (±0.7). After 6 months of treatment with sulodexide, the number of microaneurysms decreased in these patients in 13 eyes. The number of microaneurysms ranged from 4 to 13, and the average was 6.3 (±0.5). The difference was not statistically significant. The number of hard effusions ranged from 4 to 67, and the average was 52.21 (±2.9). After 6 months of treatment with sulodexide, the number of effusions decreased and amounted to an average of 33.71 (±3.2) ($p< 0.05$). These results suggest that sulodexide may be an effective conservative treatment for patients with the non-proliferative phase of diabetic retinopathy [22].

The study by Chişca et al. involved 48 patients with various degrees of diabetic retinopathy, divided into two groups: an experimental group that received sulodexide and a control group that was not treated. Patients underwent ophthalmological examinations, including imaging and electrophysiological examinations, at three time points: at the beginning of the study, after 10 days and after 60 days of treatment. The results showed that in the experimental group there was a significant improvement in both near visual acuity ($p = 0.04$) and a reduction in macular edema, which was confirmed by optical coherence tomography (OCT) ($p = 0.02$). Additionally, positive changes were found in electrophysiological parameters, such as the latency period and the amplitude of the P100 wave, suggesting an improvement in neuronal conduction. No significant changes in these parameters were observed in the control group. The study results suggest that sulodexide, due to its angioprotective and antithrombotic properties, may have a beneficial effect on retinal vessels, which leads to a reduction in the severity of symptoms of diabetic retinopathy [23].

One of the most common complications of diabetic eye disease is retinal vein clots. One study evaluated the effectiveness of sulodexide and several other drugs in reducing the risk of recurrent retinal vein occlusion after the first episode. The study results included 307 patients. After 12 months, recurrent retinal vein occlusion occurred in 22.7% of patients in the control group and in 13.2% of patients taking sulodexide and was 2.3% lower than the recurrence rate in patients taking acetylsalicylic acid [24].

A meta-analysis of randomized clinical trials demonstrated that sulodexide is effective in reducing the risk of all-cause mortality (-33%), cardiovascular mortality (-56%), myocardial infarction (-30%), and deep vein thrombosis (-56%) in patients with cardiovascular disease and other risk factors compared to placebo. The use of sulodexide was not associated with an increased risk of bleeding [25].

It is worth emphasizing that sulodexide – as research shows – not only has a beneficial effect on ocular complications in the course of diabetes, but also can be used in patients with diabetic nephropathy, trophic ulcers and peripheral vascular disease [26].

Sulodexide is available on the market in the form of soft capsules and an injection solution. There are 50 capsules in a package, with 250 LSU (lipasemic units) per capsule, and 10 ampoules of 600 LSU/ 2 ml; 1 mg of the drug corresponds to 10 LSU. In the treatment of diabetic retinopathy, one capsule is taken twice a day, between meals [27].

Summary

One of the most important elements of preventing vision loss due to pathological changes related to diabetes is screening and follow-up examinations supervised by an ophthalmologist.

According to the recommendations of the Polish Diabetes Association, such tests should be performed with a dilated pupil, using an ophthalmoscope or using a fundus camera based on a color fundus photograph. Such a test should be performed in every patient with type 1 diabetes five years after diagnosis, and in patients with type 2 diabetes immediately after diagnosis and in the absence of changes, repeated every 2 years (patients with type 1 diabetes) and every 2–3 years (patients with type 2 diabetes with well-controlled glycemia). If changes in the nature of diabetic retinopathy are detected, subsequent follow-up examinations should be scheduled by an ophthalmologist based on the current clinical condition. Tests used for more detailed imaging of changes in the retina also include optical coherence computed tomography and fluorescein angiography. It is performed to detect very early changes in the retina related to vascular leakage and to identify areas of retinal ischemia that should be subjected to laser coagulation. Optical coherence tomography angiography may be a helpful test.

Thanks to progress in the development of artificial intelligence, advanced algorithms are also used as a screening tool – they were approved for such use by the US Food and Drug Administration (FDA) several years ago. Algorithms may also be introduced to help predict the course of the disease and the risk of vision loss in individual patients. As British experience shows, proper conduct of screening tests leads to a reduction in the incidence of vision loss caused by diabetic retinopathy.

Diabetic retinopathy, from its earliest stages, involves progressive damage to the retinal vessels, which becomes more difficult to treat the later appropriate therapy is used. Sulodexide, with its effect on glycocalyx reconstruction, supports anti-inflammatory, antithrombotic, profibrinolytic, antioxidant and rheological effects and, when added to appropriate diabetes therapy, can inhibit and often reverse early changes in retinal vessels. This was confirmed in studies on experimental and clinical models. The drug's long presence on the market and dozens of clinical trials have also confirmed its safety [16].

Disclosure
Conflict of interests: none declared
Funding: no external funding
Ethics approval: Not applicable.

References:

1. *https://diabetesatlas.org/*
2. Hunt M, Wylęgała A, Wylęgała E, et al.: *1-Year Fixed-Regimen Bevacizumab Treatment in DME-Vascular Network Image Analysis in Optical Coherence Tomography Angiography Study.* J Clin Med. 2022; 11: 2125.
3. Mazur R, Wylęgała A, Świerkosz W, et al.: *Retinopatia cukrzycowa – najczęstsze powikłanie. Możliwości profilaktyki i leczenia.* Diabetol po Dyplomie. 2018; 15: 25–31.
4. Harris M, Klein R, Cowie C, et al.: *The risk of diabetic retinopathy greater in Non-Hispanic Blacks and Mexican Americans then Non-Hispanic Whites with type 2 diabetes. A.U.S population study.* Diabetes Care. 1998; 21: 1230–1235.
5. Wylęgała E, Wylęgała A: C*ukrzycowa choroba narządu wzroku*. In: Leczenie powikłań cukrzycy i chorób z nią współistniejących. Franek E (red). Wydawnictwo San Roque, Warszawa 2018.
6. Pilśniak A, Wylęgała A, Otto-Buczkowska E: O*phthalmologic disorders in adolescents with type 1 diabetes*. CD 2020; 9(6): 493–496.
7. Foote CA, Soares RN, Ramirez-Perez FI, et al.: *Endothelial Glycocalyx*. In: Comprehensive Physiology. Wiley. 2022: 3781–811.
8. Sędziak-Marcinek B, Wylęgała A, Chełmecka E, et al.: *How to achieve near-normal visual acuity with bevacizumab in diabetic macular edema patients*. J Clin Med. 2021; 10(16): 3572.
9. Wylęgała A, Wylęgała E: *Powikłania okulistyczne u chorych na otyłość.* In: Obesitologia kliniczna. Olszanecka-Glinianowicz M (red). α-medica press, Bielsko-Biała 2021: 477–482.
10. Daruich A, Matet A, Moulin A, et al.: *Mechanisms of macular edema: Beyond the surface*. Prog Retin Eye Res. 2018; 63: 20–68.

11. Antonetti DA, Silva PS, Stitt AW: C*urrent understanding of the molecular and cellular pathology of diabetic retinopathy.* Nat Rev Endocrinol. 2021; 17(4): 195–206.

12. Zhang J, Zhang J, Zhang C, et al.: *Diabetic Macular Edema: Current Understanding, Molecular Mechanisms and Therapeutic Implications*. Cells. 2022; 11(21): 3362.

13. *Zalecenia kliniczne dotyczące postępowania u chorych na cukrzycę 2024. Stanowisko Polskiego Towarzystwa Diabetologicznego*. Curr Top Diabetes. 2023; 3(1): 1–140.

14. Wilkinson CP, Ferris FL[3rd], Klein RE, et al.: Global Diabetic Retinopathy Project Group. *Proposed international clinical diabetic retinopathy and diabetic macular edema disease severity scales*. Ophthalmology. 2003; 110(9): 1677–1682.

15. Korzon-Burakowska A: *Retinopatia cukrzycowa – przewlekłe powikłanie w cukrzycy. Choroby cywilizacyjne w praktyce lekarskiej*. Kardiologia i Diabetologia listopad 2024 (nr 40), 21–24.

16. Szaflik JP, Misiuk-Hojło M, Romanowska-Dixon B i wsp.: *Wytyczne Polskiego Towarzystwa Okulistycznego. Stanowisko grupy eksperckiej w zakresie stosowania sulodeksydu jako terapii wspomagającej w łagodnej oraz średnio zaawansowanej retinopatii cukrzycowej*. Klin Oczna. 2021; 123(4): 161–165.

17. Broekhuizen LN, Lemkes BA, Mooij HL, et al.: *Effect of sulodexide on endothelial glycocalyx and vascular permeability in patients with type 2 diabetes mellitus*. Diabetologia. 2010; 53(12): 2646–2655.

18. Wylęgała A: *Sulodeksyd – nowy model leczenia wczesnych stadiów retinopatii cukrzycowej*. Ophthatherapy. 2023; Vol. 10/ Nr 4 (40).

19. Jo H, Jung SH, Kang J, et al.: *Sulodexide inhibits retinal neovascularization in a mouse model of oxygen-induced retinopathy.* BMB Rep. 2014; 47: 637–642.

20. Gericke A, Suminska-Jasińska K, Bręborowicz A: *Sulodexide reduces glucose induced senescence in human retinal endothelial cells*. Sci Rep. 2021; 11: 11532.

21. Song JH, Chin HS, Kwon OW, et al.: *Effect of sulodexide in patients with non-proliferative diabetic retinopathy: diabetic retinopathy sulodexide study (DRESS)*. Graefes Arch Clin Exp Ophthalmol. 2015 Jun; 253: 829–837.

22. Orlenko VL, Tronko KM: *Efficacy of using glucosamine (sulodexide) in the treatment of diabetic retinopathy in patients with type 2 diabetes mellitus (T2DM) with increased body mass*. Sci Eur. 2016; 8: 41–46.

23. Chişca V, Corduneanu A, Ciobanu N, et al.: *Sulodexide treatment of diabetic retinopathy: a prospective, randomized study.* Rev Ştiinţe ale Sănătăţii din Mold. 2020; 25(4): 80–88.

24. Belcaro G, Dugall M, Bradford HD, et al.: *Recurrent retinal vein thrombosis: prevention with Aspirin, PycnogenolR, ticlopidine, or sulodexide*. Minerva Cardioangiol. 2019; 67.

25. Bikdeli B, Chatterjee S, Kirtane AJ, et al.: *Sulodexide versus Control and the Risk of Thrombotic and Hemorrhagic Events: Meta-Analysis of Randomized Trials*. Semin Thromb Hemost. 2020; 46: 908–918.

26. Bignamini AA, Chebil A, Gambaro G, et al.: *Sulodexide for Diabetic-Induced Disabilities: A Systematic Review and Meta-Analysis*. Adv Ther. 2021; 38(3): 1483–1513.

27. Charakterystyka produktu leczniczego Vessel Due F.

Reprint requests to:

Professor Jerzy Mackiewicz, MD, PhD (e-mail jerzymackiewicz@umlub.pl)
Department of Vitreoretinal Surgery, Medical University of Lublin, Poland
ul. Chmielna 1, 20-079 Lublin