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Sulodexide: A new model for treating the early stages of diabetic retinopathy

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HIGHLIGHTS

One of the characteristic symptoms of diabetic retinopathy are foci of hard exudates. Sulodexide has been proven to be effective in reducing hard effusions and improving the condition of patients with diabetic retinopathy.

ABSTRACT

Glycocalyx is the surface layer of endothelial cells, it lines the blood vessels and provides a cellular barrier against damage. Sulodexide has a protective effect on the glycocalyx and allows it to be rebuilt, and has anti-inflammatory, antioxidant, anticoagulant, and lipid profile-enhancing properties. Diabetic retinopathy damages the glycocalyx and vascular endothelium in the retina. Sulodexide rebuilds the glycocalyx and increases the integrity of the blood–retinal barrier, thereby protecting the retinal vasculature retina from hyperglycemia-induced damage. Clinical studies have confirmed that in non-proliferative diabetic retinopathy, sulodexide improves visual acuity, reduces microaneurysms and hard exudates. Further in a study evaluating recurrent retinal vein thrombosis, sulodexide reduced the recurrence rate. Sulodexide is a safe and well-tolerated drug and may play an important role in the treatment of diabetic retinopathy, both in reducing symptoms and improving visual function.

Key words: glycocalyx, hard exusdates, sulodexide, diabetic retinopathy, blood vessel protection

INTRODUCTION

Diabetes is a metabolic disorder that is prevalent worldwide. It can lead to serious health complications, including microangiopathies and microangiopathies [1]. Microangiopathies, such as diabetic retinopathy (DR), nephropathy and neuropathy, are a significant health problem for patients with diabetes worldwide. Microangiopathies can cause permanent damage to the capillary system, which can negatively affect quality of life and increase the risk of death. Strict control of blood glucose and blood pressure, as well as intensified multifactorial treatment are considered the first steps in reducing the risk of diabetes complications. The worldwide incidence of diabetes is estimated to be on the rise, leading to an increase in related disabilities [2].

Microvascular and macrovascular complications in diabetes are leading causes of morbidity and death worldwide. They are responsible not only for increased mortality, primarily related to heart disease, but also for severe disabilities, including blindness, mobility limitations, and dialysis-dependent kidney failure [3].

Retinal blood vessel cells play a key role in maintaining the barrier between the retinal nerve tissue and the bloodstream. The blood–retinal barrier is particularly important as it regulates the flow of substances in the retinal blood vessels, maintains neural homeostasis, and prevents leakage of large molecules and harmful substances into the retina. The structure and function of the retina are closely related to the integrity of the blood–retinal barrier.

The development of DR is a multifaceted process that involves various factors, such as hyperglycemia, inflammation, and neurodegeneration. Damage to the blood–retinal barrier is recognized as a key mechanism leading to the development of DR [4].

As a result of hyperglycemia, glycocalyx and retinal endothelial cells are damaged by ischemia, oxidative stress, and the release of pro-inflammatory factors. Early symptoms of DR include the loss of autoregulation in retinal cells and retinal arteriovenous dilation that raises hydrostatic pressure in the capillaries, causing tissue edema [5]. Damage to the blood–retinal barrier causes fluid and protein deposits to leak from the capillaries into the retina. This leads to diabetic macular edema, which is the leading cause of vision loss in patients with diabetes [6]. During the initial stages of the disease, symptoms such as hard exudates or leakage of proteins and lipids into the retina may occur.

Disease progression may lead to more serious changes, such as retinal bleeding, macular edema, or vascular damage. Pathological angiogenesis occurs in the later stages of DR, resulting in the formation of new blood vessels that are fragile and prone to rupture. This can lead to retinal hemorrhages [7].

As diabetes becomes more prevalent, there is an urgent need for new and effective therapies, particularly for patients in the early stages of DR. Sulodexide provides promising results in combating diabetes complications, such as micro- and macroangiopathy, and can be used to treat the early stages of DR.

This study discusses the effectiveness of sulodexide as a new treatment for the early stages of DR. The evidence presented supports its use in this indication. This study discusses the effectiveness of sulodexide as a new treatment for the early stages of DR. The evidence presented supports its use in this indication.

GLYCOSAMINOGLYCANS

Glycosaminoglycans (GAGs) are complex polysaccharides found in the extracellular matrix. They are composed of repeating disaccharides of an amino sugar and a uronic acid. Additionally, most GAGs contain a sulfate group.

Glycosaminoglycans play an essential role in many physiological functions of the body.

- For instance, they affect the mechanical properties of tissues, providing them with elasticity and strength.
- They regulate the permeability of cell membranes, by controlling the exchange of ions and substances between cells and their environment.
- They are involved in inflammatory processes, by regulating the release of cytokines and inflammatory mediators.
- They play a role in repair processes by stimulating cell proliferation and differentiation [8, 9].

The endothelial glycocalyx is a carbohydrate-rich layer lining the vascular endothelium composed of glycolipids, proteoglycans, and glycoproteins. Key ingredients include heparan sulfate, dermatan sulfate, chondroitin sulfate, and hyaluronic acid.

The glycocalyx exhibits many important functions:

- protects the endothelium from mechanical and chemical damage
- regulates endothelial permeability and inflammatory processes
- participates in angiogenesis
- regulates endothelial cell interactions with leukocytes and thrombocytes
- has an antimetastatic potential
- participates in antiviral and antibacterial protection
- regulates the functions of many enzymes, including nitric oxide synthase activity, lipoprotein lipase, or superoxide dismutase.

The glycocalyx is a dynamic structure damaged by hyperglycemia, free radicals, hypertension, aging, cancer, atherosclerosis, or sepsis [10, 11]. Damage to the glycocalyx layer is considered one of the key pathogenetic mechanisms

of diabetic complications, including DR, nephropathy and neuropathy. In DR, GAG is replaced by collagen in basement membranes of retinal capillaries. This change leads to increased capillary permeability and subsequent leakage of fluid and protein to the retina [12].

PHARMACOLOGY OF SULODEXIDE

Sulodexide is a glycosaminoglycan composed of heparan sulfate and dermatan sulfate derived from porcine intestinal mucosa. Heparan sulfate has an affinity for antithrombin III, and dermatan sulfate has the ability to interact with the heparin II cofactor. Sulodexide has an average molecular weight of 7,000 Da, while dermatan sulfate has a mass of approximately 25,000 Da [13].

Sulodexide is similar to unfractionated heparin, but differs from it in several important ways. First of all, it has a much longer half-life, averaging 18.7 (±4.1) h after oral administration. Additionally, sulodexide has limited effects on blood clotting parameters and is highly bioavailable when taken orally.

Pharmacological studies in humans have demonstrated that sulodexide is well absorbed over the entire length of the gastrointestinal tract. Two peak blood levels occur at 2 and 4–6 hours after oral administration in humans. After the second peak, the drug is no longer detectable in plasma. It then reappears in the blood after about 12 h later and maintains a constant concentration until about 48 h [14].

Sulodexide exhibits antithrombotic, antiplatelet, and anti-inflammatory effects. In animal studies and experimental models, it has demonstrated the ability to inhibit thrombus formation, facilitate thrombolysis, prevent platelet aggregation, and limit thrombus mass. Additionally, sulodexide reduces blood viscosity and has antioxidative effects [15].

Sulodexide shows high affinity for various elements of the coagulation system, including antithrombin III and heparin cofactor II. The drug affects the activity of enzymes and processes that regulate platelet aggregation. It also promotes arterial relaxation via a mechanism involving endothelium-dependent nitrous oxide production; an effect that may enhance vasodilation and decrease vasoconstriction in vascular disorders [16].

The meta-analysis showed that sulodexide is effective in lowering blood pressure as it significantly lowered systolic (2.2 mmHg, p = 0.02) and diastolic (1.7 mmHg, p = 0.004) blood pressure compared to the control group. The reduction in systolic and diastolic blood pressure was great-

FIGURE 1

Proper glycocalyx function is essential for maintaining laminar flow in the vasculature as it regulates important enzymes such as nitric oxide synthase and lipoprotein lipase, acts as an anticoagulant, protects the endothelium from injury, and serves as an electrostatic barrier.

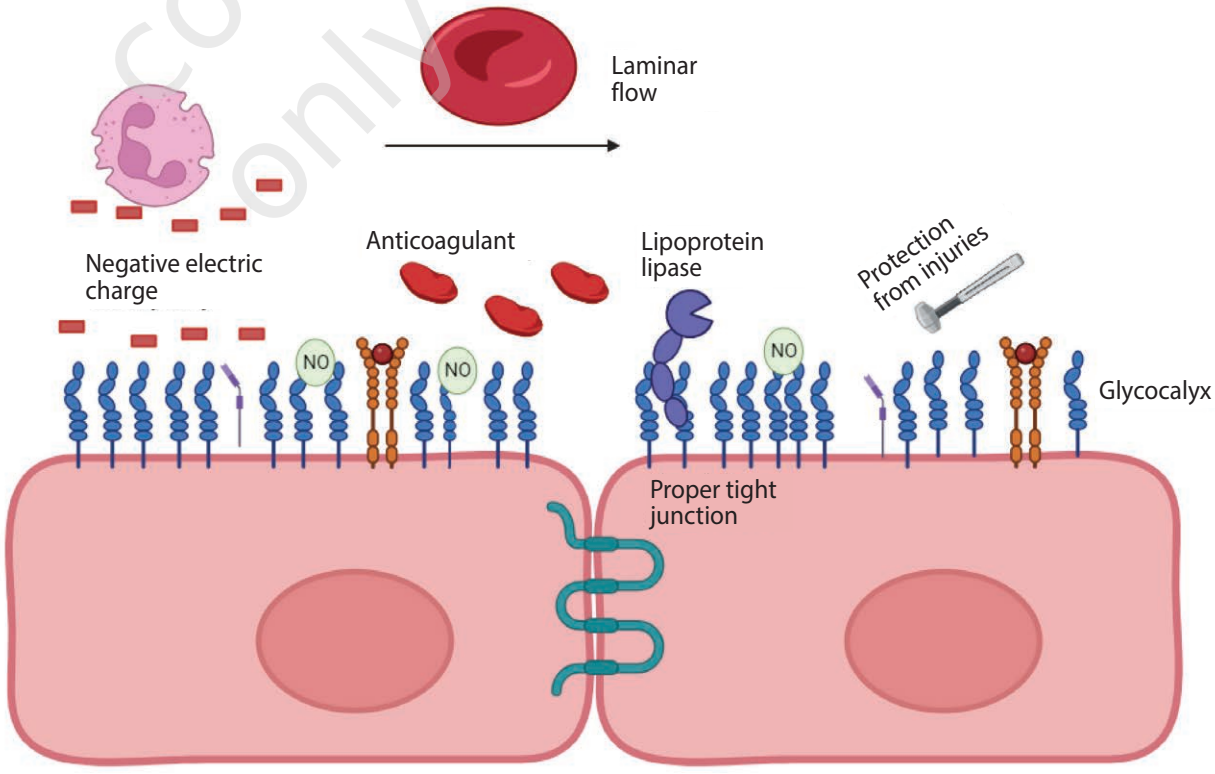
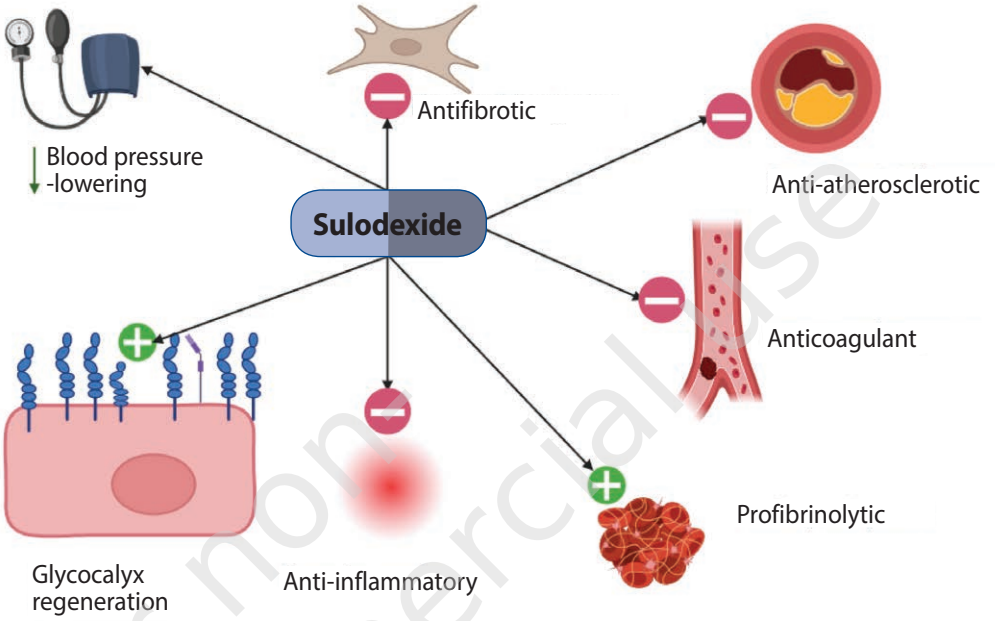


FIGURE 2

Sulodexide has systemic pleiotropic effects, including anticoagulant, anti-atherosclerotic, antifibrotic, anti-inflammatory, blood pressure-lowering, and lipid-regulating effects [23].



er in patients with hypertension than in healthy controls (10.2/5.4 mmHg, $p < 0.001$) [17].

In addition, sulodexide appears to have a beneficial effect on the endothelial function as it reduces the release of free radicals, chemoattractants and pro-inflammatory cytokines. In vitro studies have shown that sulodexide can reduce the production of oxygen free radicals and other pro-inflammatory substances, indicating its potential anti-inflammatory effects [8].

Sulodexide has the potential to reduce blood viscosity, an important factor in preventing vascular disease in patients with diabetes. Additionally, it can lower the concentration of plasma fibrinogen, further contributing to the reduction of blood viscosity [18].

It is important to note that sulodexide does not have any pro-hemorrhagic potential and does not negatively affect blood clotting processes. This is particularly important when treating patients with diabetes who are prone to vascular complications [19].

Sulodexide is commercially available as soft capsules or intramuscular ampoules. Capsules contain 250 lipasemic units (LSU) and 2 ml ampoules contain 300 LSU/ml each. 1 mg of the drug is equivalent to 10 LSU [20].

SULODEXIDE AS A DRUG

A meta-analysis showed that sulodexide is a safer drug than oral anticoagulants, vitamin K antagonists and acetylsalicylic acid in patients with venous thrombosis. It was also more effective in reducing the risk of clinically significant bleeding, death from any cause and myocardial infarction. Additionally, sulodexide showed to be more effective than acetylsalicylic acid in reducing the risk of recurrent deep vein thrombosis and pulmonary embolism. Sulodexide induced a lower risk of clinically significant bleeding compared to oral vitamin K antagonists and acetylsalicylic acid.

Therefore, sulodexide may be a promising alternative to oral anticoagulant treatment for patients with thromboembolic diseases, particularly those at high risk of bleeding or those who cannot tolerate other anticoagulants [21].

A meta-analysis of randomized clinical trials demonstrated that sulodexide is effective in reducing odds 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. Furthermore, the use of sulodexide was not associated with an increased risk of bleeding [22].

SULODEXIDE IN NON-PROLIFERATIVE DIABETIC RETINOPATHY

Sulodexide protects retinal endothelial cells from hyperglycemia-induced damage. It markedly downregulates the release of hyperglycemia-induced markers of cell damage. In addition, sulodexide maintains the properties of

blood–retinal barrier, such as electrical resistance across the endothelium, and the expression levels of tight junction proteins. Furthermore, sulodexide preserves the angiogenic capacity of retinal endothelial cells, which is their ability to generate new blood vessels. The drug suppresses the function of ERK kinase and PLA2 kinase, which are enzymes implicated in inflammation. Additionally, sulodexide suppresses the secretion of pro-inflammatory prostaglandin E_2 (PGE_2) in hyperglycemia. In retinal endothelial cells, sulodexide inhibits the expression of the NF-κB gene, a transcription factor associated with inflammation. The prophylactic effect of sulodexide persists for 24 h after drug administration in cases of hyperglycemia [24]. In mice subjected to hypoxia, intraperitoneal injection of sulodexide significantly inhibited retinal neovascularization. Researchers showed that the drug inhibits the expression of vascular endothelial growth factor (VEGF), a protein that plays a key role in neoangiogenesis [25].

Gericke et al. aimed to evaluate the effect of high glucose concentration on senescence in human retinal endothelial cells and modulation of that effect by sulodexide. The results showed that sulodexide decreased β-galactosidase activity, intracellular oxidative stress, expression of p53 gene, secretion of IL-6 and VEGF-A, and increased endothelial resistance (blood–retinal barrier) [26].

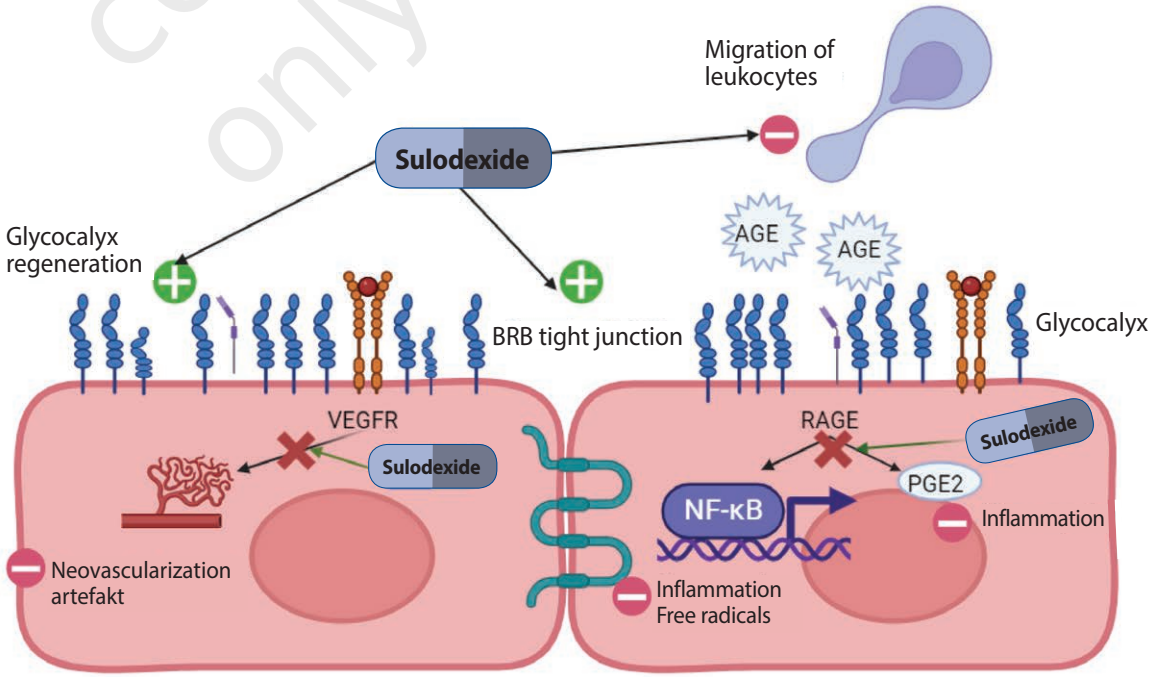
The endothelium-dependent vasodilator response to bradykinin was attenuated in porcine retinal vessels incubated with a high-concentration glucose solution compared with the control group. When vessels incubated with the hyperglycemic solution were simultaneously exposed to sulodexide, the vasodilator responses to bradykinin were similar to those observed in vessels incubated in the control group. In contrast, endothelium-independent mechanisms of retinal vasodilatation were not affected.

There was a significant increase in free radical production in the vessel wall in the group of hyperglycemia-exposed eyes. Sulodexide protected against hyperglycemia-induced free radical formation in the vascular wall and exerted a concentration-dependent protective effect in endothelial dysfunction. Although sulodexide alone has only limited antioxidant properties, it was effective in preventing hyperglycemia by overexpressing pro-oxidant redox enzymes, NOX-4 and NOX-5. The results of this study demonstrate that sulodexide has a protective effect against oxidative stress and endothelial dysfunction induced by hyperglycemia in porcine retinal arterioles, probably via a mechanism of modulating the expression of redox enzymes and protecting vasodilator mechanisms in the vessels [8].

According to Broekhuizen et al., patients with type 2 diabetes have increased vascular permeability and reduced gly-

FIGURE 3

Effects of sulodexide on retinal endothelial cells. Sulodexide protects the blood–retinal barrier, thereby reducing retinal vascular permeability and leukocyte migration; the drug reduces cellular inflammation and oxidative stress and hyperglycemia-induced VEGF production.



AGE – advanced glycation products; BRB – blood–retinal barrier; PGE2 – prostaglandin 2; VEGRF – vascular endothelial growth factor receptor).

cocalyx thickness in sublingual and retinal dimensions. The study participants were administered sulodexide, a precursor to glycocalyx. After 2 months of sulodexide administration, glycocalyx thickness increased and vascular permeability decreased [9].

The DRESS trial evaluated the efficacy of sulodexide in patients with non-proliferative DR. The trial involved 130 patients, with half receiving 50 mg of sulodexide/day and the other half receiving a placebo for 12 months. The main outcome measure was an improvement in hard exudates defined as a decrease in severity by at least 2 grades on a 10-grade severity scale.

The group that received sulodexide showed significantly greater improvement in hard exudates severity compared to the placebo group (39.0% vs. 19.3%). Logistic regression analysis yielded an odds ratio of 2.79 for the effect of sulodexide treatment. The drug has been proven to be safe, and no significant side effects have been reported. The study's findings indicate that oral sulodexide therapy over 12 months is a safe and effective treatment for hard exudates in patients with non-proliferative DR (NPDR).

Another study was conducted on 43 overweight patients with type 2 diabetes to investigate the effect of sulodexide on the course of DR for 6 months. The study found that the treatment improved visual acuity by an average of 0.25. The number of hemorrhages ranged from 3 to 84, with an average of 41.27 (±3.2). After 6 months of treatment with sulodexide, the number of hemorrhages decreased in all eyes that were studied. The study found that the number of hemorrhages varied from 1 to 54, with an average of 23.8 (±2.0) ($p < 0.001$). The number of microaneurysms ranged from 7 to 15, with an average of 7.6 (±0.7). Following a 6-month treatment with sulodexide, the number of microaneurysms decreased in 13 eyes of the patients. The study found that the number of microaneurysms ranged from 4 to 13, with an average of 6.3 (±0.5), and the difference was not statistically significant. Similarly, the number of hard exudates ranged from 4 to 67, with an average of 52.21 (±2.9). However, after 6 months of treatment with sulodexide, the number of exudates decreased significantly and averaged 33.71 (±3.2) ($p < 0.05$). These findings suggest that sulodexide may be an effective conservative treatment for patients with the NPDR [27].

Retinal vein thrombosis is a common complication of diabetic eye disease. A study was conducted to evaluate the efficacy of sulodexide and several other drugs in reducing the incidence of new retinal vein thrombosis after the first episode. Overall, 307 patients completed the study. At 12 months, recurrent retinal vein thrombosis was found in 22.7% of controls and in 13.2% of patients taking sulodexide, and was 2.3% lower than the recurrence rate in patients taking acetylsalicylic acid [28].

A cost-effectiveness analysis of sulodexide in patients with non-proliferative retinopathy showed that the drug is a cost-effective treatment option for hard exudates in patients with mild-to-moderate disease, resulting in improved vision [29].

CONCLUSIONS

Sulodexide is a promising drug for treating early-stage DR, as it can affect vascular protection and improve endothelial function, which are crucial in the context of microangiopathy pathophysiology. Sulodexide may offer a new treatment option for patients with DR due to its ability to regenerate glycocalyx and reduce inflammatory and oxidative processes. Continuing research on this promising drug is worthwhile to better understand its exact effects on DR and other complications of diabetes.

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