DOI: 10.5114/oku/177689 Received: 27.12.2023 Accepted: 28.12.2023

Vasoprotective Effect of Sulodexide in Diabetic Retinopathy

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Abstract: Diabetes is a group of metabolic diseases, considered a lifestyle disease. Diabetic retinopathy is the leading cause of blindness in working-age adults worldwide. Pathogenetically, due to the changed anionic charge, collagen gradually replaces glycosaminoglycans (GAG) in the basement membrane of retinal capillaries, affecting vascular permeability. Clinically, these changes cause leakage from the retinal capillaries, which leads to the development of microaneurysms and, consequently, the formation of hard effusions (HE). Sulodexide is a glycosaminoglycan containing 80% of small molecular weight, fast moving heparin fraction (FMH) and 20% of dermatan sulfate. An important target of sulodexide's action are vascular endothelial cells, and its protective effect is partially related to the preservation and reconstruction of the glycocalyx structure on the surface of the endothelial layer cells. Additionally, sulodexide has been documented to strengthen the glycocalyx of retinal arterioles in people with diabetes. These findings suggest that sulodexide holds promise as a potential therapeutic agent for the treatment of diabetic retinopathy.

Key words: Diabetes, diabetic retinopathy, sulodexide, vascular complications.

Introduction

Diabetes is a group of metabolic diseases, considered a lifestyle disease. The incidence of diabetes is constantly increasing in the world population. Epidemiological studies, taking into account the aging population and demographic changes, indicate that by 2045 the number of people with diabetes in the world will exceed 783 million, of which half of cases among adults will remain undiagnosed [1]. Diabetic retinopathy is an ocular manifestation of organ failure associated with hyperglycemia. It is a common complication of type 1 and type 2 diabetes and is the leading cause of blindness in working-age adults worldwide [2].

Pathogenesis of vascular disorders

The initial microscopic changes involve thickening of the retinal capillary basement membrane and degeneration of pericytes, collectively compromising capillary wall integrity and leading to pericyte loss. Over time, collagen gradually replaces glycosaminoglycans (GAGs) in the basal membrane, causing modifications in vascular permeability due to altered anionic charge. Clinically, these cumulative changes result in vascular leakage from retinal capillaries, leading to the development of microaneurysms. Persistent vascular leakage leads to the deposition of serum proteins and lipids in the retina, forming hard exudates (HE). The substitution of GAGs with collagen not only occurs in the retina but also in the kidney, causing basal membrane thickening. Similar to retinal changes, these alterations in the permeability of renal glomeruli cause the selective loss of proteins, clinically identified as albuminuria [3]. There is a proposition that disrupted GAG metabolism in individuals with diabetes may be a common pathogenic factor in diabetic vascular disease [4]. Evidence supporting a common underlying pathogenesis, involving the depletion of GAGs from the basement membrane, is found in the Wisconsin Epidemiologic Study of Diabetic Retinopathy, where micro-albuminuria was cross-sectionally associated with retinopathy in diabetes patients [5]. As current anti-hyperglycemic therapies fall short of fully preventing diabetes-related complications, there is an urgent need to identify new drugs capable of slowing or reversing the vascular micro-abnormalities that ensue [6].

Pharmacokinetics of Sulodexide

Chemically, sulodexide is categorized as a glycosaminoglycan, comprising 80% low molecular weight, fast-moving heparin (FMH), and 20% dermatan sulfate, both derived from the intestinal mucosa of pigs. Sulodexide has an average molecular weight of 7,000 Da, while dermatan sulfate has a molecular weight of approximately 25,000 Da. The primary constituent, FMH, differs from unfractionated heparin in mass and exhibits reduced anticoagulant activity, typically undetectable in standard screening laboratory tests when administered orally. First of all, sulodexide has a much longer half-life, averaging 18.7 (±4.1) h, and is characterized by high oral bioavailability. Pharmacological studies conducted in humans have shown that sulodexide is well absorbed through the gastrointestinal tract. After oral administration in humans, two blood concentration peaks are observed: the first one after approximately 2 hours and the second one between 4 and 6 hours after administration. After the second concentration peak, the drug is no longer detectable in plasma. Then, after approximately 12 hours, it reappears in the blood and maintains a constant concentration until approximately 48 hours [7]. The FMH component of sulodexide displays an affinity for antithrombin III, while dermatan sulfate inhibits factor IIa by affecting heparin cofactor II [7–9, 51].

Endovascular action of Sulodexide

A significant target of Sulodexide action is vascular endothelial cells, and its protective effect is linked, in part, to the preservation and reconstruction of the glycocalyx structure on the endothelial layer cells' surface. Certainly, Sulodexide has been documented to enhance the glycocalyx of retinal arterioles in individuals with diabetes. This strengthening effect is associated with a reduction in vascular permeability and the suppression of retinal neovascularization in vivo. These findings suggest that Sulodexide holds promise as a potential therapeutic agent for the treatment of diabetic retinopathy [10–12]. The endothelial glycocalyx is a sugar layer that envelops the surface of blood vessel endothelium. It comprises glycolipids, proteoglycans, and glycoproteins, with key components such as dermatan sulfate, chondroitin sul-

fate, and hyaluronic acid playing crucial role. The glycocalyx serves crucial functions, including maintaining vascular wall tension, protecting the endothelium from damage, regulating endothelial barrier permeability, regulates the functions of many enzymes, including nitric oxide synthase, lipoprotein lipase and responding to shear stress. It also plays a pivotal role in influencing interactions between endothelial cells, leukocytes, and platelets [13–14]. A normal glycocalyx contributes to maintaining the vessel wall's anticoagulant potential by releasing antithrombin III, heparin cofactor II, and inhibitors of tissue factor-dependent coagulation system activation. Sulodexide, through glycocalyx reconstruction, not only inhibits coagulation system activation but also enhances the fibrinolytic system's potential by inhibiting plasminogen activation inhibitor (PAI-1) and inducing tissue plasminogen activator expression [15–16].

Immunomodulatory effect

The multipotential effect of sulodexide is expressed also in immunology. Sulodexide inhibits the inflammatory reaction by suppressing adhesion molecule expression, prevents leukocyte adhesion to endothelial cell surfaces, and inhibits the release of pro-inflammatory factors and cytokines (IL-1B, IL-2, IL-6, IL-8, IL-10, IL-12) [10, 15, 17–19]. Studies also confirm Sulodexide's impact on controlling oxidative stress and reducing microcirculation vascular wall permeability [20–21]. Enzymes from the group of metalloproteinases are one of the key factors leading to the degradation of the intercellular matrix and damage to soft tissues, and are an important component of processes damaging and leading to the reconstruction of the vein wall. Sulodexide inhibits the synthesis, release, and activity of metalloproteinases [18, 20, 43, 22]. All described mechanisms of action of the described substance suggest a strong anti-inflammatory effect used in the treatment of diabetic retinopathy.

Effect on blood components

Sulodexide has the ability to reduce the concentration of fibrinogen in the blood, which contributes to the reduction of blood viscosity, which is important in the prevention of vascular diseases in patients with diabetes. However, what is important for this group of patients at risk of vascular complications, it does not have pro-hemorrhagic effects or negatively affect blood coagulation processes [23, 24].

Noteworthy study by Raffetto et al. [25], analyzed inferior vena cava's samples of rats subjected to long-term stretching. They proved that sulodexide improves vein function and augments the contractile response in veins subjected to protracted stretch. Sulodexide-induced improvement in venous constriction and restoration of venous function appears to be associated with reductions in MMP-2 and MMP-9 and may contribute to the benefits of sulodexide in chronic venous insufficiency and varicose veins.

Sulodexide in microvascular diseases of diabetes

Micro- and macrovascular complications of diabetes stand as prominent morbidities on a global scale [26]. They not only contribute significantly to increased mortality, primarily of cardiovascular origin, but also give rise to severe disabilities that compromise the overall quality of life. These complications include conditions such as blindness, limitations in mobility and renal failure necessitating dialysis. The pervasive impact of these complications underscores the urgent need for effective strategies in diabetes management to mitigate their occurrence and reduce associated health burdens [27]. As per literature reports and conducted studies, the vasoprotective effect of sulodexide is harnessed in the treatment and prevention of vascular complications associated with diabetes.

Diabetic retinopathy

Diabetic retinopathy (DR) stands out as one of the most prevalent microvascular complications associated with diabetes. As mentioned in the introduction, initially, the retinal capillary basement membrane thickens, and pericytes degenerate, compromising capillary integrity and causing pericyte loss. Over time, collagen replaces glycosaminoglycans (GAGs) in the basal membrane, altering vascular permeability. Clinically, these changes result in vascular leakage, leading to microaneurysm development. Persistent leakage causes the deposition of serum proteins and lipids, forming hard exudates (HE) in the retina.

Sulodexide supports RD treatment

Song et al. [28] performed the randomized, placebo-controlled, multicenter trial involving 130 patients who had mild-to-moderate NPDR with macular HE. Participants in the study were administered a daily dose of either 50 mg of sulodexide or an equivalent dose of placebo orally for a duration of 12 months. The primary outcome measure was an improvement in hard exudates (HE), defined as a reduction in severity by at least two grades on a 10-grade severity scale. This assessment was conducted through fundus photography over a 12-month period. The group receiving sulodexide exhibited a significantly greater improvement in hard exudates (HE) severity compared to the placebo group (39.0% vs. 19.3%; Chi-square, $P = 0.005$). The safety profile of sulodexide was found to be comparable to that of the placebo. Rubbi et al. [29] reached similar conclusions regarding the improvement in hard exudates (HE). Their study also demonstrated a decrease in the frequency of intraocular hemorrhages following sulodexide therapy. Whereas, the study conducted by Shadrichev [30] revealed a decrease in the occurrence of intraocular hemorrhage following panretinal laser coagulation with the administration of sulodexide.

Belcaro et al. [31] evaluated the number of repeated episodes of retinal vein thrombosis (RVT) in 12 months. The study assessed the effect of various drugs, including sulodexide at a dose of 500 ULS/day. Sulodexide reduced the occurrence of new RVT (-9.5% vs. standard management) without side effects.

In recent years, a large meta-analysis by Bignamini et al. [32] analyzed 45 studies with 2,817 participants monitoring any effect of sulodexide in subjects with diabetes, in relation to renal, vascular, and ocular complication. The findings from this meta-analysis suggest that Sulodexide has a positive impact on ocular diseases and may reduce the severity of diabetic retinopathy.

The clinical study led by Jo et al. [33] is particularly noteworthy, as it delves into the anti-angiogenic effects of sulodexide using an oxygen-induced retinopathy (OIR) mouse model. In OIR mice injected with sulodexide, there was a significant reduction in the distinctive central area of nonperfusion observed in sham-injected OIR mice (P17). Additionally, the number of neovascular tufts, measured by SWIFT_NV, and mean neovascular lumen number showed a significant decrease in sulodexide-injected mice. Furthermore, exposure to hyperbaric oxygen led to elevated levels of VEGF, MMP-2, and MMP-9. Notably, treatment with sulodexide resulted in a dose-dependent reduction in VEGF, MMP-2, and MMP-9 levels. These findings unequivocally demonstrate the anti-angiogenic effects of sulodexide and underscore its potential as a supplementary substance for the treatment of ocular pathologies involving neovascularization.

Regarding the potential effect of sulodexide in inhibiting VEGF expression, additional experimental studies dedicated to investigating the treatment of diabetic retinopathy are also documented. These studies contribute to a broader understanding of sulodexide's impact on VEGF and its relevance to the management of diabetic retinopathy. The study conducted by Giurdanel-

la et al. [34] suggests that sulodexide offers protection to human retinal endothelial cells from damage induced by high glucose levels. The findings propose that sulodexide acts by countering the activation of the ERK/cPLA2/COX-2/PGE2 pathway, reducing AGE-related signaling, and mitigating downstream NFκB activity. This mechanism, which is partially distinct from VEGF blockade, could potentially contribute to the therapeutic effect of sulodexide in diabetic retinopathy if it occurs in vivo.

Diabetic nephropathy

Diabetic nephropathy (DN), affecting 20–40% of individuals with diabetes, is characterized by damage to the glomerular basement membrane [35, 36]. Initial changes involve basement membrane thickening, alterations in mesangial cells and microcirculation, microparticle passage, and inflammatory reactions. These processes, accompanied by renal hemodynamic disorders like hyperfiltration and intraglomerular hypertension, often develop without overt clinical symptoms and are detected early through microalbuminuria in studies [37, 38]. Subsequent stages, marked by macroalbuminuria and declining kidney function, can contribute to disease progression and, ultimately, end-stage renal disease [39, 40].

Sulodexide in RN treatment

In experimental studies, glycosaminoglycans, including the heterogenous group represented by sulodexide, have shown promise in preventing diabetic renal morphological and functional changes. These substances demonstrated the ability to suppress renal inflammatory cytokines and vascular growth factors, including transforming growth factor-beta (TGF-beta). Furthermore, they were found to improve endothelial dysfunction and reduce albuminuria [41–44]. Preliminary data indicate the potential efficacy of this treatment in preventing the progression of renal disease in patients with type 2 diabetes who exhibit significant proteinuria.

Yongwatana et al. [45] conducted a retrospective clinical trial investigating the impact of sulodexide treatment on renal outcomes in patients with type 2 diabetes. In this study, 52 patients with proteinuria ranging from 500 to 3000 mg/ day were administered sulodexide at a dosage of 200 mg/ day for 12 months, while a control group of 56 matched patients with type 2 diabetes was established. The findings suggested that sulodexide treatment can prevent the escalation of proteinuria levels in individuals with type 2 diabetic nephropathy exhibiting significant proteinuria. However, the study did not observe any significant effect on the preservation of renal function.

In the context of diabetic nephropathy, it's essential to recognize that glycosaminoglycans play a dual role as crucial components of both the endothelial glycocalyx and the glomerular basement membrane [46]. The versatile benefits of sulodexide in individuals with renal complications of diabetes extend to inhibiting inflammatory reactions and mitigating oxidative stress [47, 48].

The previously mentioned meta-analysis [27] also analyzed articles on diabetic nephropathy. Analysis of studies presenting data on the effect of sulodexide in the treatment of diabetic nephropathy, especially monitored as urinary albumin excretion, showed a significant reduction in albuminuria compared to control groups. Sulodexide proved to be a beneficial treatment for individuals with both type 1 and type 2 diabetes, exhibiting various degrees of nephropathy, as it led to a reduction in urinary albumin excretion.

Beneficial effect of sulodexide on other vascular diseases comorbid with diabetes

The anticoagulant and profibrinolytic mechanisms, along with the inhibition of inflammatory reactions and oxidative processes generating free radicals – thus safeguarding the endothelium – coupled with lipolytic effects that enhance the activity of lipoprotein lipase, contribute to the increasing utilization of sulodexide in patients with peripheral arterial disease and critical limb ischemia. Furthermore, the induction of nitric oxide production by vascular endothelial cells in arteries results in vasodilation [49–51].

Bignamini's meta -analysis [27] also assessed the effect of sulodexide on the peripheral vascular complications of diabetes. The endpoints monitored in the relevant studies were the pain-free walking distance and the maximal walking distance. The results indicate the increase of both pain-free walking distance of 84 m (95% CI 81–86 m) and maximal walking distance of 316 m (95% CI 177–456 m). The use of sulodexide was accelerated by healing of ulcers by 27 days (95% CI 23–31 days) and increased the chance of heating [1.8 times compared to the control group (95% CI 1.4–2.4)]. Thus, the use of sulodexide in vascular diseases can significantly improve the prognosis and quality of life of patients.

Conclusion

Diabetes is a complex disease, the essence of which is microaniopathy. The effect of sulodexide on vascular endothelial cells and its role in stabilizing the glycocalyx help in the treatment of diabetes and prevent excessive initiation of the inflammatory reaction in the microcirculation and subsequent organ damage.

Disclosure
The authors declare no conflict of interest.

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