

# Nephroprotective action of glycosaminoglycans: why the pharmacological properties of sulodexide might be reconsidered

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**Abstract:** A relatively large body of evidence supports the notion that glomerular capillary wall and mesangial alterations in diabetic nephropathy involve biochemical alterations of glycoproteins in these structures. Evidence in experimental animals rendered diabetic reveals that the administration of heparin and other anionic glycoproteins can effectively prevent the biochemical alterations that promote albuminuria. Moreover, angiotensin II inhibits heparan sulfate synthesis, while heparins modulate angiotensin II signaling in glomerular cells, inhibiting aldosterone synthesis and lowering proteinuria in diabetes patients. Sulodexide, a mixture of heparin and dermatan sulfate, appears to be a promising treatment for diabetic proteinuria partially resistant to renin–angiotensin system blocking agents. Sulodexide prevents heparan sulfate degradation, thus allowing reconstruction of heparan sulfate content and restoration of glomerular basement membrane ionic permselectivity. The antiproteinuric effect appears to be mainly related to the basal proteinuria and consequently to the duration of treatment in a relatively large number of small clinical trials. On the other hand, several sulodexide pharmacodynamic properties could improve the prognosis of chronic kidney disease patients, also independently from its antiproteinuric effect. However, sulodexide development as an antiproteinuric drug needs to be continued, in order to define which kind of patients could better respond to this treatment.

**Keywords:** glycosaminoglycans, sulodexide, albuminuria, proteinuria, diabetic nephropathy

## Introduction

Diabetes mellitus is strongly associated with cardiovascular disease morbidity and mortality, accelerating the vascular aging process and in particular the pathogenesis of atherosclerosis. Diabetic nephropathy is a highly important cause of morbidity and mortality in patients with type 1 and type 2 diabetes mellitus, either directly and as a risk factor for cardiovascular disease.<sup>1</sup> In particular, diabetic kidney disease occurs in 20% to 40% of patients with diabetes mellitus and is the leading cause of chronic kidney disease and end-stage renal disease.<sup>2</sup>

Recent evidence shows that an early multipharmacological approach is able to slow the progression of diabetic nephropathy to end stage renal disease (ESRD), the disease rarely stops and slightly regresses just in few selected and optimally treated patients.<sup>3</sup> In this context, there is a strong need for new agents able to significantly modify the patient disease history.

The aim of this review is to evaluate the potential role of glycosaminoglycans (and in particular sulodexide) as antiproteinuric and kidney protective drugs.

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## Glycosaminoglycans role in proteinuria management

Glycosaminoglycans (GAGs) are long unbranched mucopolysaccharides consisting of a repeating disaccharide unit. Apart from hyaluronan, which is uniquely synthesized without a protein core and is “spun out” by enzymes at cell surfaces directly into the extracellular space, the other GAGs are usually added to protein cores in the Golgi apparatus to yield proteoglycans.<sup>4</sup> It has been proposed that hemodynamic alterations and structural changes in glomerular basement membrane glycosaminoglycans may play a role in the pathogenesis of proteinuria. The glomerular filtration barrier consists of fenestrated glomerular endothelium, podocyte foot processes/slit diaphragms, and intervening glomerular basement membrane. Its characterization as both a size- and charge-selective barrier emerged from studies conducted decades ago. The charge selectivity phenomenon is receiving renewed attention now that the identities and mechanisms of synthesis of relevant molecules are known.<sup>5</sup> Attention has focused on glomerular basement membrane heparan sulfate proteoglycans, long considered primary charge barrier components, even if recent *in vivo* manipulations of glomerular heparan sulfate proteoglycans redefined (but not excluded) their role or their anionic charge in glomerular filtration.<sup>6</sup> In fact an experimental model of non-diabetic mice, knock-out for the Ext1 gene encoding a subunit of heparan sulfate co-polymerase, develops a proteinuria that is less impressive than that expected from the available knowledge on renal physiology.<sup>7</sup> However, a relatively large body of evidence supports the notion that glomerular capillary wall and mesangial alterations in diabetic nephropathy involve pathobiochemical alterations of glycoproteins in these structures. Evidence in experimental animals rendered diabetic reveals that the administration of heparin and other anionic glycoproteins can effectively prevent the biochemical alterations that promote albuminuria.<sup>8</sup> Moreover, in renal biopsies of different human primary proteinuric diseases, pronounced tubulointerstitial heparan sulfate proteoglycans alteration are evident and strongly related to the inflammatory processes.<sup>9</sup>

Moreover, GAGs strongly influence thickness, integrity and permselectivity of the endothelial glycocalyx, a luminal layer composed of several proteoglycans and a special class of heavily glycosylated glycoproteins. Glycocalyx composition is strongly altered in diabetes patients, who typically show early sign of renal damage. The recent demonstration that angiopoietin-1 also modifies basal kidney-microvessel permselectivity acting on the glomerular glycocalyx further

supports the key role of this glycocalyx and glycocalyx composition on glomerular function.<sup>10</sup>

Angiotensin II receptor blockers are renin–angiotensin system (RAS) modulators with known antiproteinuric activity.<sup>11</sup> Angiotensin II inhibits heparan sulfate synthesis, while heparins modulate angiotensin II signaling in glomerular cells, inhibiting aldosterone synthesis and lowering proteinuria in diabetes patients (but less in other forms of proteinuric renal diseases).<sup>12</sup> In this context, heparinoids have been considered as potentially useful antiproteinuric drugs that could have synergistic effects with RAS modulator.<sup>13</sup>

## Sulodexide as an antiproteinuric agent: the available evidence

Sulodexide is a highly purified mixture of GAGs composed of a fast-moving heparin fraction (80%) and dermatan sulfate (20%), with a low molecular weight, a high oral bioavailability, and antithrombotic and profibrinolytic activity.<sup>14</sup> It also appears to be a promising treatment for diabetic proteinuria partially resistant to RAS blocking agents.<sup>15</sup> Sulodexide concentrates in renal parenchyma for a long time after administration.<sup>16</sup> From preliminary trials it has been supposed that sulodexide reduces albuminuria acting *in vivo* as a heparinase inhibitor that reaches the glomerular capillary wall and prevents heparan sulfate degradation, thus allowing reconstruction of heparan sulfate content and restoration of glomerular basement membrane ionic permselectivity.<sup>17</sup>

Recent *in vitro* experiments on umbelical human veins demonstrated that sulodexide supplementation restores the glycocalyx structure and barrier properties by increasing the trans-endothelial albumin leakage induced by hyperglycemic conditions.<sup>18</sup>

The antiproteinuric effect appears to be mainly related to the basal proteinuria and consequently to the duration of treatment.<sup>19</sup> Moreover, at least a part of the renal histological degradation observed in diabetes is related to inflammatory processes. Sulodexide seems to have powerful antiinflammatory activity in experimental models.<sup>20</sup> In a model of cultured human umbilical endothelial cells exposed to high glucose concentration, sulodexide suppresses cellular inflammation and prevents glucose cytotoxicity;<sup>21</sup> sulodexide is able to reverse the glucose-related cell release of free oxygen radicals, monocyte chemotactic protein-1 (MCP-1) and interleukin-6 (IL-6), and the inactivation of cell-repairing mechanism enabling the exposition to glucose. Moreover, in rats with streptozocin-induced diabetes, sulodexide exerts direct endothelial protective effects.<sup>22</sup>

A large number of studies, mainly carried out in type 1 and 2 diabetes patients, have strongly suggested the potential role of sulodexide as an antiproteinuric agent (Table 1). The majority of these studies, however, were small, had an open design, were of short duration, and involved inhomogeneous patient categories. However, at least 15 out of 16 studies, involving 594 patients, reported a significant antiproteinuric effect of sulodexide.

It remains to be clarified if sulodexide could exert an additive antiproteinuric effect in patients treated with fully

dosed angiotensin-converting enzyme inhibitor (ACEI) or an angiotensin receptor blocker (ARB).

In a pilot study, return to normoalbuminuria or a decrease in albumine:creatinine ratio (ACR) of at least 50% from the baseline value was achieved in 25.3% of patients with persistent albuminuria in spite of being treated with the maximum recommended dose of an ACEI or an ARB.<sup>23</sup> Interestingly, a very favorable trend for an increased rate of therapeutic success was obtained in the sulodexide group receiving the daily dose of 200 mg (33.3% versus 15.4% of patients receiving

**Table 1** Clinical trials testing antiproteinuric effects of sulodexide in diabetes patients

| Number of patients | Type of patients           | Dose  | Duration of treatment | Main results  | References                  |
|--------------------|----------------------------|---|-----------------------|---|-----------------------------|
| 18                 | Type 2 diabetes            | 600 lipoproteinlipase-releasing units/day IV  | 3 weeks               | Albuminuria fall in 89% of patients, proteinuria normalization in the 9 microalbuminuric patients                 | Shestakova <sup>19</sup>    |
| 15                 | Type 1 diabetes            | 600 lipoproteinlipase-releasing units/day IV  | 3 weeks               | Albuminuria fall after the first week, maintained also 6 weeks after treatment cessation                          | Szela-chowska <sup>46</sup> |
| 15                 | Type 2 diabetes            | 600 lipoproteinlipase-releasing units/day IM  | 4 weeks               | Albuminuria fall in the 60% of patients, reversed after   | Sorrenti <sup>47</sup>      |
| 20                 | Type 2 diabetes            | 100 mg/day  | 4 months              | Significant reduction in albumin excretion rate, fibrinogen and blood pressure                                    | Solini <sup>48</sup>        |
| 53                 | Type 2 and type 1 diabetes | 600 lipoproteinlipase-releasing units/day IM  | 3 weeks               | Significant reduction of albuminuria in 72% of patients, slower in type 2 diabetics                               | Skrha <sup>49</sup>         |
| 36                 | Type 1 diabetes            | 600 lipoproteinlipase-releasing units/day IM 5 days/week  | 3 weeks               | Significant reduction of albuminuria in 90% of patients, slower in macroalbuminuric patients                      | Dedov <sup>50</sup>         |
| 14                 | Type 1 diabetes            | 60 mg vial of sulodexide/day for 10 days, and then orally with 25 mg capsules twice a day for 21 days | 31 days               | Significant reduction of albuminuria with normalization in 40% of microalbuminurics and 25% of macroalbuminurics  | Poplawska <sup>51</sup>     |
| 35                 | Type 2 and type 1 diabetes | 600 lipoproteinlipase-releasing units/day IM 5 days/week  | 15 days               | Significant reduction of albuminuria in 70% of patients, persistent 3 weeks after treatment cessation             | Perusicová <sup>52</sup>    |
| 20                 | Type 2 and type 1 diabetes | 600 lipoproteinlipase-releasing units/day IM 5 days/week  | 3 weeks               | Quickly reversible albuminuria in all patients  | Zalevskaia <sup>53</sup>    |
| 20                 | Type 1 diabetes            | 600 lipoproteinlipase-releasing units/day IM 5 days/week  | 3 weeks               | Significant reduction of albuminuria in 70% of patients, and persisted in 60% 6 weeks after drug discontinuation  | Rasovskii <sup>54</sup>     |
| 20                 | Type 2 and type 1 diabetes | 600 lipoproteinlipase-releasing units/day IM 5 days/week  | 3 weeks               | Significant reduction in albuminuria and serum NAG activity   | Skrha <sup>55</sup>         |
| 20                 | Type 2 and type 1 diabetes | 60 mg/d IM<br>100 mg/d PO   | 3 weeks<br>8 weeks    | Albumin excretion rate reduced after both treatment phases in macroalbuminuric, but not microalbuminuric patients | Oksa <sup>56</sup>          |

(Continued)

**Table 1** (Continued)

| Number of patients | Type of patients   | Dose  | Duration of treatment | Main results  | References               |
|--------------------|--|---|-----------------------|---|--------------------------|
| 223                | Type 2 and type 1 diabetes   | 50 mg/d, 100 mg/d, or 200 mg/d PO           | 4 months              | Dose-dependent reduction in albumin excretion rate  | Gambara <sup>24</sup>    |
| 60                 | Type 2 and type 1 diabetes   | 50 mg/d PO                                  | 12 months             | Albuminuria strongly reduced in all patients vs controls and vs baseline  | Achour <sup>57</sup>     |
| 45                 | Type 1 diabetes  | 120 mg/d PO                                 | 6 months              | Reduction in albuminuria and NAG excretion, increase in renal vascular function   | Sulikowska <sup>58</sup> |
| 149                | Obese type 2 diabetics with proteinuria resistant to therapy with ACEI or ARBs | 200–400 mg/d PO in addition to ACEI or ARBs | 6 months              | 25.3% and 33.3% of the patients respectively in the two sulodexide groups combined and in the 200 mg/d group achieved a significant reduction or normalization of albuminuria vs 15.4% of the patients in the control group ( $P = 0.26$ and $P = 0.07$ , respectively) | Heerspink <sup>23</sup>  |

**Abbreviations:** ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; IM, intramuscular; IV, intravenous; PO, by mouth; NAG, N-acetyl-beta-glucosaminidase.

placebo;  $P = 0.075$ ), which was the more effective dose also in the largest published study.<sup>24</sup> In particular, this trial clearly showed for the first time that sulodexide, 200 mg/day for 4 months, was able to significantly decrease albuminuria (both versus placebo and baseline) independently of the concomitant administration of ACEI, but at an unspecified daily dosage. The decrease in the albumin excretion rate at the end of treatment was 40% and 46% versus baseline in patients receiving or not receiving ACEI, respectively ( $P < 0.05$ ).

To the best of our knowledge only one trial has tested the effect of endovenous sulodexide administration on renal disease other than that caused by diabetes.<sup>25</sup> In this trial the researchers enrolled patients with bioptic diagnosis of different glomerulonephritis, and observed after 1 month of treatment that overall 85% of patients experienced a significant reduction in proteinuria, which was significantly more impressive in patients with mesangiocapillary than in those with membrano- and mesangioproliferative glomerulonephritis. Moreover, the decline of proteinuria was more relevant in GAG(+) patients with important proximal tubular necrosis and moderate to severe myofibroblast infiltrates than in GAG(−) patients with mild interstitial involvement.<sup>26</sup>

On the basis of the above-cited preclinical and clinical evidence, the use of sulodexide has also been suggested by experts for the treatment of serious chronic kidney diseases (CKD) other than those caused by diabetes. The most interesting is probably the management of the membranoproliferative glomerulonephritis type II (or dense deposit disease), a rare and serious renal genetic disease which affect 2 to 3

people per million and leads to renal failure within 10 years in 50% of affected children, with a worse prognosis after kidney transplantation than other genetic glomerulonephritis.<sup>27</sup>

However new trials have to be carried out to confirm these preliminary results and hypotheses.

## Other sulodexide pharmacological effects potentially useful in the diabetic CKD patient

It is well known that diabetes patients are more likely to develop vein insufficiency and their related sequelae. The antithrombotic effects of sulodexide in patients affected by deep vein thrombosis<sup>28,29</sup> and venous leg ulcers<sup>30,31</sup> have been adequately investigated in different clinical trials. However, there is some evidence that sulodexide could also reduce the arterial disease risk, which is usually very high in diabetes patients with CKD,<sup>32</sup> through a large number of pharmacological actions (Table 2).

**Table 2** Potential cardiovascular beneficial effects of sulodexide and glycosaminoglycans

|   |
|---|
| Antithrombotic action                                       |
| Decrease of oxidative stress                                |
| Hypolipidemic actions                                       |
| Prevention of glucose toxicity                              |
| Suppression of cellular inflammation                        |
| Antiproteinuric effects                                     |
| Improvement of endothelial function and vascular elasticity |
| Interactions with AT-II signaling and RAS system            |

Two different meta-analyses of the available clinical trials have shown that sulodexide treatment improves the pain-free walking distance in patients affected by peripheral occlusive artery disease.<sup>33,34</sup> This effect could be related to different sulodexide activities. First, the sulodexide-treated patients have higher peak flow and rest flow in the lower limbs.<sup>35</sup> Moreover, sulodexide treatment improves the patient's lipid and hemorrheological profile.<sup>36</sup> In particular, sulodexide improves the typical lipid components of metabolic syndrome, which is a predictor of both CKD worsening and cardiovascular disease risk in CKD patients.<sup>37</sup> Recent data also support a significant anti-inflammatory action of sulodexide in the endothelial cells and a protective effect of the drug against glucose cytotoxicity. The experiments were performed on *in vitro* cultured human umbilical endothelial cells kept for 7 days in standard medium or in the same medium but supplemented with glucose. Sulodexide inhibited the intracellular generation of free radicals in a dose-dependent manner (by up to 32%), as well as monocyte chemoattractant protein-1 (MCP-1) (by up to 60%) and IL-6 (by up to 69%). Cells cultured in a medium with glucose generated more free radicals (+20%) and released more MCP-1 (+113%) and IL-6 (+26%). Cell monolayers treated with glucose had a decreased ability to heal after mechanical injury (−28%). All these glucose effects were reversed when cells were exposed to sulodexide simultaneously.<sup>19</sup>

In the long term, it is also possible that sulodexide exerts anti-atheromasic effects. In experimental models, sulodexide protects endothelium from external injuries as demonstrated by a reduced number of desquamated endothelial cells.<sup>38</sup> Sulodexide could then stop the earliest phase of atherosclerosis, at the level of endothelial dysfunction, improving endothelium-dependent relaxation in small arteries.<sup>39</sup> In a more advanced atherosclerosis phase, sulodexide inhibits neointimal proliferation after vascular injury of the carotid artery, as shown in an experimental model of restenosis after balloon angioplasty.<sup>40</sup> Furthermore, *in vitro* heparin and heparinoids inhibit the proliferation of the vascular smooth muscle cells.<sup>41</sup> This antiproliferative effect has also been supposed to be valid in humans, but only preliminary data are available.<sup>42</sup>

It has also been shown in humans that sulodexide treatment could also improve some clinical parameters in patients with vascular dementia.<sup>43</sup> Consequently it has also been used to prevent ischemic cerebral damage in patients with antiphospholipid antibodies.<sup>44</sup>

Finally, different GAGs have been reported to be of benefit to the ischemic myocardium by preserving contractile

function and reducing tissue injury. In a rabbit model, sulodexide also attenuated myocardial ischemia/reperfusion injury and the deposition of C-reactive protein in areas of infarction without affecting hemostasis.<sup>45</sup>

The prognostic value of most of these observations has yet to be demonstrated, but they appear to be interesting working hypotheses, especially in patients with either CKD and preclinical signs of cardiovascular diseases.

## Conclusion

Preclinical and clinical evidence directly or indirectly support the hypothesis that new, adequately designed, long-term studies need to be carried out to investigate the potential role of sulodexide for proteinuric CKD management in diabetes patients, in particular to understand which kind of patients could obtain the most clinical advantage from this therapeutic approach. Presently, there is a clear lack of preventive and therapeutic tools for proteinuric syndromes, and each new active compound needs to be evaluated, in order to widen the therapeutic arsenal against CKD. Considering the previously reported large spectrum of its pharmacological properties, sulodexide seems to be able to play an important role in the treatment of these patients because of its actions not only at the renal level, but also on the whole vessel tree, which is usually severely affected in diabetes patients with CKD.

In conclusion, a relatively large body of literature supports the antiproteinuric and nephroprotective effects of GAGs and sulodexide; however more basic clinical research is needed to understand which factors influence the drug's efficacy and, consequently, which patients could therefore benefit most from this treatment.

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