To the Editor:

We read with interest the article by Yang et al [1] that described the antiproteinuric effect of low-dose sulodexide in IgA nephropathy patients who were already receiving renin-angiotensin system (RAS) inhibitors. Reduction in proteinuria is the key determining factor for renoprotective effects of any given therapies for IgA nephropathy patients. RAS inhibition using angiotensin-converting-enzyme inhibitors or angiotensin receptor blockers is currently the most widely adopted renoprotective therapy for IgA nephropathy. However, it is relatively common to see IgA nephropathy patients with residual proteinuria despite being treated with a maximal dose of RAS inhibitors. Therefore, it is clinically relevant to investigate the beneficial effect of sulodexide on residual proteinuria. Sulodexide, a glycosaminoglycan extract of porcine lung and liver, is composed of fast-moving heparin sulfate (80%) and dermatan sulfate (20%). The heparan sulfate content of sulodexide has been proposed to potentially interfere with the abnormal biochemistry of the glomerular capillary wall in patients with diabetic nephropathy and reduce albuminuria. These hypoalbuminuric properties have been extensively investigated in a multiple series of clinical studies on Type 2 diabetic patients with albuminuria in contrast to the study. We recently reported that sulodexide at 200 mg/day failed to decrease urine albumin excretion in Type 2 diabetic nephropathy patients with microalbuminuria. Nevertheless, few data exist on the use of sulodexide in non-diabetic chronic kidney disease. Its potential efficacy in treatment of IgA nephropathy patients, especially those with residual proteinuria, remains to be explored.

The results of the study are interesting. However, a big limitation of the study, as underlined by the authors, is that it is a retrospective study with only a small number of patients enrolled. Therefore, the study results should be interpreted with caution. Another limitation of the study is its lack of a control group. Historical control group from the literature may not be sufficient. Whether add-on treatment of low-dose sulodexide confers a significant antiproteinuric effect in IgA nephropathy patients with residual proteinuria currently receiving RAS inhibitors is questionable.

The dose of sulodexide used in the study is considerably lower than the dosage used in other trials [1,2]. A recent randomized control trial in IgA nephropathy demonstrated an antiproteinuric effect of sulodexide only in the 150 mg arm [3]. There were some nonresponders to sulodexide treatment, as shown in Fig. 1, with an increase in urine protein creatinine ratio. As a group, RAS inhibition demonstrates a significant antiproteinuric effect, but inter-individual variability to RAS inhibitors is well known [4]. It would be interesting to see if these nonresponders are a subgroup of patients who are also resistant to RAS inhibition.

Finally, we are concerned about the some other clinical factors that might influence the antiproteinuric effects of RAS inhibition and sulodexide. Medication history is limited to only the number and duration of RAS inhibitors used. Dietary sodium and protein intake can influence urine protein excretion in patients with renal disease. A low-sodium diet and use of diuretics potentiate the antiproteinuric effects of RAS inhibitors [5]. As in any other clinical studies, more attention should be directed to dietary sodium intake.

Considering that no safety issues had occurred during the study, a larger randomized controlled trial with higher dose would be most helpful in demonstrating the future utility of sulodexide in proteinuric renal diseases.

Conflicts of interest

All contributing authors declare no conflict of interest.

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In Reply:

Dear Sirs,

We appreciate your interest in our recent paper. As you mentioned, our study has several flaws. We conducted a case series study dealing with uncontrolled paired comparisons. With a retrospective analysis, it was hard for us to get matched controls that had an equivalent additional observation period to the add-on therapy. We tried to find historical controls, but trials that were possible matches were nonhomogeneous. Besides, the small sample size could not sufficiently yield an conclusive effect, and even showed negative outcomes in some patients.

Another concern was raised regarding the sulodexide dose (50 mg daily) used in our study. We anecdotally used this dose and there was no dose escalation during the treatment period. Although Blouza et al [1] reported the efficacy of low-dose sulodexide (50 mg daily) in the management of diabetic nephropathy, we did not extrapolate their result to our study. There is a different aspect we observed as follows.

Bang et al recently published the first randomized controlled trial of sulodexide therapy in IgA nephropathy [2]. The baseline proteinuria of the patients in their trial was not significantly high, suggesting that the most of the patients would be already be in a range of partial remission [urinary protein to creatinine ratio (UPCR) < 1.0 g/g] at baseline, which means they dealt with a different study population from ours. In our study, the nearly 1-year use of low-dose sulodexide in the patients having UPCR > 1.0 g/g correlated to high response rate.

Reich et al studied a large cohort and demonstrated a relationship between time-average proteinuria and renal survival in IgA nephropathy [3]. They showed that the outcome of patients with a partial remission of proteinuria with a UPCR of 0.3–1.0 g/g was not inferior to that of patients with complete remission. Partial remission could be an alternative target in the management of IgA nephropathy, whereas complete remission is the ultimate goal.

As you pointed out, our study is lacking in some data essential to guarantee the quality of the results. Further investigations for the use of sulodexide in IgA nephropathy are needed to clarify its effectiveness.

Conflicts of interest

All contributing authors declare no conflict of interest.

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