

### **Glycosaminoglycans and diabetic nephropathy**

Pijl, J.W. van der

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## **CHAPTER 5**

# Effect of danaparoid sodium on hard exudates in diabetic retinopathy\*

Johan W. van der Pijl<sup>1</sup> Fokko J. van der Woude<sup>1,4</sup> Wouter Swart<sup>3</sup> Leendert A. van Es<sup>1</sup> Herman H. P. J. Lemkes<sup>3</sup>

Departments of Nephrology (1), Ophthalmology (2), Endocrinology (3) Leiden University Medical Center, and Fifth Medical Clinic (4) Mannheim Hospital, Germany

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#### Abstract

In diabetes mellitus, both retinopathy and nephropathy represent specific microvascular disease with increased capillary permeability resulting in hard exudates, foveal oedema, and albuminuria. The decrease of heparan-sulfate content of the glomerular-basement membrane is quantitatively related to the rate of proteinuria in nephropathy associated with insulin dependent diabetes mellitus (IDDM). Several short-term studies in patients with IDDM and non-IDDM have shown that a reduction of microalbuminuria and macroalbuminuria can be achieved with the supplementation of glycosaminoglycans. After completion of a study on the effect of danaparoid sodium on albumin excretion in patients with IDDM and macroalbuminuria, we hypothesised that treatment with danaparoid sodium also influenced retinal leakage in the patients in that trial.

In this retrospective study nine patients with nephropathy received 750 anti-Xa units of danaparoid sodium once a day for 6 weeks in a placebo-controlled double-blind cross-over study. Fundus photographs, done at baseline and at the end of the study, were semiquantatively scored for the severity of hard exudates.

At baseline fourteen eyes had a grade 1 to 5 severity of hard exudates and four eyes were without hard exudates (grade 0). There was no progression in the latter four eyes. In ten eyes an improvement was observed: four patients showed a favourable response to treatment in both eyes and two patients showed improvement in one eye. We found improvement of hard exudates after 6 weeks of treatment with danaparoid sodium.

Our uncontrolled observation indicates that the supplementation of danaparoid sodium influences both the permeability of retinal vessels as well as of glomerular vessels. Danaparoid-sodium therapy as a systemic adjuvant is worth considering for treatment strategies for foveal oedema and hard exudates in diabetic maculopathy.

#### Introduction

Both retinopathy and nephropathy represent specific microvascular disease in diabetes mellitus. Increased capillary permeability causes albuminuria in nephropathy and in foveal oedema and hard exudates in diabetic maculopathy. The glomerular-basement membrane (1) and also the retinal capillary basement membrane (2) contain heparan sulfate, which plays an important part in the charge-selective barrier function. The decrease of heparan-sulfate content of the glomerular-basement membrane is quantitatively related to the rate of proteinuria in nephropathy associated with insulin-dependent diabetes mellitus (IDDM) (3). Several short-term studies in patients with IDDM and non-IDDM have shown that a reduction of microalbuminuria and macroalbuminuria can be achieved with heparin, low-molecular-weight heparin, or heparinoid (4-7).

After completion of a study on the effect of danaparoid sodium on albumin excretion in patients with IDDM and macroalbuminuria, we hypothesised retrospectively that treatment with danaparoid sodium may also have influenced retinal leakage in our trial patients (6). Therefore, we reviewed fundus photographs which had been taken as a safety measure before and at the end of the study.

#### **Patients and methods**

The original study was designed as a phase II randomised, double-blind, placebocontrolled, cross-over study to assess putative effects of danaparoid sodium on the rate of proteinuria in IDDM patients (6). The study was approved by the ethics committee of the Leiden University Hospital, Leiden, Netherland, and all patients gave informed consent. Nine patients, eight men and one woman (median age 35 years; interquartile range [IQR] 29 - 44 years), who had IDDM (median duration 25 years; IQR 16 - 28 years) with macroalbuminuria (albumin-excretion rate > 300 mg/24 h) because of diabetic nephropathy were studied. Median mean-arterial blood pressure was 105 mm Hg (IQR 100-107 mm Hg); the use of angiotensin-converting-enzyme inhibitors and other anti hypertensive medications was by a stable dosage at least 6 weeks before the start of the study and remained unchanged. Median HbA<sub>1c</sub> was 8.3% (IQR 7.7 - 9.8%)). Six of nine patients had undergone pattern photocoagulation previously because of proliferative retinopathy. The other three patients had stable background retinopathy. At baseline, seven patients had hard exudates in both eyes.

The patients were randomly assigned to one of two treatment: 750 anti-Xa units danaparoid sodium (Orgaran, NV Organon, Oss, Netherlands) subcutaneously given once a day for 6 weeks, a wash-out period of 4 weeks, followed by 6 weeks placebo

(saline with sulphite) or the same scheme but with the placebo first. Danaparoid sodium is a mixture of sulfated glycosaminoglycans (84% heparan sulfate, 12% dermatan sulfate, and 4% chondroitin sulfate) isolated from porcine intestinal mucosa.

Fundus photography was done at baseline and at the end of the study as a safety parameter to monitor potential bleeding complications. Seven field, red-free photographs of both eyes were obtained after mydriasis with a Zeiss camera. No bleeding complications were observed. To assess the course of signs of retinal leakage a 45° photograph centred around the fovea was projected and all hard exudates were traced. Photographs were studied anonymous and masked for pretreatment or posttreatment assessment. Hard exudates were semiquantitatively graded, ranging from 1 (minimal) to 5 (extensive circinate).

#### Results

All patients completed the study. The results are depicted in Figure 1. Figure 2 shows two patients before and after the study. No hard exudates developed in the two patients who had no hard exudates before the study. In one patient the degree of hard exudates remained unchanged in both eyes. In two patients an improvement was seen in one eye, the other eye remaining unchanged. In four patients the degree of hard exudates improved in both eyes. So, in 14 eyes with hard exudates, an improvement was observed in ten eyes, four remaining unchanged, and no eye showed progression. There was no difference between patients with or without previous pattern photocoagulation. Subanalysis of the treatment order (danaparoid sodium then placebo or placebo then danaparoid sodium) was not possible due to the small number of patients in the trial.

#### Discussion

In this retrospective analysis an improvement of hard exudates was observed after 4 months that included 6 weeks of treatment with danaparoid sodium. This is an uncontrolled observation, which conflicts with data about the natural history of hard exudates. Several studies have shown that, on average, hard exudates progress, remain stable or improve spontaneously in a minority of patients (8-11).

The standard treatment of diabetic maculopathy is focal laser treatment (8). However, areas of maculopathy close to the fovea are not amenable to laser treatment. Therefore, local laser treatment is not always able to improve visual acuity or to prevent further loss of vision. Danaparoid sodium as a systemic adjuvant treatment may be of benefit. A

prospective, placebo-controlled, randomised trial that also taking into account a quantitative evaluation of macular thickness and visual acuity is needed.

A generalised defect in the heparan sulfate content of basement membranes has been shown in diabetic microvascular disease. A parallel between the established beneficial effect of danaparoid sodium and comparable agents on proteinuria and a potential effect on increased macular permeability may represent an attractive, pathophysiologically based, therapeutic concept.



*Figure 1.* Scores for hard exudates for 18 eyes before and after treatment with danaparoid sodium. In the 14 eyes with hard exudates (> 0), an improvement was seen in ten eyes, four remained unchanged, no eye showed progression.



*Figure 2.* Retinae from a man aged 44 years (upper panel) and a man aged 29 years (lower panel) before (A, C, E, G) and after (B, D, F, H) the danaparoid-sodium trial.

Upper panel- diabetes duration of 25 years without prior photocoagulation; right eye is shown with detailed view (score 5 for the whole eye before [A] and 3 after [B]) and the left eye with a global view (score 4 before [C] and 2 after [D]).

Lower panel- diabetes duration of 26 years with photocoagulation of both eyes several years earlier; left eye scored 3 before (E) and 2 after (F), the right eye scored 2 for both occasions (before [G] and after [H]).

#### **Contributors:**

Johan van der Pijl, Fokko van der Woude, Leendert van Es, and Herman Lemkes were involved in the protocol development and design of the original trial. Fokko van der Woude and Leendert van Es supervised the trial. Johan van der Pijl did the study. Wouter Swart was responsible for ophthalmological care, photocoagulation treatment, and did the scoring of the fundus photographs together with Herman Lemkes. All authors contributed to the writing of the paper.

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#### **References**

- 1. Kanwar YS, Liu ZZ, Kashihara N, Wallner EI: Current status of the structural and functional basis of glomerular filtration and proteinuria. *Semin Nephrol* 11: 390-413, 1991
- Das A, Frank RN, Zhang NL, Turczyn TJ: Ultrastructural localization of extracellular matrix components in human retinal vessels and Bruch's membrane. *Arch Ophthalmol* 108: 421-429, 1990
- Tamsma JT, van den Born J, Bruijn JA, Assmann KJM, Weening JJ, Berden JHM, Wieslander J, Schrama E, Hermans J, Veerkamp JH, Lemkes HHPJ, van der Woude FJ: Expression of glomerular extracellular matrix components in human diabetic nephropathy: decrease of heparan sulphate in the glomerular basement membrane. *Diabetologia* 37: 313-320, 1994
- 4. Myrup B, Hansen PM, Jensen T, Kofoed-Enevoldsen A, Feldt-Rasmussen B, Gram J, Kluft C, Jespersen J, Deckert T: Effect of low-dose heparin on urinary albumin excretion in insulin-dependent diabetes mellitus. *Lancet* 345: 421-422, 1995
- 5. Tamsma JT, van der Woude FJ, Lemkes HHPJ: Effect of sulphated glycosaminoglycans on albuminuria in patients with overt (type I) nephropathy. *Nephrol Dial Transplant* 11: 182-185, 1996
- van der Pijl JW, van der Woude FJ, Geelhoed-Duijvestijn PH, Frolich M, van der Meer FJ, Lemkes HH, van Es LA: Danaparoid sodium lowers proteinuria in diabetic nephropathy. *J Am Soc Nephrol* 8: 456-462, 1997
- 7. Solini A, Vergnani L, Ricci F, Crepaldi G: Glycosaminoglycans delay the progression of nephropathy in NIDDM. *Diabetes Care* 20: 819-823, 1997

- Early Treatment Diabetic Study Research Group: Photocoagulation for diabetic macular edema. Early Treatment Diabetic Retinopathy Study Report Number 1. Arch Ophthalmol 103: 1796-1806, 1985
- 9. Ferris III FL, Patz A: Macular edema. A complication of diabetic retinopathy. *Surv Ophthalmol* 28(Suppl): 452-461, 1984
- Chew EY, Klein ML, Ferris III FL, Remaley NA, Murphy RP, Chantry K, Hoogwerf BJ, Miller D, for the ETDRS Research Group: Association of elevated serum lipid levels with retinal hard exudate in diabetic retinopathy. Early Treatment Diabetic Retinopathy Study (ETDRS) Report 22. Arch Ophthalmol 114: 1079-1084, 1996
- 11. Cheng H, Blach RK, Hamilton AM, Kohner EM: Diabetic maculopathy. A preliminary report. *Trans Ophthalmol Soc UK* 92: 407-411, 1972