Transplant Int (1992) 5 [Suppl 1]: S 536–S 538

TRANSPLANT International
© Springer-Verlag 1992

Decrease of erythrocyte deformability in cyclosporine-treated renal transplant patients: correction with fish oil as well as corn oil

N. H. Schut, M. R. Hardeman, and J. M. Wilmink

Department of Internal Medicine, Renal Transplant Unit, Academic Medical Center, Amsterdam, The Netherlands

Abstract. Twenty-nine renal transplant recipients with good, stable transplant function were included in a double-blind cross-over study to investigate the effects of different immunosuppressive treatment modalities and also the effects of fish oil and corn oil supplementation on erythrocyte deformability. Ten patients were treated with cyclosporine (CyA) only, 10 patients with CyA and prednisolone, and 9 patients with azathioprine and prednisolone. Erythrocyte deformability, as measured by an ektacytometric technique, was significantly decreased in both CyA-treated groups compared with the azathioprine-prednisolone-treated group, and this decrease was corrected with fish oil and with corn oil. The cause and the clinical significance of less deformable erythrocytes due to CyA are not yet clear. However, less deformable erythrocytes could play a role in the genesis of the complications of CyA.

Key words: Cyclosporine – Erythrocyte deformability – Renal transplant recipients – Corn oil – Fish oil

Renal toxicity, hypertension, and arteriopathy are the well-known side-effects of cyclosporine (CyA) therapy. The mechanism of CyA toxicity is unknown but may involve rheological alterations, such as the impairment of erythrocyte deformability. It has been shown that a diet supplementation of fish oil can ameliorate the negative effects of CyA on kidney function and blood pressure [6]. Furthermore, erythrocyte deformability can be increased by fish oil in healthy subjects, in dialysis patients, and in renal transplant recipients [3, 10–12]. In one study, evidence was found that changes in the erythrocyte filterability were dependent on the use of CyA [11]. We therefore performed a study to evaluate whether erythrocyte deformability is changed in renal transplant recipients and whether any change is related to the use of different immunosuppressive treatment modalities. Furthermore, the effects of a supplementation of fish oil or corn oil on erythrocyte deformability were investigated.

Offprint requests to: N. H. Schut, Department of Internal Medicine, Renal Transplant Unit, f 4-215 Academic Medical Center, 1105 AZ-Amsterdam, The Netherlands

Patients and methods

Twenty-nine renal transplant recipients who received cadaveric kidney allografts between 1979 and 1988 were included in this study. All patients had good, stable renal transplant function and no signs of rejection. Twenty patients were treated with CyA at a mean dosage of 3.0 ± 0.8 mg/kg body weight (mean ± SD), aiming at whole blood trough levels of between 75 and 150 μg/l. Ten of these patients were treated with CyA only, whilst 10 other patients received prednisolone (10 mg) in addition (CP). Nine patients were treated with azathioprine (100–150 mg daily) in combination with prednisolone (5–10 mg) (AP). The clinical characteristics of the three patient groups are shown in Table 1. In a double-blind, randomised, cross-over study, all patients were given fish oil or corn oil a day for a period of 4 months each. The capsules with fish oil contained 6 g fish oil (30% C 20:5 ω 3 – eicosapentaenoic acid and 20% C 22:6 ω 3 – docosahexaenoic acid), the capsules with corn oil contained 6 g corn oil (50% C 18:2 ω 6). The patients of all three groups were randomized to receive fish oil or corn oil for 4 months, and after the first 4 months the patients were given the alternative oil for another 4 months. The study design is shown in Fig. 1. Erythrocyte deformability was measured by an ektacytometric technique, using the laser-assisted optical rotational deformability meter [5]. With this device, a suspension of erythrocytes is submitted to a shear stress of 30 pascal,

Table 1. Characteristics of the study groups

	C	CP	AP
Number	10	10	9
Age (years)	53 ± 14	51 ± 14	53 ± 7
Male/female	4/6	9/1	5/4
Months post-transplantation	56 ± 17	28 ± 8	84 ± 29
GFR (ml/min)	57 ± 16	59 ± 16	65 ± 18
Cyclosporine dose (mg/kg)	2.8 ± 0.9	3.3 ± 0.7	

mean values ± SD
C, cyclosporine monotherapy group; CP, cyclosporine and prednisolone; AP, azathioprine and prednisolone; GFR, glomerular filtration rate

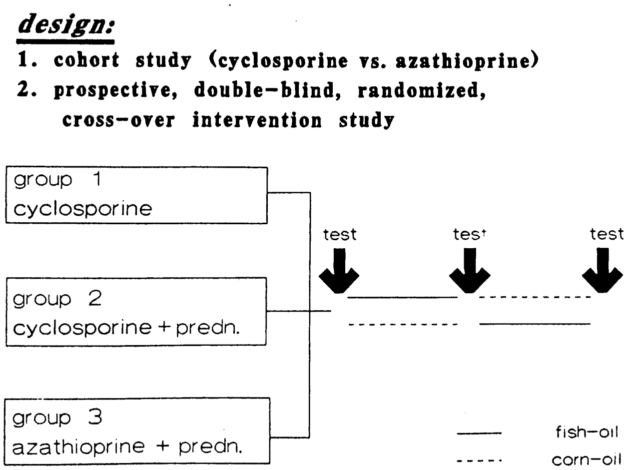

Fig. 1. Study design

generating an ellipsoid diffraction pattern. Using an ellipse-fit analysis, the long and the short axes of the Laser diffraction pattern are determined. The elongation index is the quotient of the difference between the long and the short axes divided by the sum of the long and the short axes. A lower elongation index means less deformable erythrocytes.

Results

The elongation index before intervention with fish oil or corn oil was normal in the AP group (0.583 ± 0.014) and significantly decreased in both CyA-treated groups (CyA 0.559 ± 0.014, CP 0.559 ± 0.014; CyA or CP versus AP $P < 0.005$ with Wilcoxon rank-sum W-test). During oil supplementation the elongation index increased in CyA- and CP-treated patients irrespective of the kind of oil (for each subgroup $P < 0.05$), but in the AP group the elongation index remained unaltered (subgroups after initial treatment for 4 months with fish oil: CyA 0.584 ± 0.012, CP 0.576 ± 0.005, AP 0.585 ± 0.009 and after corn oil: CyA 0.580 ± 0.007, CP 0.584 ± 0.005, AP 0.582 ± 0.009). After cross-over to the other oil, no further changes in the elongation index were observed (Fig. 2). The subgroup of AP patients who initially received corn oil and later on fish oil initially consisted of 4 patients, but after the fish oil supplementation, only 2 patients were available for follow-up study.

It is known that changes in the mean corpuscular volume (MCV) can contribute to changes in erythrocyte deformability. In these patient groups, however, changes in the MCV did not correlate with changes in erythrocyte deformability (Table 2).

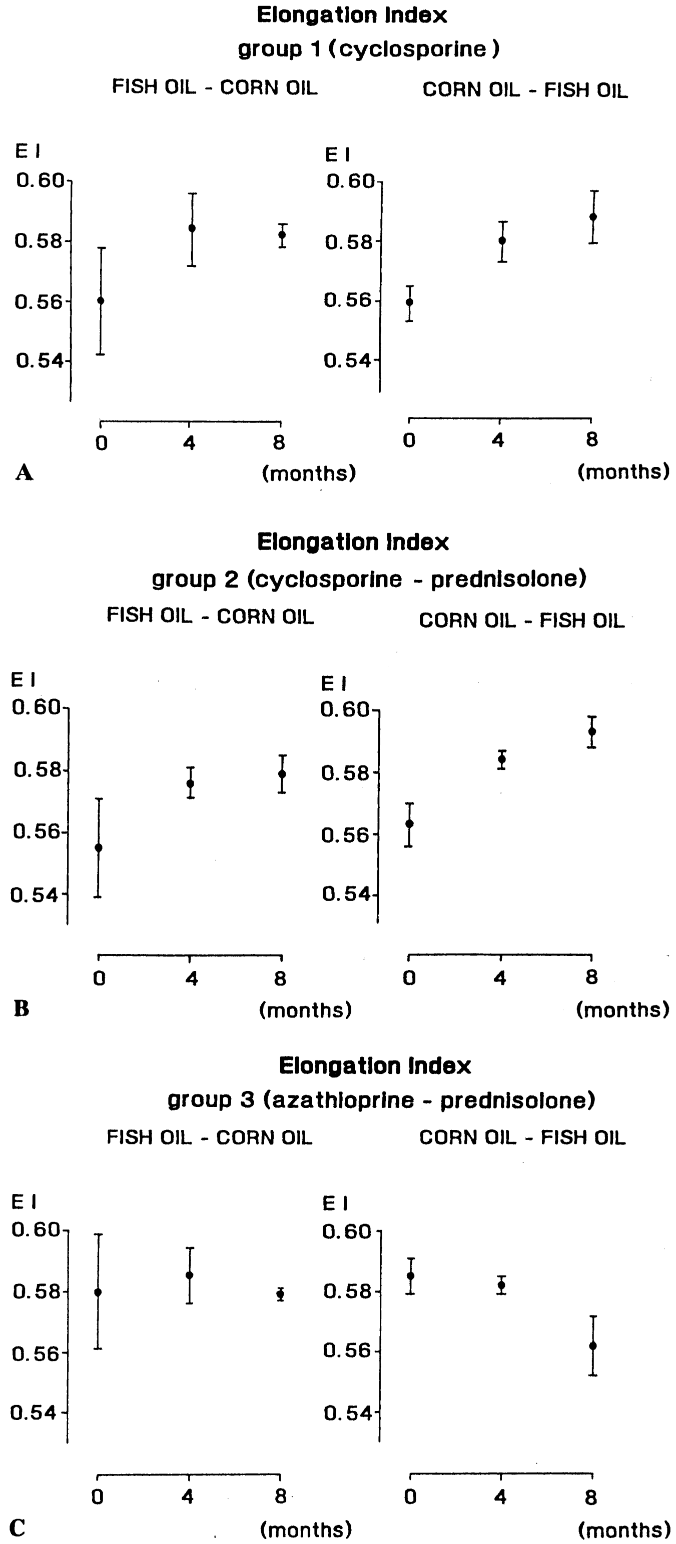

Fig. 2 A–C. The results of the intervention with fish oil and corn oil on erythrocyte deformability in the 3 patient groups

Discussion

In this study we found a lower erythrocyte deformability in CyA-treated patients, which was also previously found with a different technique [11]. We concurred that supplementation with fish oil or corn oil corrected this abnormality. The reason for the lower erythrocyte deformability in CyA-treated renal transplant recipients is not clear. Changes in the MCV cannot explain this phenomenon; other possible explanations include changes in the viscoelastic properties of the red cell membrane or changes in the viscosity of the intracellular hemoglobin milieu [2]. A decrease of the arachidonic acid content of the erythrocyte has been reported in CyA-treated renal transplant recipients [8]. This may lead to a decrease in

Table 2. Changes in the mean corpuscular volume (MCV)

	Before oil	After 4 months	After 8 months
Group I (CyA)			
Fish oil – corn oil		92.5 ± 6.4	95.5 ± 2.6
Corn oil – fish oil		92.2 ± 7.2	98.2 ± 2.7
Group II (CP)			
Fish oil – corn oil	92.5 ± 8.2	93.8 ± 7.6	94.6 ± 2.7
Corn oil – fish oil	93.7 ± 4.6	87.9 ± 4.8	94.8 ± 6.6
Group III (AP)			
Fish oil – corn oil	101.4 ± 5.4	95.0 ± 4.1	101.9 ± 3.6
Corn oil – fish oil	97.7 ± 1.5	93.9 ± 7.6	103.2 ± 11.6

MCV in fl; mean ± SD

erythrocyte deformability due to either the lower arachidonic acid content in the membrane itself or a lack of substrate for prostacyclin. Some studies have indicated an increase in erythrocyte deformability during the administration of prostacyclin analogues [4, 7]. This, however, is controversial, because other studies described a similar or lower erythrocyte deformability after prostacyclin administration [1, 9]. The potential adverse effects of a lower erythrocyte deformability in CyA-treated patients need further investigation. A beneficial effect of fish oil on the adverse effects of CyA on renal function and blood pressure has been reported [6]. However, in this study this beneficial effect could only be shown for fish oil and not for corn oil.

Acknowledgments. We are grateful to Loes Clement, Ingrid Cuales, and Peter Goedhart for their excellent technical and practical assistance and to Anneke Cloos and Yvonne Robberse for typing this manuscript. This study was supported by grant no. 89-835 from the Dutch Kidney Foundation.

References

1. Belch JJF, Lowe GDO, Drummond MM, et al (1981) Prostacyclin reduces red cell deformability. Thromb Haemost 45 (2): 189
2. Bessis M, Mohandas N, Feo C (1980) Automated ektacytometry: a new method of measuring red cell deformability and red cell indices. Blood cells 6: 315–327
3. Cartwright IJ, Pockley AG, Galloway JH, et al (1985) The effects of dietary ω-3 polyunsaturated fatty acids on erythrocyte membrane phospholipids, erythrocyte deformability and blood viscosity in healthy volunteers. Atherosclerosis 55: 267–281
4. Dowd PM, Kovacs IB, Bland CJH, Kirby JTD (1981) Effects of prostaglandins I_2 and E_1 on red cell deformability in patients with Raynaud's phenomenon and systemic sclerosis. BMJ 283: 350
5. Hardeman MR, Bauersachs RM, Meiselman HJ (1988) RBC laser diffractometry and RBC aggregometry with a rotational viscometer: comparison with rheoscope and myrrene aggregometer. Clin Hemorrheol 8: 581–593
6. Homan van der Heide JJ, Bilo HJG, Tegzess AM, Donker AJM (1990) The effects of dietary supplementation with fish oil on renal function in cyclosporin-treated transplant recipients. Transplantation 49: 523–527
7. Maurin N (1986) Influence on platelet activity and red cell fluidity of epoprostenol and two stable prostacyclin analogues in vitro. Drug Res 36 II: 1180–1183
8. Phair PG, Powell HR, McCredie DA, et al (1989) Low red cell arachidonic acid in cyclosporine treated patients. Clin Nephrol 32: 57–61
9. Slott JH, Hall K, Clark DA, Stuart MJ (1982) Prostaglandin I_2 fails to influence red cell deformability. Prostaglandins Leukotrienes Med 8: 21–22
10. Terano T, Hirai A, Hamazaki T, et al (1983) Effect of oral administration of highly purified eicosapentaenoic acid on platelet function, blood viscosity and red cell deformability in healthy human subjects. Atherosclerosis 46: 321–331
11. Urukaze M, Hamazaki T, Kashiwabara H, et al (1989) Favourable effects of fish oil concentrate on risk factors for thrombosis in renal allograft recipients. Nephron 53: 102–109
12. Van Acker BAC, Bilo HJG, Popp-Snijders C, et al (1987) The effect of fish oil on lipid profile and viscosity of erythrocyte suspensions in CAPD patients. Nephrol Dial Transplant 2: 557–561