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ERYTHROCYTE MEMBRANE STIFFNESS (OR) RED CELL DEFORMABILITY, BLOOD AND PLASMA VISCOSITY IN PROTEINURIC PATIENTS

ERİTROSİT MEMBRAN SERTLİĞİ (VEYA) ERİTROSİT DEFORMABİLİTESİ; PROTEİNÜRİK HASTALARDA KAN VE PLAZMA VİSKOZİTELERİ

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ÖZET

Son *yıllarda nefrotik sendromlu hastalardaki anemi irdelenmeye başlanmıştır. Erythropoietin eksikliği dışında proteinürik hastalardaki anemi eritrosit deformabilitesi bozulması nedeniyle kısalmış eritrosit yaşam süresi ile açıklanmaya çalışılmıştır. On iki proteinürik hasta yaş ve cins ile uyumlu iki kontrol grubu ile karşüaştırılmıştır (anemik ve sağlıklı). Eritrosit deformabilitesi ve değişik kayma hızlarında kan ve plazma viskoziteleri değerlendirildi. Hafif ve orta dereceli renal yetersizlikte proteinürinin tek başına eritrosit deformabilitesini ve değişik kayma hızlarında kan vizkositelerini azalttığı gösterilmiştir*

Anahtar Kelimeler: Anemi, eritrosit deformabilitesi, kan viskozitesi, üremisiz proteinüri

SUMMARY

In recent years, anemia in nephrotic syndrome has been the subject of investigation. In addition ***to*** *erythropoietin deficiency the anemia of proteinuric patients is tried to be explained by* ***a*** *shortened erythrocyte lifespan due to decreased red deformability. Twelve proteinuric patients were compared with two age and sex-matched control groups (anemic and healthy). Red cell deformability and viscosities at three different shear rates were evaluated. It is demonstrated that* ***in*** *proteinuric patients red cell deformability and blood viscosities at different shear rates were decreased.*

Key Words: Anemia, red cell deformability, blood viscosity, proteinuria without uremia

INTRODUCTION

In contrast to the number of publications available on the biochemical aspects of the red cell in patients with chronic renal failure or on hemodialysis, relatively few reports on their physical characteristics can be found. Physical properties of red blood cells other than filterability and osmotic fragility are even rarer to find (1). Patients without renal failure but proteinuria have not been investigated yet.

Primary nephrotic syndrome can cause severe anemia. Inappropriately low levels of erythropoietin in patients serum (2) and successful erythropoietin treatment for severe anemia in nephrotic syndrome (3) have been published in the ninetieth.

The remarkable deformability of normal erythrocytes has been the subject of studies of biophysicists, physiologists and hematologists in recent years. These investigators have regognized that normal cellular deformability is a most important determinant of red cell lifespan in vivo. The biophysical characteristics of red cells strongly influence hemorheology and red cell survival. It is assumed that premature red cell destruction will occur, whatever the primary cause, because of biophysical changes such as increased osmolar, peroxidative and mechanical fragility as well as decreased deformability (1).

We were interested in the possible changes of red cell deformability in proteinuric patients. Red cell deformability influences blood viscosity and red cell survival. The mild anemia we observed in our proteinuric patients, could be caused, besides erythropoietin deficiency, also by a shortened

erythrocyte life span due to changes of the red cell membrane. In our study we determined the red cell deformability (or the rigidity of the the red cell membrane=the erythrocyte membrane stiffness) and the viscosity of blood at three different shear rates in proteinuric patients with mild anemia and compared this group with a healthy but iron-deficient anemic control-group and a healthy non-anemic control group.

The healthy but anemic control group had to be included into the study, because anemia influences blood viscosity. Changes in blood viscosity and red cell deformability, caused by anemia, had to be excluded.

SUBJECT AND METHODS

PATIENTS AND PROTOCOL

Entry criteria were stable non-diabetic patients with glomerulonephrities of different etiology who had significant proteinuria of more than 1.8 g/day and a creatinine clearance of more than 30 ml/min (creatinine was measured with the method of Jaffe and the laboratory kit 'Fluitest '-Biocon '). The proteinuric patients (Group 2) had no hypertension evaluated by at least 5 measurements per patient. Age and sex distribution of the patients were compareable with the two other control groups. .(Mean age: patients-33±18.5; anemic control- mean age 33±14; healthy control mean age 33±10). Patient characteristics are shown in **table 1.** Six female and six male patients were enrolled into the study (hospitalized between 1998 and 1999). Seven of them had membranoproliferative glomerulonephritis, one had diffuse proliferative glomerulonephritis, three had membranous glomerulonephritis and one had amyloid nephrosis. Six patients were on no medication at study point, from the other six two received amlodipin 5 mg, the other two received dypiridamole 75 mg/twice a day and two were treated with furosemid 40 mg per day. None of the patients had to be treated for secondary hyperparathyroidstn. All patients were informed and gave their written consents for the study.

The anemia of the proteinuric group (Group 2) was a mean hematocrit of 32±5.7%. The anemic group (mean hematocrit of 35±2) (Group 1) were age (mean 33±14) and sex matched (5F;5M) 10 patients with iron deficiency anemia. This group had to be taken for comparison, because the proteinuric patients had a mild to moderate anemia with mean hematocrit of 33±5,7 %. The third group (Group 3) were age (mean 33±10) and sex matched (5F:5M) 10 healthy volunteers working at the Biophysics department with a mean hematocrit value of 40±3 %. Erythropoietin levels of the proteinuric patients were determined in the biochemistry department*. Biochemical and hematological parameters of the healthy volunteers showed no pathology and the anemic group patients were healthy but their iron deficiency. *(Routine lab. kits of Sigma Tech. Co. USA-predicted EPO, F:l l-30,M: 9-26 μ^ml)

Table 1: Patient characteristics (proteinuric-group 2)

No	Sex (F/M)	**Age** (years)	**Diagnosis**	**Creat CI (ml/min)**	**Proteinuria** (g/day)	**Hct** %	**EPO** (μ^ml)
1	M	17	MPGN	119	2.00	35	6.6
2	F	27	MPGN	21	1.80	32	7
3	M	52	MGN	**93**	4.90	38	6.2
4	M	65	MGN	**44**	11.25	30	8.8
5	F	• 17	MPGN	**99**	1.65	38	8
6	M	17	DPGN	**39**	5.85	20	7
7	F	17	MPGN	50	12.00	33	5.2
8	F	45	MPGN	**74**	2.25	40	5.4
9	M	36	AMYLO	21	12.00	33	7
10	M	26	MPGN	144	**15.00**	30	8
11	F	18	MPGN	**93** .	3.00	32	10
12	F	63	MGN	**49**	6.40	24	5.6
MEAN		33		70.5	6.5	32	7.1
STDEV		±18.5		±40	±4.8	±5.7	±1.4

Abbreviations are: F, female; M, male; Creat C, creatinine clearance^PO-Erythropoietin (normals for f:= 1] -30, for m=9-26pl/ml) MPGN. membranoprolifertive glomerulonephritis; MGP, membranous glomerulopathy; DPGN, diffuse proliferative **glomerulonephritis;** AMYLO. amyloidosis.

Two specimens of five milliliter (one heparinized) blood were taken, and send to the Biophysics Department for evaluation of blood viscosity at three different shear rates, plasma viscosity and red cell deformability (erythrocyte membrane stiffness).

Haemorheological Methods

Whole blood viscosity (Bvis)

Whole blood viscosity was measured with a differential speed rotational viscometer, a Wells-Brookfield Viscometer, Model **CV-DVIII,** Brookfield Laboratories, Staughten, Massachusettes, incoroparating a cone-plate type spindle arrangement and which circulated at constant temperature (37 C) (4). The first reading for each specimen was taken at 7.5 /sec, after one minute of rotation and subsequent readings were made at one-minute intervals with decreasing shear rates. The shear rates used, varied from 600 to 225per second. The shear rate was calculated directly from the cone angle (0.80 deg); the conversion factor related shear stress to scale reading and it was determined using viscosity standard calibrating oils.The shear rates used in our study are three different shear rates which simulate the flow in arteries, arterioles and capillaries. A shear rate of 22.5/second which means three spindle returns per minute is comparable with the flow of blood in arteries.The second shear rate with which we measured viscosity was a shear rate of 112.5/second with a return of the spindle of 15 per minute and was adequate to a flow of blood in a caliber like arterioles. The third viscosity measurement was performed with a high shear rate of 225/second, with a spindle return of 30 per minute, which was comparable to a flow of blood in a capillary with small caliber.

Plasma viscosity

The heparinized blood specimen was taken and centrifuged at 2 000 rounds per minute for ten minutes. Viscosity was measured with a Harkness-Viscometer (Coulter-Electronics CTD,serial No:6083) and was evaluated in relation to distilled water at 37 C (Bauer, JD). With a non-Newtonian liquid, each individual capillary-type viscometer was expected to produce a 'relative viscosity', dependent upon the 'rate of shear' in the viscometer. The rate of shear in turn depended upon the head of pressure used and upon the length and bore of the capillary.

Erythrocyte membrane stiffness (Erythrocyte deformability)

The measurement of erythrocyte flexibility/deformability was determined with a method consisting of a centrifuge, a stroboscope that is electrically triggered as the centrifuge rotates. This method requires a minimum quantity of whole blood and results can be obtained within several minutes. The method has been reported by Sirs, Amin and Lowe(16,17,18). A measure of erythrocyte deformability in patients with low hematocrits can be obtained by first gently centrifuging and removing some plasma to bring the hematocrit above 35 %. Hematocrit values were fixed to 40%. Samples were taken into the microhematocrit tubes and placed on the hematocrit centrifuge plate, containing millimetric scale. Erythrocyte column length which was seperated from plasma was read at 3 000 rounds per minute using a stroboscope and recorded at 10th, 15th, 30th, 45th, 60th, 90th, 120th and 240th. . An index of erythrocyte deformability is obtained by measuring the initial slope, in % per minute, from the curve of percentage hematocrit against time. The measurement blood samples are obtained by vene-puncture, using heparin to prevent coagulation, and measurements were made within four hours of collection. This anticoagulant was shown to have no discernable effect on the packing rate at the concentration of 12.5 units of heparin per ml of blood. Initial slope of the trend was obtained from hematocrit changes time-dependently and gave us erythrocyte membrane stiffness as %hematocrit per minute. The initial slope of these curves, in terms of packing rate (in % min) provides an index of erythrocyte deformability. A calibration curve is obtained of the packing rate at various hematocrits. Using the calibration curve a direct comparison of the erythrocyte deformability between individuals and in disease can be obtained by adjusting the measured packing rate to an hematocrit of 40%. The results obtained with the stroboscopic'recording centrifuge are consistent with those obtained with much more expenditure of effort and time by the single sample method (Sirs 1970 (19). This method is used since 1982 routinely to study the deformability of erythrocytes in normal and clinical subjects. It provides a method for the rapid survey of the changes of blood rheology in disease.

Statistical evaluation

Statistical evaluation was done with help of an SPSS 8.0 for Windows 1998 program. For differences between groups a Oneway-ANOVA-Post Hoc-Tukey B test and LSD were used and means were calculated with help of the descriptive statistics program of SPSS 8.0 for Windows (1998).

Results

Age and sex distribution of the three compared

groups were of no statistical difference (see material/method)

Systolic/diastolic blood pressure (RR) was **123±17/** 80±13 mmHg in the **proteinuric group 2. The anemic groupl** (103±10/ 63±9 mm Hg) and the **healthy group 3** (105±10/67±12 mm Hg) had also normal blood pressures. Total serum protein in the proteinuric group was low as 4.7±1.0 g/dl (but normal with 7.2±0.5 g/dl in groupl and 7.4±0.6 g/dl in group 3). Serum albumin in the proteinuric patients was 2.2±0.7 g/dl and 4.0±0.9g/dl in the anemic and 4.2±0.4 g/dl in the healthy control group. Mean proteinuria was 6.5±4,8 g/dl in the patients (2) and both control groups(l,3) had no proteinuria. Creatinine-Clearance was 70,5±40 ml/minute in the proteinuric patient group. The anemic (GFR 112±12 ml/minute) and healthy control groups (GFR120±15 ml/minute) had normal renal function. Serum erythropoietin in the proteinuric group was 7,1±1^1/m1 and low for the degree of the anemia as well as absolutely (normal for female in the used kit was: 11-30 µ^ml and for male: 9-26 µ^ml).

Blood viscosities at different shear rates, plasma viscosities in the three groups and erythrocyte membrane stiffness and hematocrits are shown in **table 2.**

Pvis

Although plasma protein and albumin levels were low in the proteinuric patients, no differences in plasma viscosities (Pvis) between groups were determined (p>0.05).(see **table 3)**

Erythrocyte membrane stiffness

Erythrocyte membrane stiffness, as a determinant of the **decrease of red cell deformability,** was increased significantly (p<0,0001) in the proteinuric patients (group 2). Red cell deformability was not only different from the non-anemic healthy control group, but also different from the anemic group. In proteinuric patients, red cells are less deformable. That means, the red cells of proteinuric patients are more prone to injury and may have a shorter lifespan.

Blood Viscosities at different shear rates

The different shear rates should be understood as flow through different calibers of vessels. The low shear rate of 22.5/s would be a vessel with a size of an artery, the shear stress of 112.5/s that caliber of an arteriole and 225/s shear stress could be similar to the flow through a capillary.

At low shear rates (Bvis 1) the viscosity of the proteinuric group was not different from that of the anemic control group (p=0.688), but significantly different from the viscosity of the totally healthy group (p<0.0001). This difference can be attributed to the observed anemia (see **table2,3).**

At th shear rate of 112.5/s the anemic control group showed no difference in viscosity, but in comparison to the healthy control group viscosity in proteinuric patients was high significanltly decreased (see **table2,3).**

Table 2: Results

GROUP		EMS	HCT	Bvisl	Bvis2	Bvis3	Pvis
1	**Anemic**						
Mean		9,4880	35,0000	4,9530	4,1730	3,8440	1,2010
N		10	10	10	10	10	10
Std.Deviation		1,4502	2,0548	0,7331	0,4676	0,4429	6,903E-02
2	**Proteinuric**						
Mean		**17,4333**	**32,0833**	**4,6758**	**3,4792**	**3,2558**	**1,2917**
N		**12**	**12**	**12**	**12**	**12**	**12**
Std.Deviation		**4,0191**	**5,7439**	**1,4220**	**0,7627**	**0,6471**	**0,1470**
3	**Healthy**						
Mean		5,8360	40,5500	8,7210	5,9900	3,9310	1,2950
N		10	10	10	10	10	10
Std.Deviation		0,9093	3,3204	2,2749	1,4565	0,5669	0,1089

Group l=Anemic healthy, Group2=proteinuric pateint group, Group 3=Healthy volunteers. EMSiErythrocyte membrane stiffness, Hct: hematocrit, Bvis:Blood viscosity at,Bvis 1: 22.5/sec, Bvis2: 1 12.5/sec and Bvis3: 225/ second shear rates.PvisiPlasma viscosity

Table 3: Multiple Comparisons (LSD)

						95 % Confidence Int	
Dependent Variable	**(I) GRUP**	**(J) GRUP**	**Mean Difference α-j)**	Std. Error	**Sig.**	**Lower Bound**	**Upper Bound**
EMS	1	**2**	-7,9453	1,136	**,000**	-10,2683	-5,6224
		3	3,6520	1,186	**,005**	1,2258	6,0782
proteiuric	**2**	**1**	7,9453	1,136	**,000**	5,6224	10,2683
		3	11,5973	1,136	**,000**	9,2744	13,9203
	3	**1**	-3,6520	1,186	**,005**	-6,0782	-1,2258
		2	-11,5973	1,136	**,000**	-13,9203	-9,2744
HCT	1	**2**	2,9167	1,778	**,112**	-,7201	6,5534
		3	-5,5500	1,857	**,006**	-9,3484	-1,7516
proteiuric	**2**	**1**	-2,9167	1,778	**,112**	-6,5534	,7201
		3	-8,4667	1,778	**,000**	-12,1034	-4,8299
	3	**1**	5,5500	1,857	**,006**	1,7516	9,3484
		2	8,4667	1,778	**,000**	4,8299	12,1034
Bvisl	1	**2**	,2772	,682	**,688**	-1,1185	1,6728
		3	-3,7680	,713	**,000**	-5,2257	-2,3103
proteiuric	**2**	1	-,2772	,682	**,688**	-1,6728	1,1185
		3	-4,0452	,682	**,000**	-5,4408	-2,6495
	3	**1**	3,7680	,713	**,000**	2,3103	5,2257
		2	4,0452	,682	**,000**	2,6495	5,4408
Bvis2	**1**	**2**	,6938	,417	**,107**	-,1583	1,5460
		3	-1,8170	,435	**,000**	-2,7070	-,9270
proteiuric	**2**	**1**	-,6938	,417	**,107**	-1,5460	,1583
		3	-2,5108	,417	**,000**	-3,3630	-1,6587
	3	**1**	1,8170	,435	**,000**	,9270	2,7070
		2	2,5108	,417	**,000**	1,6587	3,3630
Bvis3	**1**	**2**	,5882	,242	**,022**	9.321E-02	1,0831
		3	-8,7OOOE-O2	,253	**,733**	-,6040	,4300
proteiuric	**2**	**1**	-,5882	,242	**,022**	-1,0831	-9,3209E-02
		3	-,6752	,242	**,009**	-1,1701	-,1802
	3	**1**	8.700E-02	,253	**,733**	-,4300	,6040
		2	,6752	,242	**,009**	,1802	1,1701
PVIS	**1**	**2**	-9,0667E-02	,049	**,077**	-,1919	1,054E-02
		3	-9,4000E-02	,052	**,079**	-.1997	1,170E-02
proteiuric	**2**	**1**	9,067E-02	,049	**,077**	-1,0536E-02	,1919
		3	-3,3333E-O3	,049	**,947**	-,1045	9/787E-02
	3	**1**	9,400E-02	,052	**,079**	-1,1703E-02	,1997
		2	, 3.333E-03	,049	**,947**	-9J869E-02	,1045

* The mean difference is significant at the .05 level

the highest shear rate (225/s) the viscosity of the proteinuric patients was significantly different from both control groups ($p<0.02$ and $p<0.009$).(See tables 2 and 3, Bvis3).

In summary, we demonstrated that in proteinuric patients

1. the deformability of erythrocytes is decreased and
2. viscosity at all shear rates (the flow in capillaries) is decreased

DISCUSSION

Blood viscosity is influenced by hematocrit, plasma viscosity and red cell deformability. Because the hematocrit is a very important determinant on blood viscosity, the anemic control group was included in our study. An important factor in blood viscosity is the shape and elasticity of the red blood cell. Erythrocytes must change shape in order to be capable of passing the microcirculation and deliver oxygen to the tissues. Any decrease in deformability will result in impaired perfusion of the peripheral tissues (7,8,9,18,22).

Weed et al (10) postulated erythrocyte deformability to be a major determinant of red cell survival. This was later verified in other studies (7).

In our study we demonstrated that red cells in proteinuric patients are less deformable and may have a shorter lifespan. Microcirculation can be disturbed due to changed flow in the capillaries. We demonstrated decreased blood viscosity at all shear rates in the proteinuric patient group, at high shear rate significantly more than only could be expected from the anemia alone. At vessel calibers like arteries and arterioles anemia as well as proteinuria seemed to lessen viscosity nearly at the same level, but at very high shear rates viscosity is a direct measure for erythrocyte deformability (16).

The uremic and dialysis population are known to have decreased red cell deformability and shortened red cell survival (15). Emerson and Burrows established hemolysis as a sometimes important contributing cause of anemia in uremic patients (II). They and others assumed that uremia may cause secondary erythrocyte abnormalities such as increased mechanical fragility (13,14,15), and shortened erythrocyte survival (12,13). Although the 'hemolytic factor' could never be identified, impaired red cell membrane deformability was suggested as one of the reasons for shortened red cell survival in the uremic patient group.

The relationship between anemia of the nephrotic syndrome and erythropoietin deficiency has been reported recently and the loss of erythropoietin in urine has been suggested as a possible explanation (20,21). In our proteinuric patient group we measured low erythropoietin levels, but in addition to this, we suggest the lack of red cell deformability to contribute to the anemia in these patients.

We demonstrated the decreased red cell deformability for the first time in a proteinuric patient group with minor renal insufficiency. The decrease in viscosity was determined by the decreased red cell deformability. Anemia in this proteinuric patient group seemed not only be due to before reported erythropoietin deficiency, due to urinary losses, but also due to reduction of the red cell lifespan, determined by decreased red cell deformability.

Inspired by Machiedo et al (23), who found a negative correlation of free oxygen radicals (malonyldialdehyde) and erythrocyte deformability in sepsis, we planned a second study. Why the red cell membrane was less deformable in proteinuria and what happened to oxygen free radicals and antioxidant system in plasma and erythrocytes was the subject of interest for a second experimental study, which we performed as follow-up study.

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