

Blood Rheological Properties in Patients with Atopic Dermatitis (AD)

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Abstract—Inflammatory processes and psychological states may mutually enhance each other as well as contribute to haemorheological alterations. The objective of the recent study was to determine blood rheological profile in patients with AD at different clinical stages. Blood rheology, as estimated by blood viscosity as well as deformability (elongation index—EI) and aggregation of erythrocytes (aggregation half time (AT1/2)—expressing the kinetic aspects and syllectogram amplitude (AMP)—representing total aggregation extent) were measured in 25 female AD patients, who showed clinical features of mild to severe AD and in 14 healthy subjects. There were no significant differences in blood rheological properties between patients with mild AD and the controls. A significant decrease in erythrocytes AT1/2 and AMP as well as EI were observed in severe AD patients as compared to other groups. Whole blood and plasma viscosity were similar in all groups. Both erythrocytes deformability and aggregation may be affected by pathophysiological processes associated with AD. Only AD patients with severe skin changes showed increased aggregability and decreased deformability of erythrocytes, suggesting that the phenomenon might be related to the disease activity.

KEY WORDS: atopic dermatitis (AD); blood rheology.

INTRODUCTION

Atopic eczema/dermatitis syndrome (AD) is a chronic inflammatory skin disease which develops as a result of complex interrelationships of environmental, immunologic, and genetic factors [1]. Also psychosocial

factors, including stress and anxiety, play an important role in the course of chronic inflammatory skin diseases, including AD [2–4]. A link between psychological stress and aggravation or maintenance of the disease symptoms has been suggested [2]. Interestingly, blood rheology has been reported to be altered in various physiopathological conditions, including chronic inflammatory processes [5, 6] as well as psychological states, such as anxiety, depression, and stress [7, 8]. However, scarce information has been delivered regarding blood flow in patients with AD [9, 10].

Investigation of blood rheological properties may appear essential for comprehensive understanding of the circulatory system function, including the microcirculation flow and tissue oxygenation in AD patients. In order to characterize the rheological profile of AD patients with various degrees of clinical disease activity, the present study comprised determination of whole blood,

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plasma viscosity, red blood cells (RBCs) aggregability and deformability.

MATERIALS AND METHODS

Subjects

Twenty-five female AD patients (the median age was 21; range: 18–25 years) were enrolled for the study. The diagnosis had been established upon Hanifin and Rajka criteria [11]. The patients were divided into two groups according to their disease severity as determined by Rajka and Lageland's score [12]. The scoring system comprises an assessment of extent, course, and intensity, each on a scale of 0 to 3, giving a maximum score of 9 (score summation: 3–4=mild, 4.5–7.5=moderate, 8–9=severe). Our patients were subdivided into two groups: mild (score 3–4, $n=13$) and severe AD (score 9, $n=12$). They did not suffer from any concomitant inhalatory allergy.

Only small amounts of topically applied emollients and/or steroids were used to control the symptoms.

The control group included 14 healthy women (the median age was 22 years, range 19–24).

Individuals were not accepted into the study if they suffered from concomitant disorders, which would affect blood rheology; those included obesity, hypertension and diabetes. None of the patients or normal volunteers were smokers. BMI (below 25 kg/m²), total cholesterol, triglycerides and other lipids levels were similar in all groups.

All the subjects submitted respective written consent and the study was approved by the University Committee of Ethics.

Blood Collection

Blood samples were obtained in the morning (7.00 A.M. to 8.00 A.M.; in the fasting state) after at slight or no stasis from the antecubital vein and anticoagulated with K3EDTA for rheological tests. The samples were taken during the early to mid-follicular phase of the menstrual cycle.

Methods

Whole blood viscosity (BV) measurements were performed with the use of cone-plate Brookfield's viscometer at shear rate 150 s⁻¹ and also corrected to a standard hematocrit 0.45 l/l according to the Guidelines for measurement of blood viscosity [13].

Plasma viscosity (PV) was measured using capillary Ubbelohde's viscometer. The measurements were taken at 37°C.

Changes in red blood cells (RBC) deformability, expressed by elongation index (EL%) were measured by Laser-assisted Optical Rotational Cell Analyzer (LORCA) [14] at different shear stresses (18.49, 33.20, and 60.03 Pa); due to correlation coefficient between these values, only results obtained at 60.03 Pa are demonstrated.

Red blood cell aggregation was also determined by LORCA. The following parameters were estimated: syllectogram amplitude (AMP) and aggregation half-time ($t_{1/2}$).

In vitro IgE Tests

Serum total IgE was determined with ELISA kit (Allergopharma, Germany) according to the manufacturers' instructions.

Statistical Analysis

Data were delivered as medians and ranges. Kruskal–Wallis variance analysis was used for screening differences between the groups. Mann–Whitney *U* test was used to compare data between the patient groups and the healthy controls. Correlation coefficient was obtained by Spearman test. *P* values lower than 0.05 were considered statistically significant.

RESULTS

There were no significant differences in blood rheological properties (hematocrit, whole blood viscosity, plasma viscosity, aggregation half time, syllectogram amplitude, elongation index) between patients with mild AD and the controls (Table 1).

Statistically significant decrease in aggregation half time and syllectogram amplitude, (indexes of RBCs aggregability) as well as significant decrease in elongation index (a marker of RBCs deformability) were observed in severe AD patients as compared to other groups (Table 1). Plasma, whole blood viscosity and hematocrit were not statistically significantly different in patients with severe AD as compared with other groups.

The median value of serum total IgE was 556 kU/l (total range: 326–875) in severe AD group. No significant correlation occurred between total IgE value and RBCs aggregability indices or RBCs deformability marker in

Table 1. Rheological and Biochemical Parameters in Patients with Atopic Dermatitis (AD) and the Healthy Subjects

Analysed parameters (unit)	Controls (<i>n</i> =14) median range	AD mild (<i>n</i> =13) median range	AD severe (<i>n</i> =12) median range	Statistical significance
Hematocrit (%)	40.5 36–44	42 35–46	40 37–44.5	NS
Plasma viscosity (mPas)	1.5 1.29–1.65	1.54 1.38–1.61	1.59 1.45–1.7	NS
Blood viscosity (mPas)	3.8 3.32–4.31	4.20 3.44–5.16	4.15 3.1–5.47	NS
Corrected blood viscosity to hematocrit 45% (mPas)	4.3 3.48–4.87	4.49 3.9–5.4	4.55 3.2–5.15	NS
Aggregation half time (s)	2.06* 1.28–5.1	2.30** 1.58–3.92	1.64 1.22–2.06	<i>P</i> =0.038* <i>P</i> =0.042**
Sylectogram amplitude (au)	9.77* 0.1–14.2	10.0** 4.2–12.4	4.84 2.47–9.6	<i>P</i> =0.014* <i>P</i> =0.023**
Elongation index (EI%)	0.52* 0.41–0.61	0.5** 0.42–0.57	0.44 0.33–0.49	<i>P</i> =0.0062* <i>P</i> =0.0085**

*Significant differences between controls vs. severe AD patients; **significant differences between mild vs. severe AD patients

the severe AD group. There was no relationship between the parameters and disease severity as determined by Rajka and Lageland's score.

DISCUSSION

Decreased values of both, the sylectogram amplitude representing total aggregation extent and the aggregation half time expressing the kinetic aspects in severe AD as compared to the other groups (mild AD and healthy subjects), observed in the recent study, suggested increased RBCs aggregability. Also, we have shown that RBCs deformability, expressed by elongation index, is decreased in patients with severe AD, as compared to patients with less severe clinical disease activity as well as the healthy controls. Only AD patients with severe skin changes showed increased aggregability and decreased deformability of RBCs, suggesting that enhanced inflammatory process might have resulted in alterations of the rheological parameters. Blood rheological alterations might be either the cause or the effect of the pathophysiological processes [6]. RBCs rheological properties (aggregation and deformability), sensitive to changes in local and general homeostasis as well as different factors, including inflammatory proteins, abnormal local tissue metabolism, oxidative state, or activated leukocytes, may affect these properties [6]. We suggest that such factors might be responsible for significant alternations in RBCs properties observed in AD patients with severe inflammatory skin changes. For

example, it has been suggested that increased oxidative stress is involved in the pathophysiology of AD [15], which is known to alter RBCs membrane [16]. Moreover, AD patients show abnormalities related both to metabolism of essential fatty acids and to their incorporation into red cell membranes [17, 18]. Changes in fatty acid profile of RBCs may also have affect membrane structures and enzyme kinetics [19]. Apart from cellular factors, RBCs aggregation depends on plasma factors, including immunoglobulins and acute phase proteins, which can induce those cells aggregation [20–22]. No correlation was found between total serum IgE levels and parameters of RBCs aggregability in AD patients with severe skin changes.

Impaired red blood cell (RBCs) deformability has been found in patients with eczema [23]. The intracellular accumulation of calcium in the cells may play a key role in the events leading to the loss of membrane deformability [23].

It is known that blood viscosity is determined by hematocrit, plasma viscosity, and, to a lesser extent, on red cell deformability and aggregation [6, 24]. Plasma and whole blood viscosity did not differ significantly between the three groups.

Blood rheology is one of the determinants of perfusion whereas its main components are flow, deformability, and aggregability. Increased aggregation and decreased deformability of RBCs result in increased flow resistance and hampers the microvascular bed flow [25–27], which may lead to suppression of oxygen release from erythrocytes [28]. Similarly to other

immune-inflammatory diseases [29–31], AD is associated with increased aggregation and decreased deformation of RBCs, which could impair microcirculatory blood flow and tissue oxygenation.

Abnormalities in blood rheological properties are considered as an independent risk factor for cardiovascular diseases and play a role in atherothrombogenesis. The possible relationship among the blood rheology pattern and increased risk for cardiovascular disorders in patients with severe AD should be investigated.

CONCLUSIONS

Chronic inflammatory processes in AD is associated with changes in blood rheology (an increased aggregability and a decreased deformability of erythrocytes). Considering that only AD patients with severe skin changes showed some alternation in blood rheological properties, we suggest that severity of the skin lesions may influence blood rheology. Interpretation of the results, however, requires care because of the relatively small number of patients.

Whether haemorheological alternations in some patients with AD contribute to higher risk of cardiovascular complications is still an open question.

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REFERENCES

- Leung, D. Y., and N. A. Soter. 2001. Cellular and immunologic mechanisms in atopic dermatitis. *J. Am. Acad. Dermatol.* **44**(Suppl 1):S1–12 doi:10.1067/mjd.2001.109815.
- Picardi, A., and D. Abeni. 2001. Stressful life events and skin diseases: disentangling evidence from myth. *Psychother. Psychosom.* **70**:118–136 doi:10.1159/000056237.
- Seiffert, K., E. Hilbert, H. Schaechinger, C. C. Zouboulis, and H. C. Deter. 2005. Psychophysiological reactivity under mental stress in atopic dermatitis. *Dermatology* **210**:286–293 doi:10.1159/000084752.
- Ginsburg, I. H., J. H. Prystowsky, D. S. Kornfeld, and H. Wolland. 1993. Role of emotional factors in adults with atopic dermatitis. *Int. J. Dermatol.* **32**:656–660 doi:10.1111/j.1365-4362.1993.tb04021.x.
- Stepovaya, E. A., V. V. Novitskii, N. V. Ryazantseva, S. B. Tkachenko, and V. E. Gol'dberg. 2004. Typical changes of erythrocytes in chronic inflammation. *Bull. Exp. Biol. Med.* **137**:56–60 doi:10.1023/B:BEBM.0000024387.17208.c4.
- Baskurt, O. K., and H. J. Meiselman. 2003. Blood rheology and hemodynamics. *Semin. Thromb. Hemost.* **29**:435–450 doi:10.1055/s-2003-44551.
- Dintenfass, L. 1989. Modifications of blood rheology during aging and age-related pathological conditions. *Aging (Milano)* **1**:99–125.
- Ehrly, A. M., H. Landgraf, J. Hessler, and K. Saeger-Lorenz. 1988. Influence of videofilm-induced emotional stress on the flow properties of blood. *Angiology* **39**:341–344 doi:10.1177/000331978803900402.
- Hornstein, O. P., J. Keller, and F. Boissvain. 1992. Abnormalities of cutaneous microcirculation in atopic eczematics. *Acta Derm. Venereol. Suppl. (Stockh.)* **176**:86–89.
- Homstein, O. P., F. Boissvain, and H. Wittmann. 1991. Non-invasive measurement of the vascular dynamics of dermatographism—comparative study in atopic and non-atopic subjects. *J. Dermatol.* **18**:79–85.
- Hanifin, J., and G. Rajka. 1980. Diagnostic features of atopic dermatitis. *Acta Derm. Venereol. Stockh.* **92**(Suppl):44–47.
- Rajka, G., and T. Lageland. 1989. Grading of the severity of atopic dermatitis. *Acta Derm. Venereol. Stockh.* **144**(Suppl):13–14.
- International Committee for Standardization in Haematology. 1986. Guidelines for measurement of blood viscosity and erythrocyte deformability. *Clin. Hemorheol.* **6**:439–453.
- Hardeman, M. R., J. G. Dobbe, and C. Ince. 2001. The laser-assisted optical rotational cell analyzer (LORCA) as red blood cell aggregometer. *Clin. Hemorheol. Microcirc.* **25**:1–11.
- Omata, N., H. Tsukahara, S. Ito, Y. Ohshima, M. Yasutomi, A. Yamada, M. Jiang, M. Hiraoka, M. Nambu, Y. Deguchi, and M. Mayumi. 2001. Increased oxidative stress in childhood atopic dermatitis. *Life Sci.* **69**:223–228 doi:10.1016/S0024-3205(01)01124-9.
- de Jong, K., D. Geldwerth, and F. A. Kuypers. 1997. Oxidative damage does not alter membrane phospholipid asymmetry in human erythrocytes. *Biochemistry* **36**:6768–6776 doi:10.1021/bi962973a.
- Oliwiecki, S., J. L. Burton, K. Elles, and D. F. Horrobin. 1991. Levels of essential and other fatty acids in plasma and red cell phospholipids from normal controls and patients with atopic eczema. *Acta Derm. Venereol.* **71**:224–228.
- Lindskov, R., and G. Holmer. 1992. Polyunsaturated fatty acids in plasma, red blood cells and mononuclear cell phospholipids of patients with atopic dermatitis. *Allergy* **47**:517–521 doi:10.1111/j.1398-9995.1992.tb00675.x.
- Brenner, R. R. 1984. Effect of unsaturated acids on membrane structure and enzyme kinetics. *Prog. Lipid. Res.* **23**:69–96 doi:10.1016/0163-7827(84)90008-0.
- Imaizumi, K., and T. Shiga. 1983. Effect of immunoglobulins and IgG-fragments on the human erythrocyte aggregation, studied by a rheoscope combined with image analyzer. *Biorheology* **20**:569–577.
- Weng, X., G. Cloutier, R. Beaulieu, and G. O. Roederer. 1996. Influence of acute-phase proteins on erythrocyte aggregation. *Am. J. Physiol.* **271**:H2346–2352.
- Ami, R. B., G. Barshtein, D. Zeltser, Y. Goldberg, I. Shapira, A. Roth, G. Keren, H. Miller, V. Prochorov, A. Eldor, S. Berliner, and S. Yedgar. 2001. Parameters of red blood cell aggregation as correlates of the inflammatory state. *Am. J. Physiol. Heart Circ. Physiol.* **280**:H1982–1988.
- El-Saiee, L., and N. Meky. 1986. Deformability of red blood cells in eczema. *J. Med.* **17**:273–283.
- Stuart, J., and G. B. Nash. 1990. Red cell deformability and haematological disorders. *Blood Rev.* **4**:141–147 doi:10.1016/0268-960X(90)90041-P.
- Tateishi, N., Y. Suzuki, M. Soutani, and N. Maeda. 1994. Flow dynamics of erythrocytes in microvessels of isolated rabbit

- mesentery: cell-free layer and flow resistance. *J. Biomech.* **27**:1119–1125 doi:[10.1016/0021-9290\(94\)90052-3](https://doi.org/10.1016/0021-9290(94)90052-3).
26. Soutani, M., Y. Suzuki, N. Tateishi, and N. Maeda. 1995. Quantitative evaluation of flow dynamics of erythrocytes in microvessels: influence of erythrocyte aggregation. *Am. J. Physiol.* **268**:H1959–1965.
27. McHedlishvili, G., M. Varazashvili, and L. Gobejishvili. 2002. Local RBC aggregation disturbing blood fluidity and causing stasis in microvessels. *Clin. Hemorheol. Microcirc.* **26**:99–106.
28. Tateishi, N., Y. Suzuki, M. Shirai, I. Cicha, and N. Maeda. 2002. Reduced oxygen release from erythrocytes by the acceleration-induced flow shift, observed in an oxygen-permeable narrow tube. *J. Biomech.* **35**:1241–1251 doi:[10.1016/S0021-9290\(02\)00068-4](https://doi.org/10.1016/S0021-9290(02)00068-4).
29. Ernst, E., A. Hein, M. Meurer, and T. Ruzicka. 1991. Blood rheology in lupus erythematosus. *Ann. Rheum. Dis.* **50**:710–712 doi:[10.1136/ard.50.10.710](https://doi.org/10.1136/ard.50.10.710).
30. Ricart, J. M., A. Vaya, J. Todoli, J. Calvo, M. T. Contreras, F. Espana, J. Aznar, and D. Corella. 2005. Haemorheological alterations in Behcet's disease are not related to a tendency for venous thrombosis. *Thromb. Res.* **115**:399–404 doi:[10.1016/j.thromres.2004.08.028](https://doi.org/10.1016/j.thromres.2004.08.028).
31. Zilberman, L., O. Rogowski, M. Rozenblat, I. Shapira, J. Serov, P. Halpern, I. Dotan, N. Arber, and S. Berliner. 2005. Inflammation-related erythrocyte aggregation in patients with inflammatory bowel disease. *Dig. Dis. Sci.* **50**:677–683 doi:[10.1007/s10620-005-2556-2](https://doi.org/10.1007/s10620-005-2556-2).