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THE HAEMOSTATIC DISORDERS IN RENAL INSUFFICIENTY CAUSED BY DISORDER IN THE AGGREGATION OF PLATELETS, RAISED ANTI-THROMBIN III AND RAISED FIBRINOGEN DEGRADATION PRODUCTS IN THE BLOOD

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Chronic renal insufficienty and uraemia are very often accompanied by the disorders of haemostasis at different biological levels. There have been a number of studies of this problem in recent years, but there still exist a number of unkonwn factors in this pathological process. Attention has been paid to the anomalies in the initial phase of haemostasis and the phase of the thrombin formation, because in these phases there are a number of bio-pathological inhibitors (2, 4, 6, 11, 13, 14, 16, 22).

In this work we present our results in the study of the aggregation of platelets and the activity of natural and pathological inhibitors of thrombin in patients with renal insufficienty and uraemia.

MATERIAL AND METHODS

In 30 patients (19 females and 11 males) treated at the Internal Clinic, suffering from glomerulonephritis and chronic pyelonephritis, all having raised blood urea, 6 with haemorrhage (epistaxis, haemathemesis), we carried out the following investigations:

1 : platelet count (5),

2a: platelet aggregation with ADP, macroscopic method (5),

b: platelet aggregation with ADP, photometric method

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3 : the dosage of factors V and VII (5),

4 : the thrombin time (5),

5a: anti-thrombin III level, immunoelectrophoretic method, antiserum from Behringwerke (23),

b: anti-thrombin III level, radial immunodiffusion method, antiserum from Behringwerke (17),

c: anti-thrombin III, rocket imunoelectrophoresis method, antiserum from »Nyegaard and Co A/S« (15),

6a: fibrinogen degradation products, ethanol test (8,9),

b: fibrinogen degradation products, quantitative method (18, 19),

7 : thrombodinamography (10).

RESULTS

1 : The platelet count was in the range of 97.000 — 310.000 per mm^3. In 8 patients (26,6%) there was moderate thrombocitopenia, i. e. platelet count in the range, 97.000 — 130.000 per mm^3.

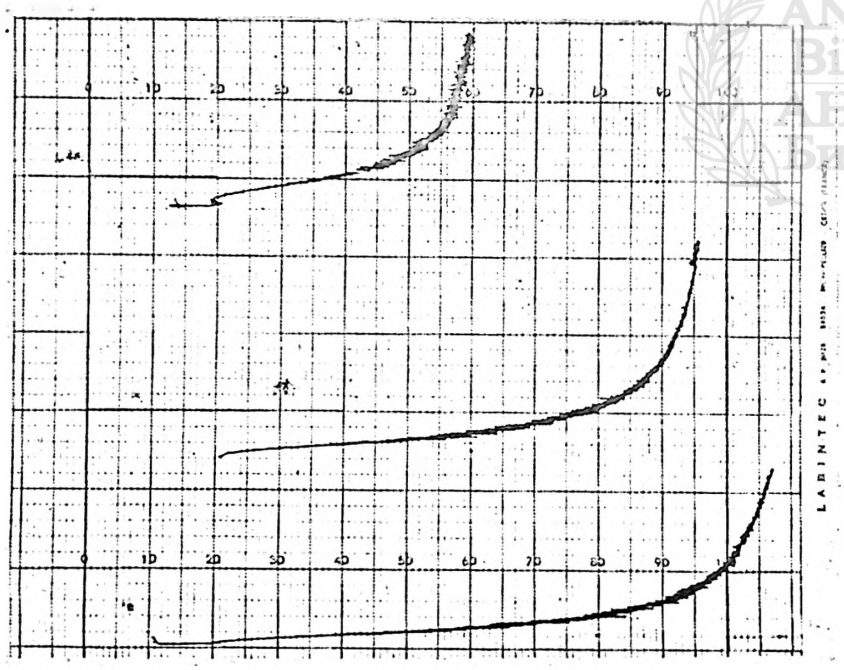
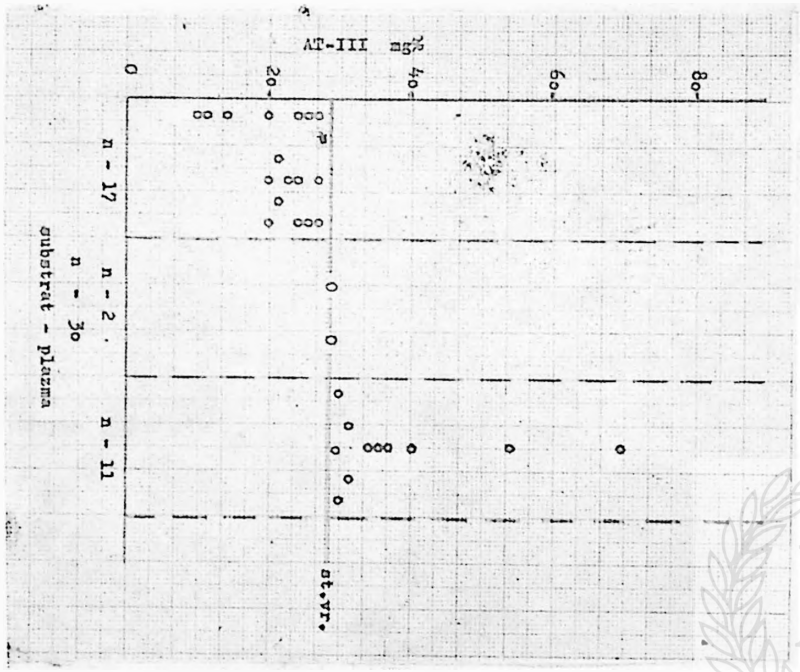


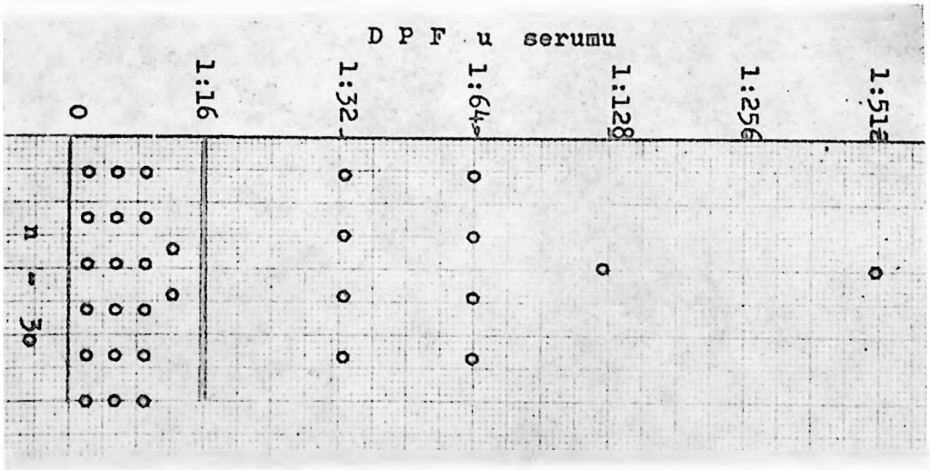
Fig. 1.

The abnormality of platellet aggregation compared to the blood ureavalues. The first curve is from the normal control; second curve is from patient with glomerulonephritis who had blood urea of 50 mg%; the third curve is from patient (A. Lj.) wtih chronic renal failure and blood urea 160 mg%.

2a&b: Platelet aggregation, macroscopic as well as graphic method with the addition of ADP in different concentrations, was diminished in 20 patients, i. e. in 66,6% (Fig. 1). There was an excellent correlation between the decreased aggregation of platelets and the level of blood urea.



Tbl. 1.
The normal values of antithrombin-III in plasma and serum (immunoelectrophoretic method of Scheidegger).



Tbl. 2.
Quantitative determination of fibrinogen degradation products (Merskey method).

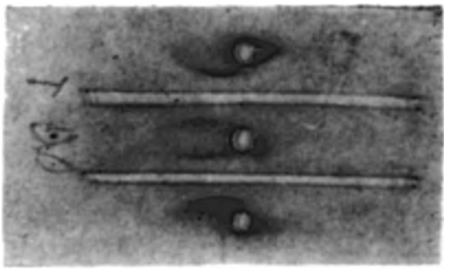


Fig. 2.
The normal values of antithroubin III in plasma and serum (immunoelectrophoretic method of Scheidegger).

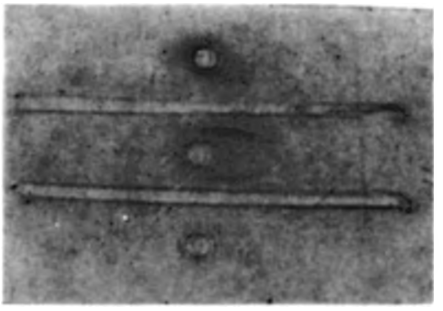


Fig. 3.
The decreased values of antithrombin III in plasma and serum in the patient with liver cirrhosis (immunoelectrophoretic method of Scheidegger).

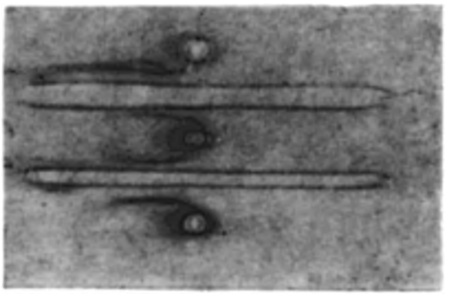


Fig. 4.
The raised values of antithrombin III in plasma and serum in the patient with chronic renal failure (immunoelectrophoretic method of Scheidegger).

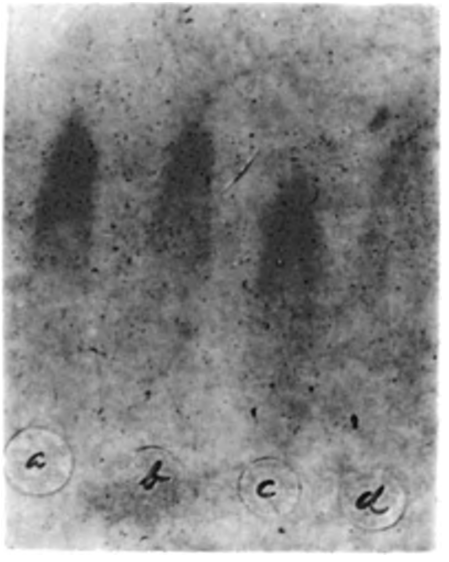


Fig. 5.
The values of antithrombin III in serum (rocket imunoelectrophoresis method of Laurell); (a) and (b) are normal controls; (c) is a patient with liver cirrhosis; (d) patient with chronic renal failure.

3 : The factor V was decreased in 5 patients (10,6%); factor VII was decreased in 6 patients (20%).

4 : Thrombin time was prolonged in 15 patients (50%).

5a; b&c: The values of anti-thrombin III were normal in only 2 patients, decreased in 17 patients (56,6%) and raised in 11 patients (36,6%), Tbl. 1, Fig. 2, Fig. 3, Fig. 4, Fig. 5.

6a&b: Raised values for fibrinogen degradation products using Merskey method were found in 10 patients (33,3%) Tbl. 2), while the ethanol test was positive in 8 patients (20,6%) which demonstrates this method to be less sensitive than the Merskey method.

7 : Thrombodinamography showed no change in the chronological or structural coagulation process in those patients who exibited only abnormal anti-thrombin-III values (Fig. 6).

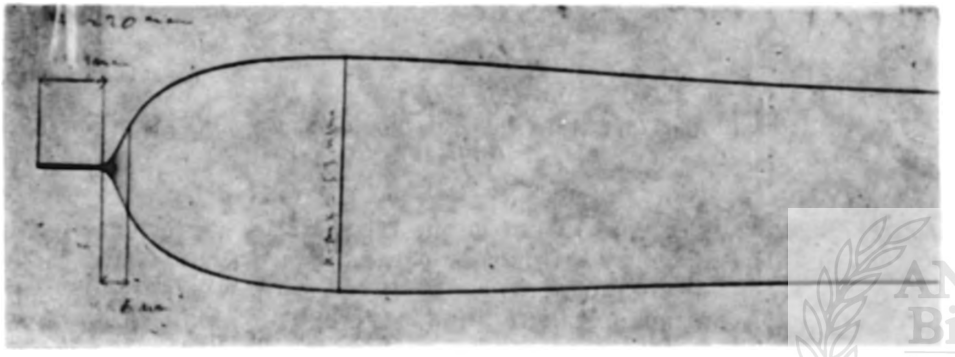


Fig. 6.

Thrombodinamogram curve in patient (B. S.) who had antithrombin-III of 57.3 mg%, FDP 1:512 and factor V and VII in normal range. Clinically the patient had haemorrhage (epistaxis).

DISCUSSION

The initial phase of haemostasis is the most important. In this phase the platelets and the integrity of the walls of blood vessels exibit their role in haemostasis. If either of these two components are abnormal, spontaneous bleeding might occur. We established in almost two thirds of our patients abnormal platelet aggregation, even where there has been no marked decrease in the platelet count. This corresponds with the findings of other authors (21). The impaired platelet aggregation may be the cause of spontaneous bleeding. This same observation has been made by the author of a previous study (4) with the interesting conclusion that the disorder of platelet function with manifest bleeding is a bad prognostic sign in patients with renal insufficienty.

The second important process in haemostasis in the phase of coagulation time, is the formation of thrombin and its activity upon fibrinogen, resulting in clot formation. If this phase of coagulation is impaired, whether due to an anomaly in the formation of thrombin or the increased activity of thrombin inhibitors, a clot will not be for-

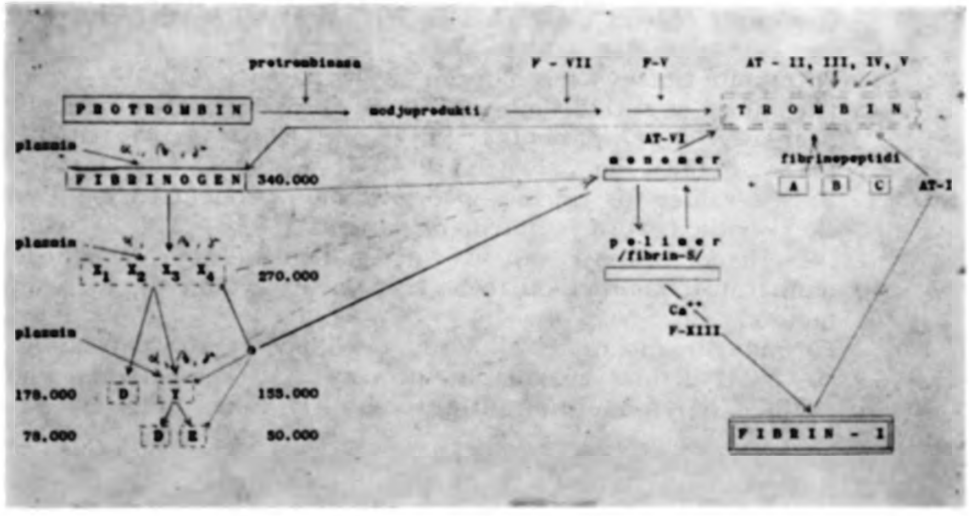


Fig. 7.
The antithrombin-III activity in the course of thrombin and fibrin formation.

med (Fig. 7). The role of anti-thrombin III inhibitors is especially important at this stage, they are normally formed in the liver (1, 2, 3, 7). Lately, there has been much evidence to show that in patients with chronic renal insufficienty there may be great variation in the concentration of these thrombin inhibitors. Von Kaula, using the coagulation method, established that patients with chronic renal insufficienty and uraemia frequently have abnormal values of anti-thrombin III, while Hedner and Nilsson (11,12) using the radial immunodiffusion method found in 19% of cases of renal insufficienty increased concentrations of anti-thrombin III. As it can be seen from the Table 1, we observed the variations in the anti-thrombin III values in our patients, and only two patients had normal anti-thrombin III values. Increased anti-thrombin activity, acquirred as in liver insufficienty or after the use of oral contraceptives, or inherited, very often predicts the appearence of venous thrombosis and lung embolism (3). In one of our patients we observed extremely low values of anti-thrombin III (10 mg%), but at the same time he had no clinical signs of thrombosis. The same patient had fibrin deposits in glomeruli by immunofluorescence, and increased fibrinogen degradation products in his serum and urine. However, fibrinogen degradation products especially fragments »Y« and »E« even when they are the apparent biological sign of intravascular coagulation, have an inhibitory effect on fibrinogen synthesis in the liver, platelet aggregation and thrombin activity. From this we can explain the occurence of clinically manifest bleeding in 6 our patients with increased concentrations of thrombin inhibitors and greatly increased levels of fibrinogen degradation products in their blood.

In the course of our study we observed that there exists a direct correlation between platelet aggregation, the level of anti-thrombin III and raised fibrinogen degradation products in the sera of patients with

renal insufficienty and manifest bleeding. We found no relationship between the values of anti-thrombin III, of factors V and VII, and thrombin time.

We also concluded that the method of thrombodinamography was not sufficiently sensitive for estimating the concentrations of anti-thrombin III and fibrinogen degradation products, even when these factors were present in large quantity as could be seen from Fig. 7.

CONCLUSIONS

The impaired haemostasis in patients with renal insufficienty is caused by a number of factors. These include impaired platelet aggregation, lowerred thrombin activity due to raised levels of anti-thrombin III and fibrinogen degradation products. Due to this impairment of haemostasis at two levels (the initial phase and phase of thrombin formation), therapy and the correction of these anomalies of haemostasis in patients with renal insufficienty is very difficult and represents a very important problem for further study.

ACKNOWLEDGEMENT

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ANOMALIJE HEMOSTAZE U TOKU RENALNE INSUFICIJENCIJE ZBOG POREMEĆENE AGREGACIJE TROMBOCITA, POVIŠENIH VRIJEDNOSTI ANTI-TROMBINA III I PRODUKATA DEGRADACIJE FIBRINOGENA U KRVI

KRATAK SADRŽAJ

Poremećaj hemostaze kod bolesnika sa renalnom insuficijencijom uslovljen je djelovanjem niza činilaca. Prema našim zapažanjima važnu ulogu imaju poremećaji agregacije trombocita, smanjenje aktiviteta trombina uslovljeno povišenjem vrijednosti anti-trombina III i povišene vrijednosti degradacionih produkata fibrinogena. Hemostaza u toku renalne insuficijencije je poremećena na dva značajna nivoa (inicijalna faza hemostaze i faza formacije trombina), te je korekcija poremećaja hemostaze, odnosno njihovo liječenje u toku hronične renalne insuficijencije izvanredno teško i pretstavlja značajan problem za dalja istraživanja.

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