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ABSTRACTS

(All are verbatim summaries)

Almér, Lars-Olof; and Pandolfi, Maurizio (Koagulationslaboratoriet and Dept. of Intern. Med., Allmänna, Malmö, Sweden): FIBRINOLYSIS AND DIABETIC RETINOPATHY. Diabetes *25* (Suppl. 2):807, 1976.

The spontaneous fibrinolytic activity of the blood is abnormally low significantly more often in persons with diabetes mellitus than in nondiabetic controls. The fibrinolytic response stimulated by venous occlusion is poor six times more frequently in diabetics than in controls, and the fibrinolytic activity of the endothelial cells is abnormally low in one-fourth of the diabetics tested. These changes are not related to the duration of diabetes. However, if patients with long-standing diabetes (> 10 years) are separated into those with retinopathy and those without, it is found that those who remain free from ophthalmoscopically visible retinopathy have an almost normal fibrinolytic response on stimulation, while the others have a significantly lower response. This difference seems to be caused by a faulty plasminogen activator release mechanism. Compared with the other diabetics, those with retinopathy also have a significantly increased level of fibrinogen and of α_2-macroglobulin, a protein that acts as an inhibitor of fibrinolysis. These findings imply a poor defense mechanism against fibrin deposits in the vessel walls in diabetes, which might contribute to the development of diabetic microangiopathy.

Almér, L. O.; Pandolfi, M.; and Osterlin, S. (Coagulation Lab., Dept. of Ophthal. and Dept. of Intern. Med., Univ. of Lund, Malmö, Sweden): THE FIBRINOLYTIC SYSTEM IN PATIENTS WITH DIABETES MELLITUS WITH SPECIAL REFERENCE TO DIABETIC RETINOPATHY. Ophthalmologica (Basel) *170*:353, 1975.

The fibrinolytic system has been studied in 168 patients with diabetes mellitus (DM) and compared to that of a group of 153 sex- and age-matched control subjects. The following determinations were made: spontaneous fibrinolytic activity of the blood; fibrinolytic response to standardised venous stasis (stimulated fibrinolytic activity, 'fibrinolytic capacity'); histochemical determination of fibrinolytic activators in the walls of superficial veins collected by biopsy.

Diabetic patients were found as a group to have an impaired fibrinolytic system with the above fibrinolytic parameters decreased to various degrees in comparison with those of the controls. Less clear differences were observed between patients with and without ophthalmoscopically visible diabetic changes of the retina. However, patients with beginning angiopathy were found to have a significantly higher amount of fibrinolytic activators in their vessel walls than patients with more advanced retinopathy and without ophthalmoscopically detectable retinopathy. Furthermore, unlike patients without retinopathy, patients with retinopathy increased less or did not increase at all their spontaneous and stimulated fibrinolytic activity along the duration of the disease.

The defective fibrinolytic system of diabetic patients may contribute to the occurrence of the vascular complications frequently seen in this disease. In the diabetic group, those patients who develop retinopathy show an impaired fibrinolytic defense with the duration of the disease.

Bensoussan, D.; Levy-Toledano, S.; Passa, P.; Caen, J.; and Canivet, J. (Dept. of Endocrin. and of Haemostasis and Exper. Thrombosis, Univ. Paris-VII, Hosp. Saint Louis, Paris, France): PLATELET HYPERAGGREGATION AND INCREASED PLASMA LEVEL OF VON WILLEBRAND FACTOR IN DIABETICS WITH RETINOPATHY. Diabetologia *11*:307, 1975.

In 18 insulin-dependent diabetics (6 without retinopathy, 6 with proliferative retinopathy and 6 with proliferative retinopathy treated by hypophysectomy) matched for age and duration of diabetes, in vitro haemostasis was studied using ADP induced platelet aggregation, ristocetin induced platelet aggregation which allows von Willebrand factor (VIII VWF) assay, and de-

termination of antihemophilic factor procoagulant activity (VIII AHF). Using gel filtration-isolated platelets, the ADP induced hyperaggregation previously reported in diabetics with severe retinopathy untreated by hypophysectomy appeared to be related to a platelet and not a plasma factor; the normal results of thrombin induced aggregation suggests that the presumed abnormal platelet factor is related to the platelet plasma membrane. High level of plasma VIII VWF was observed in diabetics with proliferative retinopathy while the VIII AHF level was within normal limits.

Colwell, John A.; Halushka, Perry V.; Sarji, Kay; Levine, Jon; Sage, Julius; and Nair, M. G. (VA Hosp. and Endocrin.-Metab.-Nutrition and Clinic. Pharmacology Divs., Depts. of Med., Pharm., and Biochem., Med. Univ. of South Carolina, Charleston, SC): ALTERED PLATELET FUNCTION IN DIABETES MELLITUS. Diabetes *25* (Suppl. 2):826, 1976.

An increased sensitivity of platelets to aggregation from ADP and epinephrine is described in diabetics with or without vascular disease. This sensitivity correlates with elevated levels of von Willebrand factor (vWF), which, in turn, appears to be influenced by growth hormone. VWF activity correlates with previously described "plasma factor" activity.

Platelets from diabetic subjects are more sensitive than platelets from normal subjects to arachidonic-acid-induced aggregation. This sensitivity is abolished by aspirin, which is a prostaglandin synthetase (cyclo-oxygenase) inhibitor. Platelets from diabetic subjects synthesize increased amounts of PGE_2-like material (iPGE) in response to ADP, epinephrine, collagen, and arachidonic acid. The latter finding suggests that a fundamental mechanism for increased platelet aggregation in diabetes is increased prostaglandin synthetase activity.

Therapeutic endeavors that would lower growth hormone levels, vWF activity, and/or prostaglandin synthetase activity may be of benefit in the prophylaxis of diabetic vascular disease. Prospective studies are needed to explore these hypotheses, as are more studies on the precise mechanisms of platelet aggregation in diabetes mellitus.

Garg, S. K.; Lackner, H.; and Karpatkin, S. (Dept. of Med., NY Univ. Med. Sch., New York, NY): THE INCREASED PERCENTAGE OF MEGATHROMBOCYTES IN VARIOUS CLINICAL DISORDERS. Ann. Intern. Med. 77:361, 1972.

Large platelets, or megathrombocytes, have been shown to be young platelets recently released from the marrow. The percentage of megathrombocytes was measured in patients with clinical disorders and normal platelet counts where increased platelet turnover might be suspected. Increased megathrombocytes were noted in 68% of 41 patients with systemic lupus erythematosus; 47% of 14 patients with chronic autoimmune thrombocytopenic purpura in apparent remission; 52% of 10 patients with disseminated intravascular coagulation; 14% of 22 surgical patients, 2 hours after surgery; 48% of 19 patients with rheumatic heart disease and severe valvular impairment; 20% of 25 patients with prosthetic heart valves and rheumatic heart disease; and 30% of 15 patients with diabetes mellitus and retinopathy. We observed that [1] clinical "remission" in patients with chronic autoimmune thrombocytopenic purpura may be more apparent than real; [2] the diagnosis of disseminated intravascular coagulation can be suspected if there is a normal platelet count but an increase in the percentage of megathrombocytes; [3] there was less evidence for increased platelet turnover in patients with prosthetic heart valves and rheumatic heart disease than in patients with rheumatic heart disease and severe valvular involvement.

Heath, H.; Brigden, W. E.; Canever, J. V.; Pollock, J.; Hunter, P. R.; Kelsey, J.; and Bloom, A. (Dept. of Biochem. Path., Univ. Col. Hosp. Med. Sch., London, England): PLATELET ADHESIVENESS AND AGGREGATION IN RELATION TO DIABETIC RETINOPATHY. Diabetologia 7:308, 1971.

Platelet adhesiveness, ADP-activated platelet aggregation and the activity of the ADP-splitting enzymes in blood and plasma have been studied in 22 diabetics with severe retinopathy, 22 long-duration diabetics with minimal or no retinopathy and 28 control subjects. The rate of platelet aggregation under the influence of 5, 3, 2 and 1 μM ADP, the maximum aggregation attained and the rate of disaggregation of these aggregates were measured. The platelets from actively deteriorating retinopaths were found to be more sensitive to the effect of low concentrations of ADP; a significant increase in the extent of aggregation and a decrease in the rate of disaggregation of platelet aggregates formed under the experimental conditions, *in vitro* were observed. If this should occur *in vivo*, then capillary occlusion might ensue. This increased sensitivity to ADP and inability to disaggregate, was not due to any differences in the activity of the ADP-splitting enzyme systems in blood. Significant differences in the parameters were not observed when the large diabetic groups were compared with the control subjects. Contrary to some reports, an increase in platelet adhesiveness was not apparent in either diabetic group.

Kwaan, H. C.; Colwell, J. A.; Cruz, S.; Suwanwela, N.; and Dobbie, J. G. (Dept. of Med. and Ophthal., Northwestern Univ. Med. Sch., Chicago, Ill., and the Med. Services of the VA Res. Hosp., Chicago, and Passavant Mem. Hosp., Chicago): INCREASED PLATELET AGGREGATION IN DIABETES MELLITUS. J. Lab. Clin. Med. *80*:236, 1972.

The effect of diabetic plasma on normal platelet aggregation was studied in 87 diabetic subjects and 62 healthy controls. The degree of platelet aggregation induced by 1 μM of ADP per milliliter was measured in mixtures of 1:8 v/v of diabetic plasma and normal platelet-rich plasma. A significant increase ($P < 0.001$) of aggregation over controls (0 $\pm$ 9.5 per cent S.D.) 4 minutes after addition of ADP was observed in diabetics (27.6 $\pm$ 20.5 per cent S.D.). Thirty-seven diabetics with retinopathy and 22 with nephropathy had significantly greater platelet aggregation enhancing activity ($P < 0.001$) than diabetics without these complications. A positive correlation ($r = 0.778$) was noted between the activity and severity of retinopathy as established by retinal photography and fluorescein angiography in 37 diabetics. Activity also was greater ($P < 0.001$) in 6 diabetics with renal failure and nephrotic syndrome (59.8 $\pm$ 11.8 per cent S.D.) than in 6 nondiabetic patients with renal failure and nephrotic syndrome (22.0 $\pm$ 15.5 per cent S.D.). No correlation existed between this aggregation-enhancing activity and age, body weight, height, therapy, insulin dosage, hematocrit, or fasting plasma levels of glucose, triglyceride, cholesterol, free fatty acids (FFA), albumin, and the FFA:albumin molar ratio. The aggregation-enhancing activity was present in both plasma and serum, was nondialyzable, heat resistant, and unaffected by aspirin treatment.

It did not spontaneously aggregate platelets but enhanced the second phase of aggregation induced by ADP, or by epinephrine. We conclude that in some diabetics a plasma factor is present enhancing the second phase of platelet aggregation. Its correlation with retinopathy and nephropathy suggests a role in the genesis of diabetic microangiopathy.

Mayne, E. E.; Bridges, J. M., and Weaver, J. A. (Dept. of Clin. Path. and Sir George E. Clarke Metab. Unit, Royal Victoria Hosp., Belfast, N. Ireland): PLATELET ADHESIVENESS, PLASMA FIBRINOGEN AND FACTOR VIII LEVELS IN DIABETES MELLITUS. Diabetologia *6*:436, 1970.

Platelet adhesiveness and the levels of two coagulation factors, fibrinogen and factor VIII, were studied in a series of diabetic and nondiabetic control subjects. All three measurements were significantly abnormal in the diabetic patients. The increase in platelet adhesiveness was capable of distinguishing the diabetics on a group basis, but not on individual results. The greatest increase in platelet adhesiveness was demonstrated in patients with ischaemic heart disease and diabetes. Increased platelet adhesiveness was seen in individuals of both diabetic and control groups, in whom no clinical or electrocardiographic evidence of ischaemic heart disease was found. This finding is discussed, also the relationship between platelet adhesiveness levels and the age, sex, duration of disease, blood glucose and serum lipid levels of the diabetic patients.

Nordöy, Arne; and Rödset, J. M. (Med. Dept. A and Inst. for Thrombosis Res., Rikshospitalet, Univ. Hosp., Oslo, Norway): PLATELET PHOSPHOLIPIDS AND THEIR FUNCTION IN PATIENTS WITH JUVENILE DIABETES AND MATURITY ONSET DIABETES. Diabetes *19*:698, 1970.

Platelet factor-3 activity and availability, platelet phospholipids and their fatty acid and aldehyde composition were examined in patients with juvenile diabetes of long duration and in patients with maturity onset diabetes.

Increased coagulant activity was found in platelet rich and platelet poor plasma from patients with juvenile diabetes, whereas plasma from patients with maturity onset diabetes reacted as the control group. Platelet rich plasma exposed to ADP, kaolin or freezing and thawing three times reacted not significantly differently from the controls.

Increased amount of lipid-P was present in platelets from both patient groups. In patients with juvenile diabetes the increase was mainly caused by an increase of serine phosphoglycerides and in the other patient group all main phospholipid fractions were increased. The phospholipid/protein ratio of platelets was not significantly different in the three groups. Only moderate changes were observed in the fatty acid pattern of the various phospholipids.

Pandolfi, Maurizio; Almér, Lars-Olof; and Holmberg, Lars (Coagulation Lab., Eye Clinic and Med. Clinic, Malmo Hosp., Univ. of Lund, Sweden): INCREASED VON WILLEBRAND-ANTIHAEMOPHILIC FACTOR A IN DIABETIC RETINOPATHY. Acta Ophthalmol. *52*:823, 1974.

The von Willebrand factor-Factor VIII (vW-AHF) related protein and the AHF (antihaemophilic factor A) activity have been measured in the blood of 63 diabetic patients with and without diabetic retinopathy. Compared to normals, diabetic patients showed a clear increase in both vW-AHF related protein and AHF activity. Patients with retinopathy had a level of vW-AHF related protein significantly higher than patients without retinopathy. Since the von Willebrand factor is involved in the mechanism of platelet adhesion and aggregation these findings may contribute to an explanation of the increased platelet stickiness known to occur in diabetics and especially in those with retinal changes.

Sagel, Julius; Colwell, John A.; Crook, Lynn; and Laimins, Marta (VA Hosp. and the Endocrin., Metabolism, and Nutrition Div., Dept. of Med., Med. Univ. of South Carolina, SC): INCREASED PLATELET AGGREGATION IN EARLY DIABETUS MELLITUS. Ann. Intern. Med. *82*:733, 1975.

In view of the tendency toward vascular disease in diabetes mellitus, we studied platelet aggregation in 15 normal, 7 prediabetic, 12 latent, and 20 frankly diabetic subjects. Platelets from latent and frank diabetics showed increased platelet aggregation 4 minutes after adding adenosine 5′-diphosphate (60% versus 29% at 1.0 μM), epinephrine (46% versus 14% at 0.25 μM), and collagen (72% versus 17% at 0.25 μg/ml). Three prediabetics had increased platelet aggregation. Platelet sensitivity to aggregating agents was most marked in frank diabetics, intermediate in latent diabetics, and least in prediabetics. Second-phase platelet aggregation was reversed with acetylsalicylic acid, intravenous tolbutamide, and oral glucose administration. We conclude that platelet aggregation may be increased early in diabetes mellitus and may be involved in the genesis of diabetic microangiopathy. Prospective studies on the effect of therapeutic agents such as acetylsalicylic acid on the natural course of diabetic vascular disease are indicated.