301

HYPOGLYCEMIC EFFECT OF INDOBUFEN,AN ANTIAGGREGATING AGENT,IN ELDERLY DIABETIC PATIENTS

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Inibition of platelet aggregation is of value in therapy for Transient Ischemic Attacks(TIA).We observed 2 consecutive elderly patients with type 2 diabetes mellitus(DM)and TIA,in whom chronic treatment with Indobufen(I) provoked a reduction of blood glucose levels;for this reason we started a cross-over study to assess the possible hypoglycemic effect of I in elderly patients with DM.Ten patients(5 males,mean age 75±5 years)with DM and TIA have been included in our study. After 1 month of diet treatment(1)all patients took either placebo tablets$2)or I 200mg every 12 hours for 4 weeks in a random cross-over fashion.After each period a daily blood glucose profile has been obteined. Results are the following:

time	8am	12am	2pm	6pm	9pm	12pm
	mg%	mg%	mg%	mg%	mg%	mg%
1	150±36**	172±57*	207±73**	163±63*	183±48*	156±36***
2	152±37°°	170±52°	215±75°°	169±61°	188±50°	161±37°°°
3	111±18	115±25	131±21	102±19	139±26	111±17

1 versus 3 *=p 0,05;**=p 0,02;***=p 0,01
2 versus 3 °=p 0,05;°°=p 0,02;°°°=p 0,01

Indobufen in the dose of 200 mg every 12 hours has an hypoglycemic effect. This side effect can be dangerous in patients already treated with hypoglycemic agents, but can be usefull as a single drug therapy for aged patients with type 2 diabetes mellitus and atherosclerotic vascular disease.

302

RELATIONSHIPS BETWEEN HAEMOSTATIC ENDOTHELIAL FUNCTIONS AND GLOMERULAR FILTRATION RATE IN SHORT-TERM TYPE I DIABETES MELLITUS.

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It is known that the increase of glomerular filtration rate (GFR) represents an early sign of diabetic nephropathy. The changes of endothelial functions observed in diabetes might play a role in this respect. As F VIII vWF and fibronectin are synthetized by endothelial cells, we evaluated these components in 33 diabetic patients with short-term Type I (insulin dependent) diabetes mellitus, without retinopathy and macrovascular complications. 15 pts. (mean age 29 ± 7 yrs; mean diabetes duration 2.9 ± 0.9 yrs) presented high GFR (154 ± 19 ml/min per 1.73 m^2; albuminuria 7.2 ± 3.2 µg/min) and 18 pts. (mean age 30 ± 6 yrs; mean diabetes duration 3.0 ± 1 yrs) normal GFR (105 ± 11 ml/min per 1.73 m^2; albuminuria 5 ± 2.8 µg/min).

The following results were obtained:

	Normal GFR	High GFR	
HbA_{Ic}%	9.5 ± 0.61	8.0 ± 0.81	p<0.01
F VIIIR:Ag%	226 ± 58	133 ± 18.7	p<0.001
Fibronectin (mg/dl)	39 ± 9.9	29 ± 4.8	p<0.01

In conclusion the significant increase of FVIIIR:Ag and fibronectin levels in short-time type I diabetic patients with high GFR suggests an early endothelial cell function damage also related to the poor metabolic control.

303

MOLECULAR MARKERS OF ENDOTHELIAL CELL DYSFUNCTION: OBSERVATIONS ON EXTRINSIC FIBRINOLYSIS IN SURVIVORS OF MYOCARDIAL INFARCTION AND IN TYPE-1 DIABETES MELLITUS.

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We have studied the extrinsic fibrinolytic system in survivors, below 70 years, from myocardial infarction (AMI) treated in Umeå during 1983; in 43 type-1 diabetics; and in controls. Elderly controls underwent chest x-ray, ECG, EEG, brain CT scan to verify their health. Tissue plasminogen activator (tPA) activity was measured with a fibrin-stimulated rate assay, before and after a 10 min venous occlusion test (VO), tPA antigen (Ag) with an ELISA, and plasminogen activator inhibitor (PAI) by incubating samples with purified tPA and measuring remaining tPA with a polylysine-stimulated rate assay.
In the diabetics, PAI and tPA:Ag were similar to the controls. tPA:Ag correlated with age (r=0.6). Diabetics had much higher specific activity of tPA (61,300 vs 21,900), and had also much higher tPA activity after VO (2.2 vs 1.2 U/ml). The tPA activities after VO correlated well with HbA1c (r=0.39). A significant effect of smoking was disclosed. Smoking diabetics had higher PAI and tPA antigen but also lower specific activity of tPA (60,600 vs 115,700 U/mg). Ex-smokers were very similar to smokers, not to the non-smokers. Retinopathy, nephropathy, or hypertension didn't appear to affect fibrinolysis independently.
In the AMI survivors (sampled 3 months after discharge from hospital), PAI was 6-fold higher than in elderly controls (p less than 0.0001). tPA activity after VO was much higher (3.2 vs 1.2 U/ml), as was tPA:Ag. tPA specific activity was lower. Among AMI patients with PAI over 10 U/ml, PAI correlated with triglycerides (r=0.4) and negatively with age (r=-0.4): these relations were not seen in the patients with PAI less than 10. The effects of smoking seen in diabetics were not observed among the AMI patients. von Willebrand factor was not increased among AMI nor diabetic patients, except for those with retinopathy.
The results suggest that the tPA/PAI system is a more sensitive indicator than vWF of endothelial cell dysfunction. It relates to effects of age, atherosclerotic vascular disease, and among diabetics also to degree of metabolic control and to tobacco smoking habits.

304

DISTINCTIVE FEATURES OF PROCOAGULANT RESPONSE OF MONOCYTES FROM DIABETIC PATIENTS.

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Hypercoagulability is one of the possible factors reported in genesis or aggravation of vascular complications in diabetes mellitus. We therefore examined procoagulant activity (PCA) of disrupted monocytes from 26 patients with Type I diabetes and 6 with Type II, versus 32 control subjects (male/female ratio = 1 in each group).

Diabetes monocytes exhibited a slight but detectable PCA before any incubation or in vitro stimulation, whereas control monocytes did not. Data obtained with coagulation factor deficient plasmas or phospholipase C indicated that PCA was tissue factor (TF) alone in 22 cases and TF associated with a significant amount of factor VII/VIIa activity in 10 cases.

Incubation in serum free medium led to significant raise of PCA in diabetes cells when stimulated with endotoxin or not, and in control cells only after stimulation. Furthermore, PCA appeared earlier in diabetes monocytes than in control ones, (4 hours, versus 20 hours). PCA from control cells was FT-like. PCA from diabetes cells was FT-like when no VII/VIIa activity was present on non-stimulated cells, and prothrombinase-like when VII/VIIa activity was early associated with the cells. In the latter case, trace amounts of factor X activity were also detectable. Whether factor VII and factor X activities were of plasmatic origin and associated to the cells, or synthesized in vitro by the cells remains unclear. The characteristics of PCA were not correlated with clinical features (age, diabetic complications) nor with the type of diabetes.

Our data suggest that in diabetes patients, monocytes exhibit an increased PCA, possibly corresponding to a baseline stimulation, or at least a higher responsiveness to undergoing stimuli in vitro.