Overweight diabetics en los sujetos control.

A group of twenty three overweight diabetic patients and control subjects. Seventy three overweight patients of our Diabetes Unit chosen at random (16 males/7 females) with type 2 diabetes mellitus were enrolled.

The clinical characteristics of these patients were: age 61.3 ± 12.3 years, body mass index (BMI) 27.2 ± 3.9 kg/m² and duration of diabetes 8.4 ± 6.7 years. A group of twenty three voluntary controls chosen at random (15 males/15 females) without diabetes were studied. The clinical characteristics of this group were: age 62 ± 13 years and BMI 27.6 ± 3.1 kg/m². All patients (diabetics and controls) underwent the following examinations: plasma/activator inhibitor type 1 (PAI-1), thrombomodulintrombina III complex (TAT), tissue plasminogen activator (t-PA), von Willebrand antigen (vW), protein C (PC), protein S (PS), thrombomodulin (TH), activated VII factor, D dimer (DD), plasmin-antiplasmin (PAP), and plasminogen activator inhibitor fragment F1+2 (F12). Haemostasis parameters were compared in both groups and within the diabetic subjects in the subgroups with and without micro and macroangiopathy. In both groups, correlation analysis was performed between selected clinical and pathological parameters.

Results. Overweight diabetic patients showed an increment in procoagulant parameters (F12 1.38 ± 0.4 vs 1.21 ± 0.25 mU/ml; p < 0.05; t-PA 12.6 ± 5.1 vs 7.4 ± 3.1 ng/ml; p < 0.05) and a decrease in fibrinolytic parameters (F12 0.03 ± 0.02 vs 0.1 ± 0.04 ng/ml; p < 0.05) and anti-anticoagulant parameters (Thrombomodulin 27.4 ± 11.7 vs 45.1 ± 21.7 ng/ml; p < 0.05), with a greater difference in D dimer (DD) of 23.3 ± 26.8 vs 9.7 ± 5.4 ng/ml; p < 0.05) and (F12 1.38 ± 0.4 vs 1.21 ± 0.25 ng/ml; p < 0.05). In diabetic patients, there was no difference according the absence or presence of microangiopathy or macroangiopathy. In a correlation analysis between HbA1c and haemostasis parameters, only protein C and tPA showed significant negative correlations (r = -0.34; p < 0.01 and r = -0.32; p < 0.05, respectively). A correlation analysis between diabetes and haemostasis parameters was also performed between BMI and haemostasis parameters and only FvW was correlated with BMI (r = 0.32; p < 0.05). No correlations were found between haemostasis parameters with BMI and HbA1c in controls.

Conclusion. Hypercoagulable state is present in diabetic patients which with present knowledge, can be viewed as a risk factor for chronic complications.

Key words: Type 2 diabetes mellitus. Haemostasis. overweight.

High risk haemostasis patterns in overweight patients with type 2 diabetes mellitus

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PATRÓN DE HEMOSTASIA DE ALTO RIESGO EN PACIENTES CON SOBREPESO Y DIABETES TIPO 2

Introducción. Algunos estudios han demostrado un estado de hipercoagulabilidad en los pacientes diabéticos.

Objetivo. Compara el patrón de hemostasia entre pacientes diabéticos con obesidad y controles.

Diseño. Un total de 23 pacientes con diabetes mellitus tipo 2 y sobrepeso atendidos en nuestra unidad fueron incluidos en el estudio (16 varones/7 mujeres). Las características clínicas de los pacientes fueron: 61,3 ± 12,3 años, índice de masa corporal (IMC) 27,2 ± 3,9 kg/m² y duración de la diabetes 8,4 ± 6,7 años. Un grupo de 23 voluntarios sanos fue elegido al azar entre donantes de sangre sin diabetes mellitus (15 varones/8 mujeres). Las características clínicas de estos pacientes fueron: 62 ± 13 años e IMC 27,6 ± 3,1 kg/m². A todos los sujetos, casos y controles, se les realizaron las siguientes pruebas: inhibidor del activador del plasminógeno: tipo 1 (PAI-1), complejo trombina/antitrombina III (TAT), activador titular del plasminógeno (t-PA), antígeno Von Willebrand (vW), proteína C (PC), proteína S (PS), trombomodulina (TH), factor VII activado, dimero D (DD), plasmina-antiplasmina (PAP) y fragmento activado protrombina F1 + 2 (F12). Estos parámetros fueron comparados en ambos grupos, y dentro de los diabéticos en los grupos con y sin micro y macroangiopatía. En ambos grupos, se realizó un análisis de correlación entre los parámetros clínicos y los hemostáticos.

Resultados. Los pacientes diabéticos con sobrepeso evidenciaron un incremento en los factores procoagulantes (F12 1.38 ± 0.4 frente a 1.21 ± 0.25 mU/ml; p < 0.05; t-PA 12.6 ± 5.1 frente a 7.4 ± 3.1 ng/ml; p < 0.05), con un incremento en los niveles de dimero D (DD 23.3 ± 26.8 frente a 9.7 ± 5.4 ng/ml; p < 0.05) y t-PA 12.6 ± 5.1 frente a 7.4 ± 3.1 ng/ml; p < 0.05). En los pacientes diabéticos no hubo diferencia en función de la ausencia o presencia de micro o macroangiopatía. La proteína C y tPA mostraron una correlación negativa (r = -0.34; p < 0.01) y r = -0.32; p < 0.05, respectivamente) con la hemoglobina glucosilada (HbA1c). FvW se correlacionó de una manera positiva con el IMC (r = 0.32; p < 0.05). No se encontraron correlaciones entre los parámetros de hemostasia, con el IMC y HbA1c, en los sujetos control.

Conclusion. En los pacientes con diabetes tipo 2, hay un estado de hipercoagulabilidad que puede influir en las complicaciones crónicas de esta población.
De Luis DA, et al. High risk haemostasis patterns in overweight patients with type 2 diabetes mellitus

INTRODUCTION
Diabetes mellitus is an independent risk factor for the development of atherosclerosis. The possible mechanisms are unclear. It is postulated that chronic inflammation may contribute to increase the risk of coronary heart disease in different ways: increasing serum concentrations of acute phase reactants (such as fibrinogen or C reactive protein) or modifying the serum lipid pattern (such as decrease of HDL-cholesterol and increase of triglycerides). Another factor involved in the atherogenesis of diabetic patients is the promotion of the oxidation of LDL-cholesterol since oxidation enhances the atherogenic capacity of these molecules. More recently, some authors have shown that diabetic patients had a hypercoagulable state.

The aim of our study was to compare the haemostasis pattern between overweight patients with diabetes mellitus type 2 and a control group.

MATERIALS AND METHODS
Population
Twenty-three overweight patients of our Diabetes Unit (16 males/7 females) and twenty three controls (blood donors) (15 males/8 females) without diabetes were studied. Both groups were chosen at random and their characteristics are shown in table 1. Patients and controls did not take either anti-hypertensive or hypolipidemic drugs. Diabetic patients took sulphonylureas as antihyperglycemic agents. The study was approved by the local ethical committee and each patient gave informed consent to participate in the study.

Design
All patients (diabetic and controls) underwent the following examinations: plasminogen activator inhibitor type 1 (PAI-1), thrombin-antithrombin III complex (TAT), tissue plasminogen activator (t-PA), von Willebrand antigen (vW), protein C (PC), protein S (PS), thrombomodulin (TH), activated VII factor, D dimer (DD), Ddimer (DD), factor VIIa (normal range 5-85 Mu/ml) was determined by coagulometry, (normal range 70-150% for both). Thrombomodulin activation fragment F1+2 (F12). Blood samples for coagulation testing were collected into sodium citrate solution (normal range 14-55 ng/ml), and prothrombin activation fragment F1+2 (F12) (normal range 0.4-1.1 nmol/L) were determined by enzyme immunoassay (TintElize (t-PA), von Willebrand antigen (vW), protein C (PC), protein S (PS), thrombomodulin (TH), activated VII factor, D dimer (DD), Ddimer (DD), factor VIIa (normal range 5-85 Mu/ml) was determined by coagulometry, (normal range 70-150% for both). Thrombomodulin activation fragment F1+2 (F12). Blood samples for coagulation testing were collected into sodium citrate solution between 07:00 and 09:00 am, after the subjects had fasted for 12 h. Samples were centrifugated for 15 min at 2500 × g at room temperature.

Haemostasis assessment
Plasminogen activator inhibitor type 1 (PAI-1) (normal range < 10 U/ml) and tissue plasminogen activator (t-PA) (normal range 1-12 ng/ml) were determined by enzyme immunoassay (Tinaquant TAP; Inverness, France). Thrombomodulin (normal range 1-10 U/ml) and von Willebrand factor (vWF) were determined by enzyme immunoassay (George King Bio-Medical, Inc., Overland Park, KS, USA). Protein C and S were determined by coagulometry, (normal range 70-150% for both). Thrombomodulin activation fragment F1+2 (F12). Blood samples for coagulation testing were collected into sodium citrate solution (normal range 14-55 ng/ml), and prothrombin activation fragment F1+2 (F12) (normal range 0.4-1.1 nmol/L) were determined by enzyme immunoassay (TintElize (t-PA), von Willebrand antigen (vW), protein C (PC), protein S (PS), thrombomodulin (TH), activated VII factor, D dimer (DD), Ddimer (DD), factor VIIa (normal range 5-85 Mu/ml) was determined by coagulometry, (normal range 70-150% for both). Thrombomodulin activation fragment F1+2 (F12). Blood samples for coagulation testing were collected into sodium citrate solution between 07:00 and 09:00 am, after the subjects had fasted for 12 h. Samples were centrifugated for 15 min at 2500 × g at room temperature.

TABLE 1. Clinical characteristics of overweight diabetic patients and controls

<table>
<thead>
<tr>
<th></th>
<th>Diabetic patients (n = 23)</th>
<th>Control subjects (n = 23)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>61.3 ± 12.3</td>
<td>62.1 ± 13</td>
<td>NS</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>16/7</td>
<td>15/8</td>
<td>NS</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27.2 ± 3.9</td>
<td>27.6 ± 3.1</td>
<td>NS</td>
</tr>
<tr>
<td>Diabetes duration (years)</td>
<td>8.4 ± 6.7</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>HbA₁c (%)</td>
<td>8.9 ± 2.4</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Macrogromopathy (%)</td>
<td>12.8%</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Microgromopathy (%)</td>
<td>48.9%</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>
| T wave inversion, ST segment depression and Q waves. Patients with signs or symptoms of cerebrovascular disease were evaluated with a CNS computerized tomography. The final diagnosis was reviewed by a neurologist.

Peripheral vascular disease was clinically defined by the presence of intermittent claudication, absent or weakened peripheral pulses, or both. Retinopathy was documented by standard fundus eye examination and diagnosed on the presence of microaneurysms, venous dilatation, cotton-wool spots, neovascularization or hemorrhages. Clinical neuropathy was defined by an abnormal neurologic examination, consistent with the presence of peripheral sensorimotor neuropathy. Nephropathy was defined by the presence of urinary albumin excretion of 30 mg or more per 24 hours.

Statistical analysis
The results were expressed as mean ± standard deviation. The distribution of variables was analyzed with Kolmogorov-Smirnov test. Quantitative variables with normal distribution were analyzed with a two-tailed, paired Student’s t test. Non-parametric variables were analyzed with the U-Mann-Whitney test. Qualitative variables were analyzed with the chi-square test, with Yates correction as necessary, and Fisher’s test. Pearson and Spearman tests were used in correlation analysis. A p-value under 0.05 was considered statistically significant.

RESULTS
Twenty three overweight diabetic patients and 23 over-weight no diabetic patients were enrolled in the study. The mean age and BMI were similar in both groups (table 1). The diabetes duration was of 8.9±2.4 years, macrogromopathy was present in 48.9% and microgromopathy in 12.8% of diabetic patients.

Table 2 shows differences between both groups with an increase in pro-coagulant parameters in diabetic patients, with decrease of urinary albumin excretion of 30 mg or more per 24 hours.
a significant increase in prothrombin activation fragment F1+2 and factor VIII(a). Values of PAI and TAT did not have statistical differences. Fibrinolytic parameters showed significant differences in TPA and D dimer (increased) and PAP (decreased), without differences in FvW. A decrease in anti-coagulant parameters was observed in diabetic patients (thrombomodulin), without differences in protein S and C.

All haemostasis parameters were compared in diabetic patients in the group with (48.9%) and without microangiopathy (51.1%), but no differences were found. In a correlation analysis between HbA1c and haemostasis parameters, only protein C and TAP showed significant inverse correlations (r = –0.34; p < 0.01 and r = –0.32; p < 0.05, respectively). Another correlation analysis was performed between BMI and haemostasis parameters, only FvW was correlated with BMI (r = 0.3; p < 0.05). No correlations were found between haemostasis parameters with BMI and HbA1c in non-diabetic subjects.

No correlations were found among diabetes evolution, age or microalbuminuria levels with haemostasis parameters in diabetic patients.

DISCUSSION

Patients with type 2 diabetes mellitus have a variety of coagulation dysfunctions, which could contribute to microvascular and macrovascular complications. The hypercoagulable state has been demonstrated in a group of overweight diabetic patients under strict metabolic control who had an increase in TAT levels. In our study no significant differences in TAT levels were detected between overweight diabetic and control subjects, but F1+2 and activated factor VII were increased in diabetic patients, showing a hypercoagulable state. In diabetic patients, it has been shown that fibrinolytic parameters, such as PAI-1 and tPA antitrypsin were strongly related to insulin resistance, whereas the link with factor VII and other procoagulant parameters remained weak. These alterations might contribute to increase cardiovascular mortality in diabetes. For example, Mortishie et al. showed significantly higher levels of TAT, fibrinogen and PAI-1 in 22 diabetics patients with coronary heart disease than 51 patients without diabetic microangiopathy.

Another haemostasis alteration in overweight diabetic patients is a decrease in the anticoagulant system. Patients with diabetes have activated protein C resistance, suggesting that final steps of the protein C/S inhibiting system might constitute a potential trigger for haemostatic dysfunctions, which could contribute to microangiopathy. In relatives of type 2 diabetic patients, who in a case-control study exhibited levels of prothrombin F1+2 and D dimer lower than control subjects.

An additional point of interest is the relationship between some haemostasis parameters and BMI. One possibility is that changes in these parameters are related to adipose tissue derived cytokines.

In conclusion, hypercoagulable state is present in diabetic patients which with present knowledge can be viewed as a risk factor for chronic complications. The role of adipose tissue as a possible cause of chronic inflammatory activity in diabetic patients requires further investigation.

REFERENCES


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