

The Role of Antithrombin III in the Pathogenesis of the Thrombotic Status in Type 2 Diabetes Mellitus

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Diabetes mellitus is one of the costliest chronic pathology worldwide with a continuous rising incidence. Diabetes mellitus is linked to frequent cardiovascular events. It is associated with vascular events, especially when the glycated hemoglobin has elevated values. Diabetic patients seem to develop abnormalities of the haemostatic process, such as alterations of the thrombocytic function, modifications of the coagulation and of the fibrinolysis that lead to a thrombophilic status. The acquired thrombophilia present in diabetic patients may be due to the non-enzymatic glycosilation of clotting inhibitors such as antithrombine. Antithrombin III has both an anticoagulant and an antiinflammatory effect. The anticoagulant effect appears after acting upon endothelial heparan sulfate or on the molecule of heparine, thus leading to an inhibition of thrombin. A decrease in antithrombin III levels may lead to a diminished neutralisation of thrombin and a lower activity of proteins C and S, thus inducing procoagulant consequences and increasing the susceptibility for thrombotic events. Our research tried to establish whether the levels of antithrombin III in type 2 diabetic patiens are modified, thus creating a predisposition for thrombotic events. Therefore we conducted an observational study on a sample composed of 60 patients having a diagnostic of type 2 diabetes associated with coronary artery disease, controlled with diet or with oral antidiabetics and we evaluated the levels of antithrombin III in function of the metabolic, inflammatory and coronarographic parameters. Our research showed that even though all patients were characterized by the diabetic dyslipidemia, there was no statistic relationship between antithrombin III and the lipidic fractions. As a result we cannot say that the adverse cardiac events seen in type 2 diabetic patients are influenced by the levels of antithrombin III, as a marker of an increased clotting activity.

Keywords: Diabetes mellitus, glycated hemoglobin, fibrinolysis, thrombophilia, protein C, protein S

Diabetes mellitus has become one of the most costly chronic pathology worldwide that has a continuous rising incidence. There is a close link between diabetes and cardiovascular events, the cardiovascular disease being one of the most frequent causes of morbidity and mortality in diabetic patients [1-3]. Type 1 diabetes and type 2 diabetes are both associated with vascular events, especially when the glycated hemoglobin has values higher than 7.0% [4-6].

During diabetes an acquired thrombophilia is present that is due to the non-enzymatic glycosilation of clotting inhibitors such as antithrombine thus leading to a hypercoagulable state [7-10]. Antithrombin III is a α_2 -globuline that has both an anticoagulant and an antiinflammatory effect [9, 11-13]. Antithrombin is a serpin (serine protease inhibitor) and is thus similar in structure to most other plasma protease inhibitors (fig1).

The anticoagulant effect appears after acting upon endothelial heparan sulfate or on the molecule of heparine, thus leading to an inhibition of thrombin, while the antiinflammatory effects are based on an interaction with neutrophils mediated via the syndecan-4 receptor [9, 12-15, 34], a G-protein-coupled transmembrane proteoglycan receptor on endothelial cells and neutrophils [13, 16-18].

A decrease in antithrombin III levels may lead to a diminished neutralisation of thrombin and a lower activity of proteins C and S, thus inducing procoagulant consequences and increasing the susceptibility for thrombotic events [19-21]. While the link between diabetes and cardiovascular events has been clearly established, the relationship between diabetes and venous thromboembolism is still debated.

Our research tried to establish whether the levels of antithrombin III in type 2 diabetic patiens are modified, thus creating a predisposition for thrombotic events.

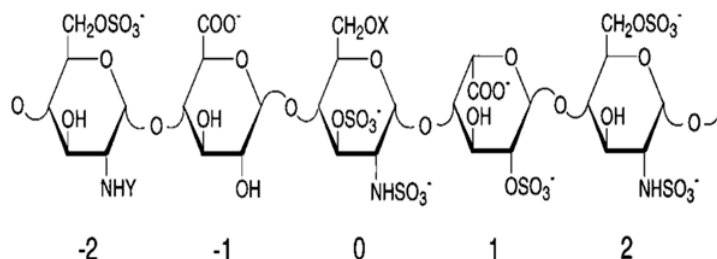


Fig 1. Structure of antithrombin III pentasaccharide binding site - www.researchgate.net

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Experimental part

Methods

Study design and participants

We conducted an observational study on a sample composed of 60 patients attending the cardiology department of the Hospital of Carcassonne (France) between May and October 2015, aged between 42 and 92 years, with an average age of 75 years, having a diagnostic of type 2 diabetes associated with coronary artery disease, controlled with diet, or with oral antidiabetics, but not with insuline. We included in the study type 2 diabetic patients, having duration of diabetes between 5 and 15 years, treated with diet or with oral antidiabetic drugs. The patients receiving a medication that might have interfered with the prothrombotic status were excluded. Only patients who freely gave informed consent were included in the study.

Clinical Evaluation

We evaluated clinical features such as: gender (men or women), age, duration of diabetes, height (cm, measured with a stadiometer), weight (kg). The BMI (kg/m^2) was calculated and included in a classification of the degree of obesity. Obese patients were defined as having BMI index superior to 30 and were divided in three grades: class I: BMI 30-34.9, class II: BMI 35-39.9, class III: BMI >40.

Laboratory Evaluation

The laboratory evaluation consisted in measuring the metabolic parameters such as glycemic profile (consisting in serum glucose and glycated hemoglobin), lipidic profile (total cholesterol, LDL, HDL, triglycerides) and renal function indicators like: creatinine, creatinine clearance (MDRD), uric acid, natremia and potassium levels, which were assessed after 12 h of fasting. In order to assess the haemostatic process we measured the levels of fibrinogen, the thrombocytes count and their morphology and the antithrombin III plasmatic activity. The antithrombin III levels were measured through the chromogen method (which is an activity test) that is based on the inhibition of clotting factor IIa (thrombin), by forming a complex between antithrombin and heparin, while the remaining free clotting factor IIa will fragment a chromogen substrate, which will induce a color change; the absorbance

measured at 405 nm is inversely correlated with the plasmatic antithrombin activity. In order to assess the severity of coronary artery disease all patients underwent a coronarographic examination.

Statistical Analysis

Statistical analysis was carried out using SPSS version 18. ANOVA test was done in order to analyze the dispersion of the dependent variable: intra and intergroup. When assessing the significant difference between two or more groups, we used for the quantitative variables: the t-student test and the F test (ANOVA). To compare clinical and laboratory biochemical and physiological parameters in relation to the studied SNPs and nutritional status, the Kruskal-Wallis and Pearson correlation coefficient were done. Significance was considered to be $p = 0.05$. We realized the ROC (Receiver Operator Characteristic) curve, in which on the abscise was the false positive level (specificity) and on the ordinate the true positive level (sensitivity) in order to evaluate the sensibility/ specificity balance.

Results and discussions

The age of patients ranged between 42 to 92 years, the average age being 75.17 ± 11.32 years. On the studied sample there was a preponderance of patients with obesity class I (53.3%), more than half being women (68.8%) and patients older than 75 years (50%). The duration of type 2 diabetes mellitus varied between 5 and 11 years, with a significant superior value found in the group of patients older than 75 years (8.47 vs 6.87 years, $p=0.022$). When correlated with gender, it was proven that the duration of type 2 diabetes was slightly elevated in women than in men.

Antithrombin III registered values between 80-135% (the normal range being 80-120%), 16.7% of patients having increased plasmatic levels. The mean antithrombin III concentration was slightly elevated in women compared to men (112.60% vs 106.60%; $p=0.226$) and in the group of patients aged under 75 years (112.33% vs 106.87%; $p=0.271$). There were no differences of antithrombin III levels due to the nutritional status (109.63% vs 109.59%; $p=0.995$) (table 1).

Table 1

MEAN VALUES OF THE EPIDEMIOLOGICAL AND BIOLOGICAL MARKERS IN FUNCTION OF ANTITHROMBIN III

Parameter	Num ber	Mean	Std. Deviation	Std. Error	Confidence interval 95%		Min	Max	Test t- Student p
					-95%CI	+95%CI			
Gender									0.226
Masculin	30	106.60	16.39	4.23	97.53	115.67	80	135	
Feminin	30	112.60	9.12	2.35	107.55	117.65	90	125	
Age									0.271
< 75 years	30	112.33	11.05	2.85	106.21	118.45	90	135	
≥ 75 years	30	106.87	15.26	3.94	98.42	115.32	80	130	
Nutritional status									0.995
Preobesity	16	109.63	19.55	6.91	93.28	125.97	80	135	
Obesity	44	109.59	10.95	2.33	104.74	114.45	85	125	

Our research showed that antithrombin III levels were significantly correlated with the duration of diabetes, 36.5% of the patients with higher antithrombin III levels had a longer duration of type 2 diabetes mellitus ($r = +0.365$; $R^2 = 0.1335$; $p = 0.047$) (fig. 2).

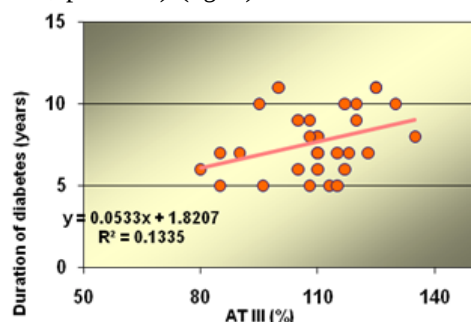


Fig. 2. Correlation between the levels of antithrombin III and the years of diabetes, showing that a long period of diabetes is associated with increased antithrombin levels.

Regarding the glycemic profile, all patients had elevated values of the glycated hemoglobin, thus indicating a deficient therapeutic control of diabetes. The mean value of the glycated hemoglobin (HbA1C) was slightly higher in women (7.89% vs 7.75%; $p = 0.765$), in patients that had less than 75 years (8.08% vs 7.56%; $p = 0.239$) and in overweight patients (7.94% vs 7.78%; $p = 0.751$). The concentrations of glycated hemoglobin were directly correlated with antithrombin III levels ($r = +0.266$; $R^2 = 0.0706$; $p = 0.156$) and with the duration of diabetes ($r = +0.342$; $R^2 = 0.1169$; $p = 0.064$), but the results weren't statistically significant (fig. 3).

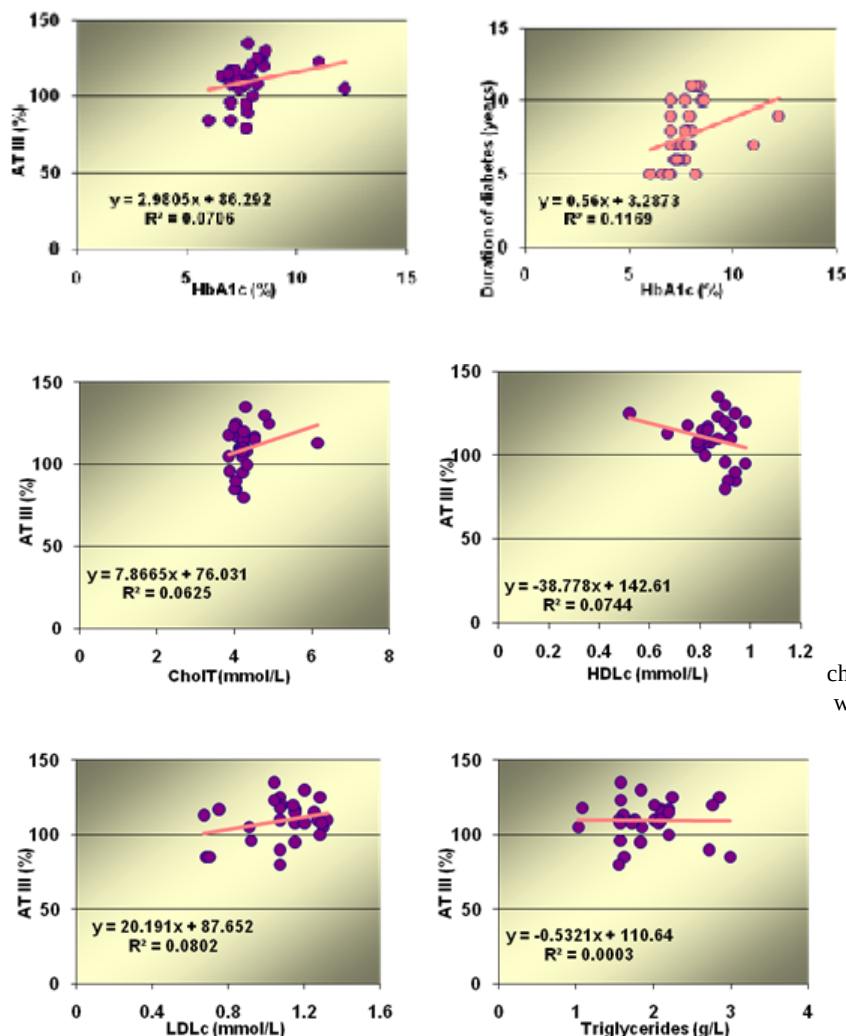


Fig. 3. Relationship between the levels of antithrombin III and HbA1C and between the levels of HbA1C and the duration of diabetes. HbA1C levels may be slightly higher in patients who have had diabetes for a longer time and have a direct correlation with antithrombin III levels, but these correlations have no statistical significance.

Fig. 4. Relationship between the levels of antithrombin III and the lipidic fractions. The antithrombin III was directly correlated with total cholesterol and LDL-cholesterol levels, and indirectly with the concentration of HDL-cholesterol, but there was no statistical significance. There was no correlation between antithrombin III levels and triglycerides concentrations.

Regarding the lipidic profile, the total cholesterol levels varied between 3.85 and 6.14 mmol/L, 90% of patients having normal cholesterol levels. The mean value of total cholesterol was slightly higher in men (4.34 vs 4.19 mmol/L; $p = 0.336$), in patients that had less than 75 years (4.27 vs 4.26 mmol/L; $p = 0.960$) and in obese patients (4.27 vs 4.25 mmol/L; $p = 0.918$). Total cholesterol levels were directly correlated with antithrombin III concentrations ($r = +0.250$; $R^2 = 0.0625$; $p = 0.183$), 25% of patients having both high total cholesterol levels and high antithrombin III concentrations, but the correlation wasn't statistically significant. HDL cholesterol ranged between 0.52 and 0.98 mmol/L, all patients having had diminished levels, with no difference regarding age, gender or nutritional status. HDL cholesterol was indirectly correlated with antithrombin III ($r = -0.273$; $R^2 = 0.0744$; $p = 0.145$) and had a slight direct correlation with the duration of diabetes ($r = +0.046$; $R^2 = 0.0021$; $p = 0.811$), but these correlations weren't statistically significant (fig. 4).

The LDL cholesterol levels were between 0.67 and 1.32 mmol/L, less than half of patients having had normal or diminished LDL cholesterol levels, with no significant differences due to age or nutritional status. The LDL cholesterol levels were directly correlated with antithrombin III concentrations ($r = +0.283$; $R^2 = 0.0802$; $p = 0.129$) and with the duration of diabetes ($r = +0.214$; $R^2 = 0.0456$; $p = 0.257$), but there were no statistical significant correlations. The triglycerides values were comprised between 1.03 and 1.99 g/L, 93.3% of patients having high individual levels, with no significant distinctions due to gender or age, but with significant higher levels in

obese patients (2.04 vs 1.69 g/L; $p=0.05$). The triglycerides levels had a direct slight correlation with the duration of diabetes ($r= +0.262$; $R^2= 0.0687$; $p=0.162$), but with no statistical significance. There was no correlation between antithrombin III levels and triglycerides concentrations ($r= -0.019$; $R^2= 0.0003$; $p=0.922$).

In order to evaluate the inflammatory status, we measured the fibrinogen and CRP levels. The fibrinogen concentrations varied between 4.01 and 4.89 g/L, all patients having had slightly elevated levels, with no differences due to gender, age or nutritional status. The fibrinogen levels were correlated in a significant direct manner with antithrombin III levels, 36.5% of patients with high antithrombin III levels having elevated fibrinogen concentrations ($r= +0.365$; $R^2= 0.1312$; $p=0.049$). The C reactive proteine (CRP) ranged between 4-72 g/L, all patients having had elevated levels, with a higher mean value in the group older than 75 years (40.53 vs 28.69 g/L; $p=0.05$), but with no differences due to gender or nutritional status. The CRP values were directly correlated with antithrombin III concentrations ($r= +0.301$; $R^2= 0.0906$;

$p=0.106$) and with the duration of diabetes ($r= +0.190$; $R^2= 0.0362$; $p=0.314$), but these correlations didn't have a statistical significance.

The patients included in the sample group underwent a coronarographic investigation, thus allowing us to assess the severity of coronary artery disease. On the studied sample the vast majority of the group had triple vessel coronary artery disease (70%), more than half being men (52.4%) and patients older than 75 years (52.4%) (table 2).

The duration of diabetes was higher in patients with triple vessel coronary artery disease (7.50 years vs 7.33 years), but with no significant differences of the mean values compared with the other groups of patients with coronary artery lesions ($p=0.919$) (table 3).

The mean antithrombine III levels were slightly elevated in patients with double vessel coronary artery disease (109%) or with multivessel disease (111.52%), compared to the group with univessel disease (97.33%), but there was no significant statistical difference. The highest mean level of glycated hemoglobin was found in the triple vessel coronary artery disease group (8.38%), but there was no

Coronary artery lesions	Number of cases	%	Men		Age > 75 years	
			n	%	n	%
1 vessel	6	10,0	4	66.6	4	66.6
2 vessels	12	20.0	4	33.3	2	33.3
3 vessels	42	70.0	22	52.4	22	52.4
Kruskal Wallis test (p values)			0.003		0.003	

Table 2
STRUCTURE OF SAMPLE IN FUNCTION OF THE TYPE OF CORONARY ARTERY LESIONS

Marker	Coronary artery lesions			Test F (ANOVA) P
	1c (n=6)	2c (n=12)	3c (n=42)	
Epidemiological data				
Duration of diabetes	7.33±2.31	7.50±2.07	7.76±1.97	0.919
BMI	27.67±3.21	31.50±3.02	31.33±2.76	0.120
Markers of the renal fonction				
AT III	97.33±18.61	109.00±8.30	111.52±13.46	0.233
Creatinine	98.67±26.31	87.33±7.74	87.90±19.52	0.632
Markers of the glucidic metabolism				
HbA1c	7.53±0.29	8.38±1.97	7.70±0.98	0.437
Markers of the inflammatory process				
Fibrinogen	4.38±0.26	4.44±0.21	4.44±0.27	0.922
CRP	24.33±10.02	29.67±18.35	37.50±16.85	0.035
Markers of the lipidic metabolism				
CholT	4.32±0.17	4.11±0.25	4.30±0.48	0.620
HDLc	0.90±0.08	0.87±0.07	0.84±0.10	0.479
LDLc	1.12±0.05	1.07±0.14	1.09±0.21	0.927
Triglyceride	1.86±0.33	1.90±0.59	1.97±0.47	0.895
Hematological markers				
PLT	213266±86519	278953±64333	266296±48848	0.245
RBC	4.29±0.04	4.49±0.31	4.40±0.49	0.801
WBC	8955±1899	10007±934	8854±1879	0.198

Table 3
MEAN VALUES OF THE EPIDEMIOLOGICAL AND BIOLOGICAL MARKERS IN FUNCTION OF THE CORONARY ARTERY lesions

statistical significant difference between the coronary artery lesions groups. Regarding the inflammatory parameters, the fibrinogen mean levels didn't differ between the different coronary artery disease group, while CRP had significant elevated levels in patients with multivessel disease ($p=0.035$).

Plasmatic fibrinogen levels promote thrombosis, may influence the rheology of the blood stream, the blood viscosity and the platelet aggregation, thus being an independent cardiovascular risk factor [22-25]. Most studies found increased fibrinogen levels in type 2 diabetic patients, regardless of the presence of microangiopathic complications that may be responsible for the prothrombotic status found in hyperglycemic states [17, 26-29]. Even more, the haemostatic balance seems to be altered in favor of thrombosis, due to platelet modifications. The metabolic intrathrombotic alterations and the modifications of the intraplatelet signaling pathway concur to an increase of platelet reactivity that characterizes patients with type 2 diabetes mellitus [18]. Our research showed that there were slightly elevated plasmatic levels of fibrinogen in all patients, with no differences due to gender, age or nutritional status. The fibrinogen levels were correlated in a significant direct manner with antithrombin III levels, thus suggesting a modification of antithrombin III either due to a hypercoagulable state, or due to an inflammatory process, or maybe due to both types of modifications which are present in diabetic patients. The other inflammatory parameter, the C reactive protein (CRP), was elevated in all patients, indicating the presence of the inflammatory status that characterizes diabetic patients. Our study revealed that CRP levels were directly correlated with antithrombin III concentrations, but this relation had no statistical significance. Therefore we are inclined to consider the direct relationship between fibrinogen and antithrombin III levels as a result of the thrombophilic status, than rather due to the inflammatory process. The existing data regarding the modifications of antithrombin III concentration in diabetic patients is rather contradictory, some studies showing decreased antithrombin III levels (as a result of its consumption in the clotting pathway), some having proved no significant relation and others indicating the presence of elevated antithrombin III activity in hyperglycemic status. Our results tend to indicate that high fibrinogen levels in diabetic patients are associated with elevated antithrombin III concentrations, probably as a result of an indirect mechanism, derived from the increased thrombin clotting activity seen in patients with type 2 diabetes.

Recent studies proved that patients with type 2 diabetes and with increased cardiovascular risk have a prothrombotic status, derived both from an increase in the clotting activity and a decrease in the endogenous fibrinolysis. Thus the metabolic modifications found in diabetes that determine modifications of the platelet activity, clotting process or fibrinolysis tend to lead to a hypercoagulable state. These systemic modifications can activate an extensive atherosclerotic process, derived also from the thrombophilic status, which can partially explain the frequent development of atherosclerotic plaques in the coronary arteries of diabetic patients. Even more, the hypercoagulable state found in diabetic patients may be responsible of the preponderant microvessel localization of coronary atherosclerosis (19, 30-33). On the studied sample the vast majority of the group had multivessel disease, more than half being men and patients older than 75 years. The mean antithrombin III levels were slightly elevated in patients with bivessel coronary artery disease

or with triple vessel coronary disease, but there was no significant statistical difference between the different coronary artery lesions groups. Regarding the inflammatory parameters, the fibrinogen mean levels didn't differ between the different coronary artery disease groups, while CRP had significant elevated levels in patients with multivessel disease. Therefore we can assume that patients with multivessel disease have an increased inflammatory process that may be responsible for the extensive atherosclerosis, but our results didn't show an increase of the thrombotic status at these patients. When analyzing the link between the lipidic profile and the clotting parameters, our research showed that even though all patients were characterized by the diabetic dyslipidemia, there was no statistic relationship between antithrombin III and the lipidic fractions. Therefore we cannot say that the adverse cardiac events seen in type 2 diabetic patients are influenced by the levels of antithrombin III, as a marker of an increased clotting activity.

Conclusions

So, our data pointed out an interesting aspect regarding the implication of antithrombin III in the pathogenesis of type 2 diabetes mellitus, thus revealing that the relationship between antithrombin III and the metabolic parameters is rather null, although data on larger population is needed and should be evaluated not only as retrospective analysis. Additional research is needed to better understand the disease process and to be able to clearly identify the factors that contribute to the prothrombotic status found in type 2 diabetes mellitus.

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