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Genetic and Metabolic Determinants of Plasminogen Activator Inhibitor 1 (PAI-1) in Tunisian Type 2 Diabetes Patients

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Abstract

Background: PAI-1 (plasminogen activator inhibitor-1) is a powerful regulator of fibrinolysis and plasma level is high in type 2 diabetes and cardio-vascular disease, which is determined by genetic polymorphisms in PAI-1 gene and environmental factors. The aim of the study was to examine the determinants of plasma PAI-1 Ag level among type 2 diabetes patients. **Methods**: 491 Tunisian type 2 diabetes patients had clinical evaluation (weight, high, BMI, Waist Circumference), laboratory investigations including FBG Hb1Ac, cholesterol, triglyceride; HDL-cholesterol was done; plasma PAI-1 antigen level was done with ELISA; −675 4G/5G and −844 G/A polymorphisms of PAI-1 gene was done by PCR-ASA and PCR-RFLP respectively. **Results**: The mean age for our patients was 58.3 ± 10.5 years; sex-ratio = 0.92; mean PAI-1 level was 34.6 ± 21.3 ng/ml. We didn't find correlation between PAI-1 level and BMI, but we have found significant correlation between PAI-1 and waist circumference ($p = 0.032$), most enhanced in men ($P = 0.002$), T2D patients who have FBG > 11 mmol/l had PAI-1 Ag level higher than those who have FBG < 11 mmol/l ($P = 0.034$), but no difference found between T2D with high Hb1Ac > 8% and those with Hb1Ac < 8%, significant correlation was seen between PAI-1 level and LDL-cholesterol ($P = 0.05$), high correlation between PAI-1 Ag level and −675 4G/5G polymorphism genotype was seen, 4G/4G carriers had the highest PAI-1 level, 4G/5G had intermediary level and 5G/5G had the lowest level ($P < 0.001$). No correlation was seen between PAI-1 Ag level and −844G/A polymorphism genotypes. Using multiple variable linear regression analysis, the independent factor associated with plasma PAI-1 level was −675 4G/5G polymorphism (regression coefficient $\beta = 4.6$, P

< 0.01). **Conclusion**: the present study identifies −675 4G/5G not −844 G/A polymorphism of PAI gene as the principal determinant of plasma PAI-1 level in Tunisian T2D patients, the android fat distribution, dyslipidemia and hyperglycemia play a modest role in this variation.

Keywords

Plasminogen Activator Inhibitor 1, Polymorphism, PCR,
Type 2 Diabetes Mellitus, Metabolic Syndrome X

1. Introduction

Most patients with type 2 diabetes (T2D) die from complication of atherosclerosis [1].

PAI-1 (plasminogen activator inhibitor-1) is a major regulator of fibrinolysis [2], plasma PAI-1 Antigen (PAI-1Ag) level is increased in type 2 diabetes patients [3] [4] and that may explain excess risk of cardiovascular disease. It also elevated in coronary artery disease patients [5] and its plasma level is determined by genetic [6] and environmental factors [7].

The PAI-1 gene has been localized to q21.3-q22 of chromosome 7 [8]. Several polymorphisms within the PAI-1 gene influence PAI-1 levels [9]. The most known polymorphism which influences PAI-1 level is −675 4G/5G insertion-deletion mutation-of PAI-1 promotor gene [6] and another single nucleotide polymorphism is −844 G/A [10] [11] [12].

Environmental factors, like obesity and metabolic syndrome features also plays a role in Plasma PAI-1 variation in type 2 diabetes patients and in non diabetics [7] [13]. The aim of this study was to examine the determinants of plasma PAI-1Ag level among adult patients with type 2 diabetes in Tunisia.

2. Patients and Methods

This was a cross sectional study involving 491 type 2 diabetic patients recruited from the outpatient's endocrinology department at Farhat-Hachad hospital in Sousse-Tunisia during 2005-2006 period, written informed consent was obtained from participants, the study was approved by hospital ethic comity, inclusion criteria was: known type 2 diabetes, exclusion criteria were: cancer, coagulation disorders, pregnancy, end stage chronic kidney disease, all patients had clinical examination including (weight, high, BMI, Waist Circumference (WC)), laboratory investigations (Fasting blood glucose (FBG), Hb1Ac, cholesterol, triglyceride, HDL-cholesterol,) LDL was calculated by Fridewald formula(LDL (mmol/l) = total cholesterol –HDL-TG/2.26), after clear write consent plasma PAI-1 antigen level was done with ELISA, −675 4G/5G. PAI-1 gene promoter polymorphism genotyping was done by PCR-ASA(allele specific amplification) using common primer for 2 alleles in 5'P side and 2 specific primers for 2 alleles in 3'OH side and −844 G/A polymorphism genotyping was done by PCR-RFLP

(restriction fragment length polymorphism) using 2 specific primers for 2 alleles and DNA was digested with restriction enzyme, allelic frequency was calculated with hardy-Weinberg law $(p + q)^2 = p^2 + 2pq + q^2 = 1$, with p = n1 + n2/2n and q = n3 + n2/2n, n = number total of patients, n1 = 4G/4G carriers, n2 = 4G/5G, and n3 = 5G/5G, P = allele 4G frequency, q = 5G frequency. The same procedure was made with −844 G/A, and statistical analyses was performed using SPSS version 10.0 software.

3. Results

The mean age of our T2D population was 58.3 ± 10.5 years, male/female-ratio = 0.92, mean PAI-1 level was 34.6 ± 21.3 ng/ml.

Table 1 shows PAI-1Ag level was not correlated with BMI, but was significantly correlated with waist circumference (P = 0.032), this correlation was most evidenced in men (P = 0.002) (Table 2).

No significant difference found in PAI-1 Ag level between type 2 diabetes patients with hypertension and T2D without hypertension (Table 3).

In multivariate analysis, we found significant relationship between PAI-1 level and LDL-cholesterol (P = 0.05) (Figure 1).

T2D patients who have FBG > 11 mmol/l had PAI-1 Ag level higher than those who have FBG < 11 mmol/l (P = 0.034), but no difference found between T2D with high Hb1Ac > 8% and those with Hb1Ac < 8% (Table 4).

The Table 5 shows high correlation between PAI-1 Ag level and -675 4G/5G polymorphism genotypes, 4G/4Gcarriers had the highest PAI-1 level, 4G/5G had intermediary level and 5G/5G had the lowest level ($P < 0.001$), No correlation was seen between PAI-1 Ag level and −844G/A polymorphism genotypes.

Using multiple variable linear regression analysis, the independent factor associated with plasma PAI-1 level was −675 4G/5G polymorphism (regression coefficient $\beta = 4.6$, $P < 0.05$).

Table 1. PAI-1 Ag level in diabetics in function of BMI (kg/m^2).

PAI-1 (ng/ml)	BMI < 25	25 < BMI < 30	BMI > 30	*P*
Mean ± SD (Range)	34.1 ± 21.4 (11 - 88.9)	35 ± 20.6 (11 - 92)	34.7 ± 22 (10 - 111)	NS

SD: Standard Deviation; *P*. *P*-Value; NS: Non Significant.

Table 2. Mean PAI-1 Ag level in type 2 diabetes patients in function of WC (cm) and sex.

	WC (cm)			
	Men		Women	
PAI-1 Ag (Mean ± SD)	WC < 102 cm	WC > 102 cm	WC < 88 cm	WC > 88 cm
	29.7 17.7 ng/ml	44.3 ± 22.3 ng/ml	35.3 ± 22.4 ng/ml	33.5 ± 18.4 ng/ml
P	<0.001		NS	

SD: Standard Deviation; *P*. *P*-Value; NS: Non Significant.

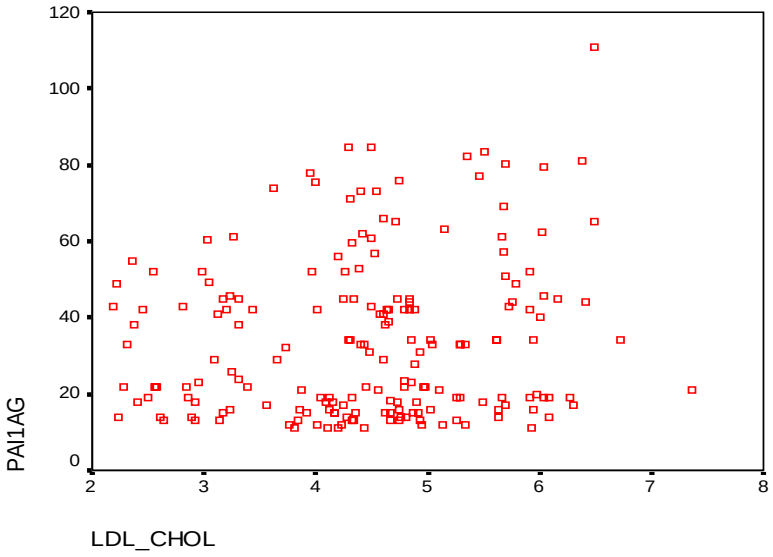

Figure 1. MeanPAI-1-Ag in relation to LDL in T2D patients.

Table 3. Mean PAI-1 Ag level in T2D patients in function of hypertension.

PAI-1 (ng/ml)	T2D with hypertension (n = 197)	T2D without hypertension (n = 294)	*P*
Mean ± SD (range)	33.7 ± 21.7 (11 - 92)	35.3 ± 20.9 (10 - 111)	NS

SD: Standard Deviation; *P*. *P*-Value; NS: Non Significant.

Table 4. Mean PAI-1 Ag in T2D in function of FBG (fast blood glucose) and Hb1Ac.

PAI-1 (ng/ml)	FBG		*P*
	<11 mmol/l	>11 mmol/l	
Mean ± SD	32.2 ± 20.6	36.5 ± 21.5	0:034
	Hb1Ac		
	<8%	>8%	
Mean ± SD	35.4 ± 21.2	34 ± 21.3	NS

SD: Standard Deviation; *P*. *P*-Value; NS: Non Significant.

Table 5. Correlation between PAI-1 –Ag level and −675 4G/5G and -844G/A genotypes in T2D patients.

Génotype	PAI-1 (ng/ml) Mean ± SD (range)	*P*
4G/4G	59.4 ± 18.7 (31 - 111)	
4G/5G	35.2 ± 20.6 (11 - 89.6)	<0.001
5G/5G	23 ± 11.4 (10 - 56)	
A/A	34.8 ± 21.7 (11 - 111)	
G/A	35.8 ± 21.8 (10 - 89)	NS
G/G	32.7 ± 20 (11 - 89.6)	

P. *P*-Value; NS: Non Significant.

4. Discussion

PAI-1 level is increased in type 2 diabetic patients [3] [8] [14] [15] [16] in comparison with non diabetic.

In IRAS (insulin resistance atherosclerosis study) [17] high level of PAI-1 was a predictor of type 2 diabetes incidence, in multiple regression analyses, PAI-1 level still significantly linked to type 2 diabetes incidence. In the same study high PAI-1 level was linked to diabetes incidence. [18], In Health, Aging and Body Composition Study [19] similar results were found.

In Framingham Offspring Study [20], high PAI-1level was a risk factor of type 2 diabetes with relative risk (RR) of 1.4 for people who have PAI-1 level in upper normal range, this risk is independent of obesity and classical risk factors. In Strong Heart Study [21], relationship between PAI-1 level and diabetes incidence was found but this relationship become non-significant after adjustment with other variables (age, sex, BMI, BP, triglyceride, CRP, fibrinogen and insulin), antidiabetic drug vildagliptin decrease PAI-1 level [22].

A recent metanalysis [23] shows moderate association between PAI-1 and T2D independent of established diabetes risk factors.

In our study mean PAI-1 Ag level was 34.6 ± 21.4 ng/ml. we didn't have control group due to financial limits (cost of dosage) and the comparison with other studies is difficult because measurements methods are different and non-standardized.

The PAI-1 level is correlated to insulin resistance markers (BMI, Waist circumference, glucose level and insulin) [4] [24].

In our study we didn't find a positive correlation between BMI and PAI-1 but we found correlation between PAI-1 and WC which was most evident in men.

We had found correlation between PAI-1 and LDL cholesterol, LDL and VLDL cholesterol stimulate PAI-1 gene expression *in vitro* [8], that may explain this correlation

The patients who have FBG > 11 mmol/l have PAI-1 level more than patients who have FBG < 11 mmol/l.

Glucose stimulate PAI-1 gene expression *in vitro* and that may explain relationship between PAI-1 and diabetes [8], but this relationship is largely explained by metabolic syndrome.

Some studies found that PAI-1 level is linked to android fat distribution and endocrines and metabolic features of metabolic syndrome [4] [5] [25].

People who have Metabolic syndrome with or without diabetes had elevated PAI-1 level [3] [24] improvement of metabolic syndrome with weight loss decrease PAI-1 level [13].

Some studies had found higher PAI-1 level in people with hypertension [26].

In our study, we didn't find significant difference between mean PAI-1 level of diabetic patients who have hypertension and diabetics without hypertension.

Pronounced elevations of PAI-1 antigen levels were seen in 4G carriers of −675 4G/5G polymorphism of T2D patients in a large number of studies, [4] as

well as non-diabetic and in different ethnic populations like Tunisians [27] [28] [29].

The most significant variation in PAI-1 expression resides in the PAI-1 4G/5G alleles. Unlike the 5G allele that binds a transcription repressor, resulting in low PAI-1 expression, the 4G allele does not bind a transcription repressor, thus conferring a "high PAI-1 expressor" nature to the allele I [30].

Martinez-Calatrava [31], had found that 4G allele is the principal determinant of PAI-1 level in study of 631 persons, independent of metabolic disorders.

These results are in agreements with our study who shown that −675 4G/5G polymorphism not metabolic disorders was the principal determinant of PAI-1 level. Another study show metabolic syndrome components explain only 12% of PAI-1variability in T2D patients [4].

4G allele has been shown as a risk factor in cardio vascular disease in some studies [32] not others [6], some studies show 4G as a risk factor of diabetes [33] [34], some studies show 4G allele association with obesity [35] [36] and metabolic syndrome [37] [38].

About second polymorphism −844 G/A, we don't found relationship between this polymorphism and PAI-1 level, this results is in agreement with the literature [11] [12] [27].

A Mexican study revealed a relationship between −844 G/A and metabolic syndrome [39]. Another study revealed an association with cardio-vascular disease and dyslipidemia [40].

5. Conclusion

The present study identifies −675 4G/5G not −844 G/A polymorphism of PAI gene as the principal determinant of plasma PAI-1 level in adult type 2 diabetes patients in Tunisia, and the android fat distribution, dyslipidemia and hyperglycemia play a modest role in this variation.

Conflicts of Interest

All authors declare no conflicts of interest.

Author's Participation

All authors had participated actively in manuscript realization.

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