THE INFLUENCE OF TISSUE FACTOR (TF) POLYMORPHISMS ON CORONARY CALCIFICATIONS IN CHRONIC KIDNEY DISEASE PATIENTS

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Background/ Aim

Tissue factor (TF), a key initiator of the haemostatic cascade (see **Fig. 1**), is expressed in atheromatous plaques and contributes to their thrombogenicity. Its colocalization in calcified regions was recently reported. It is well-recognized that TF expression in pathological processes could be modulated by genetic factors including TF gene polymorphisms. Common variants have been described within the TF gene promoter defining two almost equally frequent haplotypes in Caucasian populations (the 18 nucleotides insertion/deletion at position c.-1208 defining the I/D-alleles respectively)(see **Fig. 2**). The purpose of this study was therefore to evaluate the potential association of TF-1208I/D alleles with calcifications occurrence in chronic kidney disease (CKD) patients, a population at high risk of developing cardiovascular (CV) events.

Methods

One hundred and eighty five non dialyzed CKD patients (109M/76F, median age: 71 [27-95]) at various stages of kidney disease were tested for TF genotyping and underwent chest multi-detector computed tomography for coronary calcification scoring. In addition, a standard carotid doppler ultrasound was used to identify occlusive carotid atheromatous plaques. A detailed medical history including history of atherosclerotic CV disease (defined by the presence of at least: (i) coronary heart disease, (ii) cerebrovascular disease or (iii) peripheral vascular disease) was also recorded.

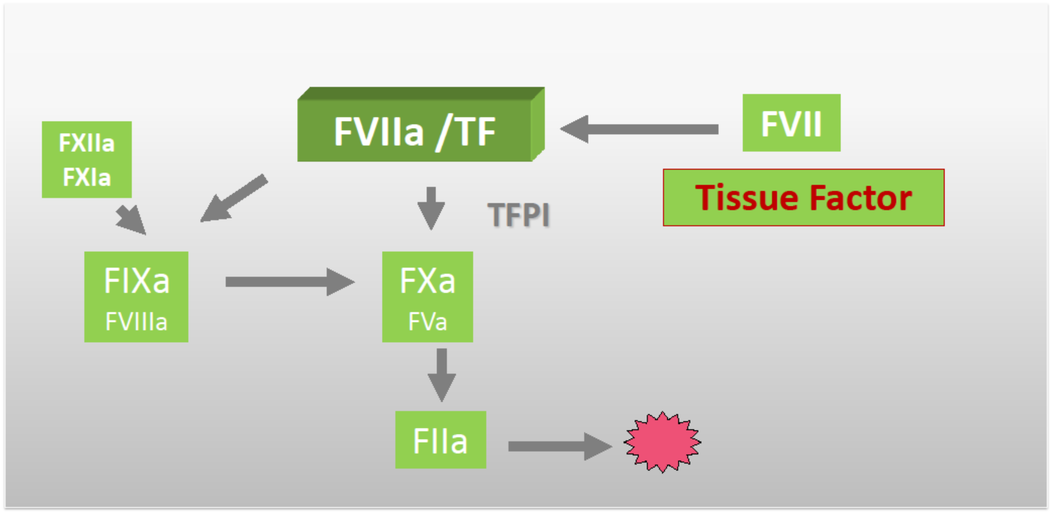

Figure 1. Coagulation cascade pathway

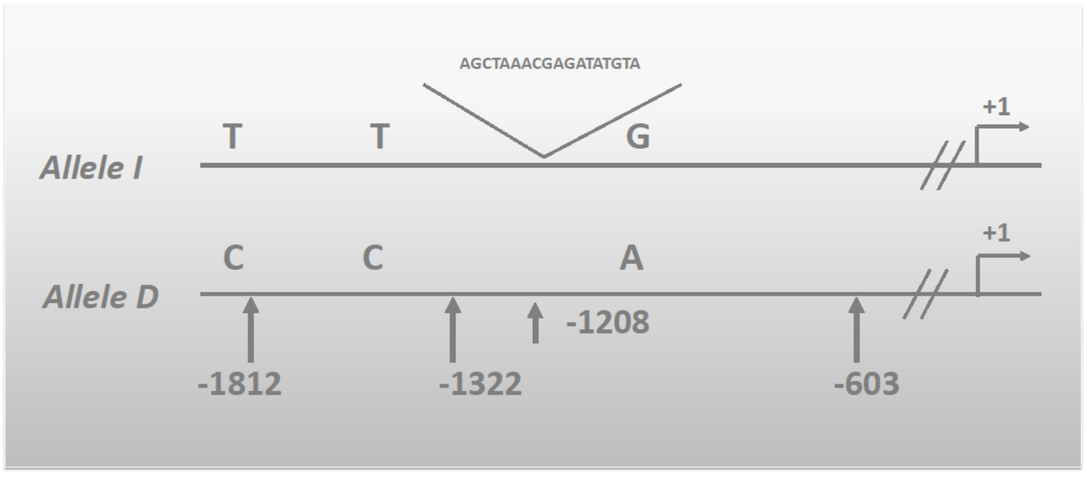

Figure 2. Schematic representation of the main TF promoter polymorphisms (from Terry et al., *J Thromb Haemost*, 2, 1351-1358)

Results

1. Clinical and biological characteristics for the 185 CKD patients are summarized in **Table 1**.

Parameter	Value
BMI *kg/m²*	26.6 [14.3-47.7]
Smoking habits (current and past)	90 (49.5%)
Diabetes	58 (31.4%)
Hypertension	170 (91.9%)
Coronary heart disease	39 (21.1%)
Cerebrovascular disease	14 (7.6%)
Peripheral vascular disease	30 (16.2%)
Presence of atheromatous plaque	99 (53.5%)
eGFR (MDRD) *mL/min/1.73m²*	33.3 [6.5-91.9]
>60 mL/min/1.73m²	19 (10.3%)
60-30 mL/min/1.73m²	87 (47.0%)
<30 mL/min/1.73m²	79 (42.7%)
Total cholesterol *mmol/L*	5.2 [2.3-9.2]
LDL-cholesterol *mmol/L*	2.9 [1.1-6.5]
HDL-cholesterol *mmol/L*	1.5 [0.6-3.4]
Hs-CRP *mg/L*	2.1 [0.1-56.1]
Calcium *mmol/L*	2.4 [1.7-2.7]
Phosphate *mmol/L*	1.07 [0.58-2.34]
PTH *pg/mL*	47.0 [4.0-493.0]
Coronary calcium scoring	188 [0-3942]

Table 1. Characteristics of the chronic kidney disease patients.

2. Patients carrying at least one copy of the TF-1208D allele 1 presented higher calcium scoring (p=0.02) after adjustment for confounding factors whereas a weak association (p=0.04) was observed with atheromatous plaques.
No further adjustment was done since no relationship was evidenced. By contrast, no significant association between TF polymorphism and CV history was demonstrated.

Genotype analysis	Tissue Factor -1208D allele Cases (%)	Tissue Factor -1208D allele Cases (%)	*P*-value
	DD and DI	**II**	
Calcium scoring >100	91 (83.5%)	18 (16.5%)	0.02
Calcium scoring <100	56 (73.7%)	20 (26.3%)	
CV History	50 (82.0%)	11 (18.0%)	0.66
No CV History	97 (78.2%)	27 (21.8%)	
Atheromatous plaque (-)	42 (72.4%)	16 (27.6%)	0.04
Atheromatous plaque (+)	82 (82.8%)	17 (17.2%)	

Table 2. Association of TF polymorphism with CAC, atheromatous plaque and CV history.

Conclusion

These results suggest a role of TF in cardiovascular morbidity and mortality in CKD patients.