ASSOCIATION OF MGP T-138C POLYMORPHISM WITH CAROTID INTIMA MEDIA THICKNESS IN PATIENTS WITH DIABETIC KIDNEY DISEASE

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OBJECTIVES

Vitamin K-dependent Matrix Gla Protein (MGP) inhibits vascular calcification (VC). Modification by g- carboxylation is necessary for MGP to become biologically active. Vitamin K deficiency leads to accumulation of high levels of the inactive dephoshorylated uncarboxylated form of MGP (dp -ucMGP), in calcified vessels. Vitamin K epoxide reductase complex subunit 1 (VKORC1) mediates the recycling of vitamin K, a cofactor involved in g- carboxylation of MGP. Single nucleotide polymorphism of VKORC1 -1639 G>A results in lower activity of VKORC1 in subjects with the AA genotype & probably higher levels of dpucMGP. Also, the T-138C polymorphism of MGP has been associated with progression of VC. We sought to determine the association between VKORC1 -1639G > A & MGP T-138C polymorphisms & plasma levels of dp - ucMGP, as well as their effect on carotid intima-media thickness (cIMT) in diabetes mellitus type 2 (DMT2) patients with kidney disease. We also investigated the frequency of MGP T-138C genotypes in this group of patients according to disease severity.

METHODS

In this study VKORC1 -1639G > A & MGP T-138C polymorphisms were determined by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) analysis in 40 diabetic patients without nephropathy (controls) &118 patients at different stages of diabetic nephropathy including patients on hemodialysis. Patients were stratified in all five stages of CKD based on eGFR using the CKD-EPI equation. Measurements of cIMT were performed using real-time B-mode ultrasonography. Plasma levels of dp -ucMGP were determined in a subgroup of 67 patients by ELISA.

TABLES AND FIGURES

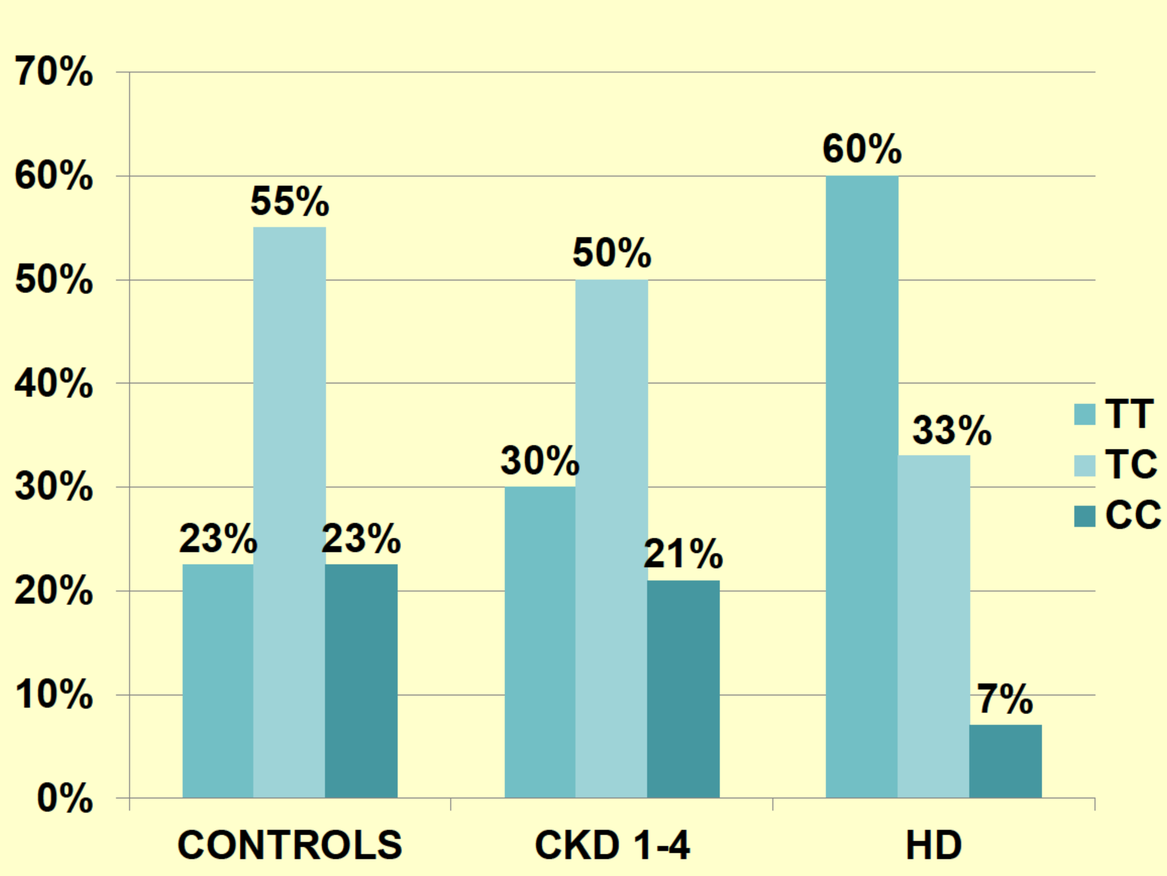
Table 1: Anthropometric, clinical, and biochemical characteristics of patients at different stages of Diabetic Nephropathy.

	Stage of Diabetic Nephropathy					P
N=158	**Controls (n=40)**	**1&2 (n=23)**	**3 (=34)**	**4 (n=31)**	**5-HD (n=30)**	
Age (years)	64.7(8.0)	68.4 (8.5)	68.8 (7.8)	70.8 (9.1)	69.8 (10.4)	**0.04**
Gender (M/F)	17/23	11/12	19/15	22/9	14/16	0.16
SBP (mm Hg)	133.6 (18.0)	139.4 (11.9)	143.7 (15.8)	140.9 (16.1)	134.4 (23.2)	**0.04**
DBP (mm Hg)	76.1 (8.6)	77.7 (7.8)	79.2 (7.8)	77.8 (10.3)	77.3 (11.2)	0.53
Duration of T2DM (years)	11.4 (6.2)	13.5 (6.9)	16.0 (8.9)	18.1 (8.5)	16.0 (6.6)	**0.004**
dpucMGP (pM)	239.6 (71.0-589.0)	500.5 (87.0-770.0)	657.0 (325.0-2155.0)	1080.0 (519.0-2743.0)	965.0 (770.0 -1839.0)	**<0.0001**
Mean cIMT (mm)	0.76 (0.40-1.50)	0.86 (0.60-1.30)	0.90 (0.60-1.50)	0.80 (0.50-1.50)	0.95 (0.70-1.50)	**<0.0001**

Table 2. Association of cIMT with MGP T-138C polymorphism

MGP T-138C genotypes	Mean cIMT (mm)	P
TT (n=53)	0.90 (0.60-1.50)	0.01
TC (n=76)	0.80 (0.43-1.50)	
CC (n=29)	0.78 (0.40-1.16)	
TT (n=53)	0.90 (0.60-1.50)	0.006
TC/CC (n=105)	0.80 (0.40-1.50)	

Figure 1. Distribution of MGP T-138C genotypes promoter polymorphism in T2DM controls, CKD (stages 1-4) and HD patients. TT versus TC+CC (p=0.002, Chi-square test).



RESULTS

Plasma dp -ucMGP levels & cIMT values increased significantly with severity of diabetic nephropathy (p<0.0001 & p=0.004 respectively, Kruskal-Wallis test)-Table 1. Although there was not an association between VKORC1 -1639G > A polymorphism & cIMT, MGP T-138C polymorphism was significantly associated with cIMT in all patients studied. TT homozygotes had higher values of cIMT compared to TC & CC genotypes (p=0.01, Kruskal-Wallis test)- Table 2. The association between MGP T-138C and cIMT became even stronger when the genotypes were grouped (TT vs TC+CC genotypes, p=0.006, Kruskal-Wallis test)- Table 2. Levels of dp -ucMGP were not associated with any of the two polymorphisms studied or with cIMT. MGP -138TT homozygotes were more frequent in the hemodialysis group in comparison with patients in other stages of diabetic nephropathy & controls (p=0.002, Chi-square test).

CONCLUSIONS

Our study demonstrated a strong association between the TT genotype of MGP T-138C polymorphism and cIMT, a surrogate marker of subclinical atherosclerosis in subjects with diabetic nephropathy of all stages, independently of serum dp-ucMGP concentrations. This study also showed that MHD patients have a different distribution of MGP T-138C gene polymorphism, as compared with diabetic patients with normal renal function (control group) and patients with diabetic nephropathy at . stages 1-4, with the TT genotype being more frequent. Since MGP is an important inhibitor of tissue & vascular calcification, our findings provide evidence on a genetic basis probably underlying the calcification development in diabetic nephropathy.

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