Vitamin K Epoxide Reductase Gene (VKORC1) Polymorphisms are Associated with Cardiovascular Disease in Chronic Kidney Disease (CKD) Patients on Haemodialysis

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Objectives:

Vitamin K is necessary for the carboxylation of clotting factors and matrix Gla protein. Vitamin K epoxide reductase (VKOR) is the enzyme responsible for recirculation of vitamin K increasing its tissue availability. It is possible that polymorphisms of VKOR may alter the function of matrix Gla protein, thereby influencing vascular calcification. We conducted this study to investigate the relationship of VKORC1 gene polymorphisms to vascular calcification and clinically overt cardiovascular disease in CKD patients on hemodialysis.

Methods:

- The study included 54 CKD patients on hemodialysis. We excluded those with diabetes or anticoagulant therapy
- Vascular calcification was measured in the aorta using CT scans of the abdominal aorta and lateral lumbar roentgenograms. Peripheral vascular calcification was assessed using plain roentgenograms of the pelvis, forearms, hands and upper thighs. Calcification of the pelvic vessels was further assessed using CT scans of the pelvis.
- Prevalent clinically overt cardiovascular disease was reported based on the presence of evidence of documented pre-existing major cardiovascular events, namely myocardial infarction, heart failure, acute coronary syndrome, non-haemorrhagic cerebrovascular disease and/or significant peripheral vascular disease.
- Genotype detection for the gene VKORC1 C-1173T and G-1639A polymorphisms was carried out by PCR. Clinicians collecting the data were blinded to the results of the gene study.

Results:

C-1173T polymorphisms

• We found a significant association between C-1173T polymorphisms and vascular calcification(O.R. 43, p=0.001). This association was valid after correction for age, diabetes mellitus, BMI, duration on hemodialysis and systolic blood pressure using logistic regression analysis (P = 0.001).
•Moreover, the mutant T allele was also linked with higher odds of vascular calcification (O.R.= 8.880, 95% C.I. 3.1-25.4, P=0.001)and clinically overt cardiovascular disease (O.R. = 4.7, 95% C.I. 1.5-14.7, P=0.005.

G-1639A polymorphisms

•VKORC1 G-1639A polymorphisms were not associated with vascular calcification but were associated with lower prevalence of clinically overt cardiovascular disease (O.R. 0.07, 95% C.I. 0.01-0.4, p =0.001). This was confirmed by logistic regression corrected for age, BMI, diabetes mellitus, smoking, duration on CKD and vascular calcification, P = 0.02.
•Nonetheless, the mutant allele (A) was linked to lower odds for the presence of overt cardiovascular disease (O.R.= 0.07, 95% C.I.= 0.02-0.3, P <0.001) and vascular calcification(O.R.= 0.12, 95% C.I.= 0.03-0.4, P=0.001).

Conclusions:

VKORC1 gene polymorphisms were associated with prevalent cardiovascular calcification and clinically overt cardiovascular disease in patients with CKD on hemodialysis. C-1173T polymorphisms were associated with higher risk for disease and G-1639A with lower risk

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