ASSOCIATIONS OF SINGLE NUCLEOTIDE POLYMORPHISM OF THE CALCIUM-SENSING RECEPTOR GENE (CASR RS7652589) WITH NEPHROLITHIASIS AND SECONDARY HYPERPARATHYROIDISM IN HEMODIALYSIS PATIENTS

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Introduction and Aims: Nephrolithiasis, secondary hyperparathyroidism (sHPT), and cardiovascular complications are all associated with disturbances in Ca handling and contribute to morbidity and mortality during hemodialysis (HD). Allosteric activators of the calcium-sensing receptor (CaSR) provide an effective means of reducing PTH secretion in sHPT. Polymorphism in CaSR gene (CASR) influences Ca-related clinical and laboratory parameters, however it was not shown in HD patients for CASR rs7652589. The aim of the study was to determine the associations of the CASR rs7652589 SNP with nephrolithiasis-related ESRD, Ca, P, ALP, PTH, response to treatment with cinacalcet, prevalence of coronary artery disease as well as all-cause and cardiovascular mortality in HD patients.

Methods: Frequency of CASR rs7652589 nucleotide variants in HD patients (n=1162) was compared to that of healthy controls (n=918) to exclude uremia-related association. HD subjects were also genotyped for T helper cell cytokine-associated genes and vitamin D signaling pathway genes. Patients receiving cinacalcet (n=162, 30-180 mg daily) were evaluated in respect to their CASR-related response to this drug defined as a decrease in serum PTH by at least 40% of the initial level. CASR rs7652589 polymorphic variants were genotyped by high-resolution melting curve analysis.

Results: There were no significant differences in frequency (%) of CASR polymorphic variants between HD subjects (GG 36.6, AG 48.5, AA 14.9) and healthy controls (GG 38.2, AG 47.3, AA 14.5). In HD group, AA patients compared to GG ones showed higher frequency of nephrolithiasis-related ESRD (OR 1.54, 95%CI 1.13-2.10, P=0.007), and the allele A frequency was higher in nephrolithiasis patients than in the other ones (OR 1.47, 95%CI 1.11-1.95, P=0.007). The allele A was an independent predictor of nephrolithiasis-related ESRD among other determinants (B 0.09, P<0.02). In nephrolithiasis group, there was an epistatic interaction between rs7652589 and rs1024611 in the chemokine (C-C motif) ligand 2 gene. Higher serum Ca levels were associated with significantly increased frequency of A allele (36% in hypocalcemic, 40% in normocalcemic, and 46% in hypercalcemic subjects). Hypercalcemic compared with hypocalcemic patients showed higher frequency of the allele A (1.48, 95%CI 1.16-1.88, P=0.002). Distribution of CASR rs7652589 polymorphic variants differed in patients showing serum PTH >500 pg/mL and those having PTH ≤500 pg/mL (P=0.035, P=0.035): higher PTH levels were associated with A allele (P=0.04). Serum PTH >500 pg/ml was independently associated with the AA genotype (B 0.09, P=0.008). In genotype selected groups, there was no significant difference in frequency (%) of responders to cinacalcet (61.5 in GG, 59.4 in AG, and 71.4 in AA subjects), prevalence of CAD, including myocardial infarction, P, and ALP. All-cause and cardiovascular mortality rates were not associated with CASR rs7652589 polymorphisms.

Conclusions: In HD subjects, the allele A in CASR rs7652589 is a risk allele for nephrolithiasis-related ESRD. The AA genotype is associated with more severe sHPT, but PTH-decreasing response to treatment with cinacalcet does not seem to be related to CASR rs7652589.

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