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KLOTHO 1818T polymorphism associated with myocardial infarction, abdominal aortic calcification and lower creatinine clearance in community-dwelling older subjects: the Sao Paulo Ageing & Health Study (SPAH)

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Introduction. The KLOTHO gene was discovered in 1997 when its defective expression in mice led to a syndrome that resembles human ageing (short lifespan, arteriosclerosis, and osteoporosis). Since then, at least 10 mutations and single-nucleotide polymorphisms (SNPs) were described in humans. Nonetheless, the effects of each SNP in human ageing is still obscure.

Objectives. This study aims to evaluate three KLOTHO gene polymorphisms in an elderly population and their potential association with the prevalence of senility-related outcomes.

Methodology. This study was based on data from the Sao Paulo Ageing & Health Study (SPAH), conducted on 65 year-old and over community individuals. Local ethics committee approved the study and participants provided written informed consent.

Of the original 1020 participants, 601 (381 men/220 women) had DNA samples collected. Genomic DNA was isolated from peripheric blood leukocytes using salting-out methodology. The TaqMan allelic discrimination method was employed for genotyping, using specific probes. The analyzed SNPs were 1818 C>T (rs564481), 395 G>A (rs1207568), and 1117 G>C (rs9527025), all chosen due to previous data in literature.

The patients were followed for 4.06±1.07 years, and had data collected about mortality, history of cardiovascular events (angina pectoris, myocardial infarction [MI], and stroke), fractures and other outcomes as follows: osteoporosis was diagnosed by densitometry. Aortic calcification was quantified using Kauppila’s method. Clearance was calculated using CKD-EPI formula.
Allele frequencies were estimated using the gene counting method, and departures from the Hardy–Weinberg equilibrium were tested using a $\chi^2$ test. Data with normal distributions are expressed as median and were compared using the Mann-Whitney’s or Kruskal-Wallis tests, depending on the number of groups. Categorical variables are expressed as relative frequencies and were analyzed using the Pearson’s chi-squared test. P values $\leq 0.05$ were considered significant.

**Results.** Of the 601 subjects, 27 (4.49%) presented MI. Analyzing the 1818 C>T SNP, 1818 TT genotype was associated with a higher frequency of developing MI (TT: 8.3%/ CT: 6.7%/ CC: 1.7%; P=0.006). 395 G>A and 1117 G>C had no statistically significant association with MI.

Subjects with the 1818 TT and 1117 GG genotypes independently featured lower creatinine clearances [mL/min/1.73m²] (TT: 55.5 / CT: 58.2 / CC: 58; P=0.047 and GG: 50 / GC: 60.1 / CC: 57.3; P=0.046, respectively). Furthermore, the presence of 1818 C allele determined higher clearances (TT: 55.5 / CC+CT: 58.1; P=0.033). 395 G>A had no statistically significant association to creatinine clearance.

Regarding abdominal aortic calcification scores, the 1818 TT genotype and the absence of the 1818 C allele determined a tendency to higher scores (TT: 4.0 / CT: 2.0 / CC: 2.0; P=0.068 and TT:4.0 / CC+CT:2.0; P=0.065, respectively). 395 G>A and 1117 G>C had no statistically significant association with abdominal aortic calcification.

No statistically significant association between the three SNPs and osteoporosis, sarcopenia or mortality were found.

**Discussion and Conclusion.** Our study provides an original finding that the KLOTHO 1818 TT genotype was associated with MI, lower creatinine clearance and a tendency to higher aortic calcification in Brazilian community-dwelling older adults, supporting the involvement of KLOTHO polymorphism in cardiovascular outcomes and the concept that the related pathogenesis is multifactorial.

**Keywords:** Polymorphisms; Myocardial infarction; Aortic calcification.