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TUMOR NECROSIS FACTOR RECEPTOR 2 POLYMORPHISM (RS1061622) AND INFLAMMATORY RESPONSE IN END-STAGE RENAL DISEASE PATIENTS UNDER DIALYSIS

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Background and Aims: Enhanced levels of soluble tumor necrosis factor receptor 2 (sTNFR2) are known to associate with progressive chronic kidney disease (CKD), and is pointed as a potential biomarker for early detection of CKD; moreover, it has been reported as an independent predictor of all-cause mortality in end-stage renal disease (ESRD) patients under dialysis. Despite the increase in TNFR2 and in other inflammatory markers, recognized as risk factors for mortality in dialysis patients, the hypothesis that genetic polymorphisms of those biomarkers might modulate the inflammatory response and, thereby, the patients' survival predisposition, has been poorly studied.

Concerning TNFR2 genetic variants, a single nucleotide polymorphism in TNFR2 (+ 676 T/G; rs1061622), that results in amino acid change at position 196 (Met/Arg), was associated with higher levels of sTNFR2 in inflammatory conditions. The aim of this study was to determine the allelic frequencies of TNFR2 in ESRD patients and controls, and to evaluate its relationship with the circulating levels of inflammatory biomarkers.

Method: We studied 277 ESRD patients on dialysis and 32 controls, matched for gender, body mass index, and, as far as possible, for age. Real time PCR TaqMan SNP genotyping assay was used to assess allelic frequencies of TNFR2 (rs1061622). We also evaluated the circulating levels of TNF-alpha, sTNFR2, ferritin, hepcidin, elastase and cell-free DNA (cfDNA). Deaths occurring along 1-year follow-up period were recorded and mortality rates were assessed.

Results: ESRD patients presented higher levels of all studied biomarkers, as compared to controls; their overall mortality rate was 10.5%. Allelic frequencies in ESRD patients and controls were similar for TNFR2 (rs1061622) considering the homozygous and heterozygous individuals (χ^2, $p = 0.518$). Concerning sTNFR2 values, no significant differences were observed between patients with genotypes TT, GG or TG. The GG genotype patients, compared to TT genotype carriers, presented significantly lower ferritin ($p = 0.048$), hepcidin ($p = 0.038$), elastase ($p = 0.006$) and cfDNA levels ($p = 0.016$); and compared to TG genotype patients, showed significantly lower ferritin ($p = 0.039$) and a trend towards lower values of hepcidin ($p = 0.097$), elastase ($p = 0.079$) and cfDNA ($p = 0.0164$). TG genotype patients showed higher TNF-alpha ($p = 0.049$) and a trend towards lower elastase ($p = 0.081$) than TT genotype subjects. The GG genotype patients presented a trend towards lower mortality rate (6.3%, 7.5%, and 12.4% for GG, TG and TT, respectively).

Conclusion: No differences were found in the allelic frequencies between controls and ESRD patients. The GG genotype patients for TNFR2 rs1061622 polymorphism showed decreased levels of inflammation, suggesting a more favorable inflammatory response, which is usually associated to a lower mortality risk in these patients. In accordance with the scientific community, recommending studies on genetic survival predisposition in dialysis patients, the polymorphisms of TNFR2 and of other inflammatory biomarkers deserve further studies. Acknowledgements: This work was financed by CESPU, through the project SNPsCKD-GI2-CESPU-2022; FCT, through the project UIDP/04378/2020 and UIDB/04378/2020 of the Research Unit on Applied Molecular Biosciences—UCIBIO and the project LA/P/0140/2020 of the Associate Laboratory Institute for Health and Bioeconomy—i4HB.