OXIDATIVE STRESS AMPLIFIES THE ALKALINE PHOSPHATASE - DEPENDENT RISK FOR MORTALITY IN ESKD PATIENTS ON DIALYSIS

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INTRODUCTION

High tissue non-specific alkaline phosphatase (AlkPhos) is a powerful predictor of death in patients with end-stage kidney disease (ESKD). Inflammation and oxidative stress strongly induce AlkPhos in various tissues and may interact with AlkPhos in the high risk of death in this population. Like AlkPhos, γ-Glutamyltransferase (GGT) -a robust marker of oxidative stress- is an independent risk factor for all cause and cardiovascular death in ESKD (1)

METHODS

The hypothesis that oxidative stress can interact with AlkPhos in the high risk of death in dialysis patients was tested in a cohort of 993 dialysis patients enrolled in the PROGREDIRE Study. The mean follow-up in this cohort was 2.9 years. Systemic inflammation was estimated by C reactive protein (CRP). γ-Glutamyltransferase (GGT) - a robust marker of oxidative stress and a strong predictor of death in ESKD - was adopted as an indicator of the reactive oxygen species burden. Tissue non-specific Alk-Phos and GGT were measured by standard methods adapted to multichannel analyzers.

RESULTS

During the follow-up 405 patients died (death rate: 14 per 100 patients/year). At the univariate analysis AlkPhos failed to predict the considered outcome, whereas GGT was a strong predictor of mortality both at univariate and fully adjusted analysis (HR_{GGT} increase:10 IU/L: 1.04, 95% CI: 1.02-1.06, P<0.001). AlkPhos levels interacted strongly with GGT levels both in unadjusted Cox's regression (P=0.004) and in analysis adjusting for Framingham risk factors, uremia-related factors and markers specific of liver function (P=0.01). In multivariate adjusted analyses, the HR for mortality associated to a fixed increase in AlkPhos (50 IU/L) was progressively higher across GGT levels, being minimal and non-significant at 20 IU/L of GGT (HR: 1.03, 95% CI: 0.97-1.09), intermediate at 40 IU/L (HR: 1.16; 95% CI: 1.04-1.28) and highest for values of GGT higher than 40 IU/L (HR: 1.30, 95% CI: 1.08-1.55) (P for the effect modification: 0.01) (Fig. 1). No effect modification by CRP on the AlkPhosh–mortality relationship was found in this cohorts. These findings were fully confirmed in sensitivity analyses excluding patients with pre-existing liver disease (P=0.03), excessive alcohol intake (P=0.01) or altered liver disease biomarkers (P=0.03) (Fig. 2).

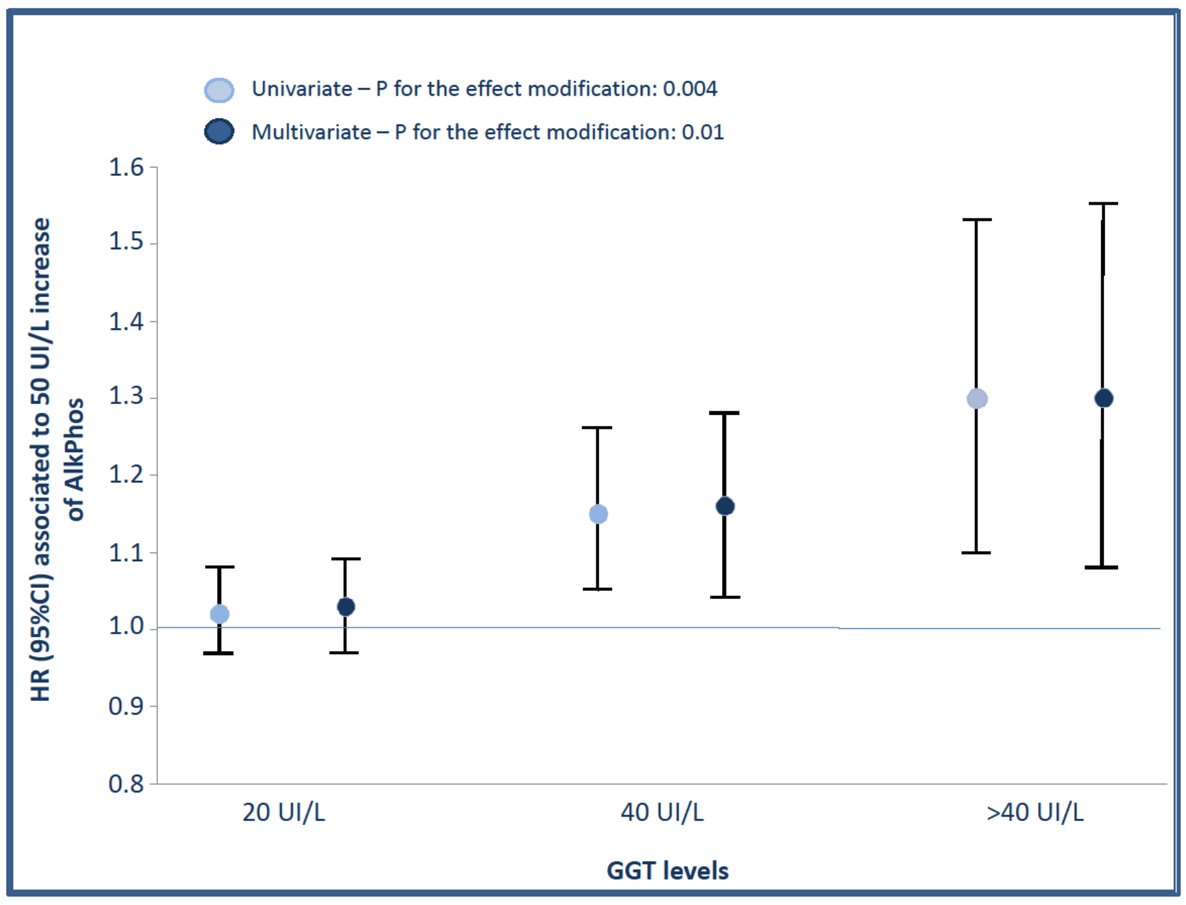
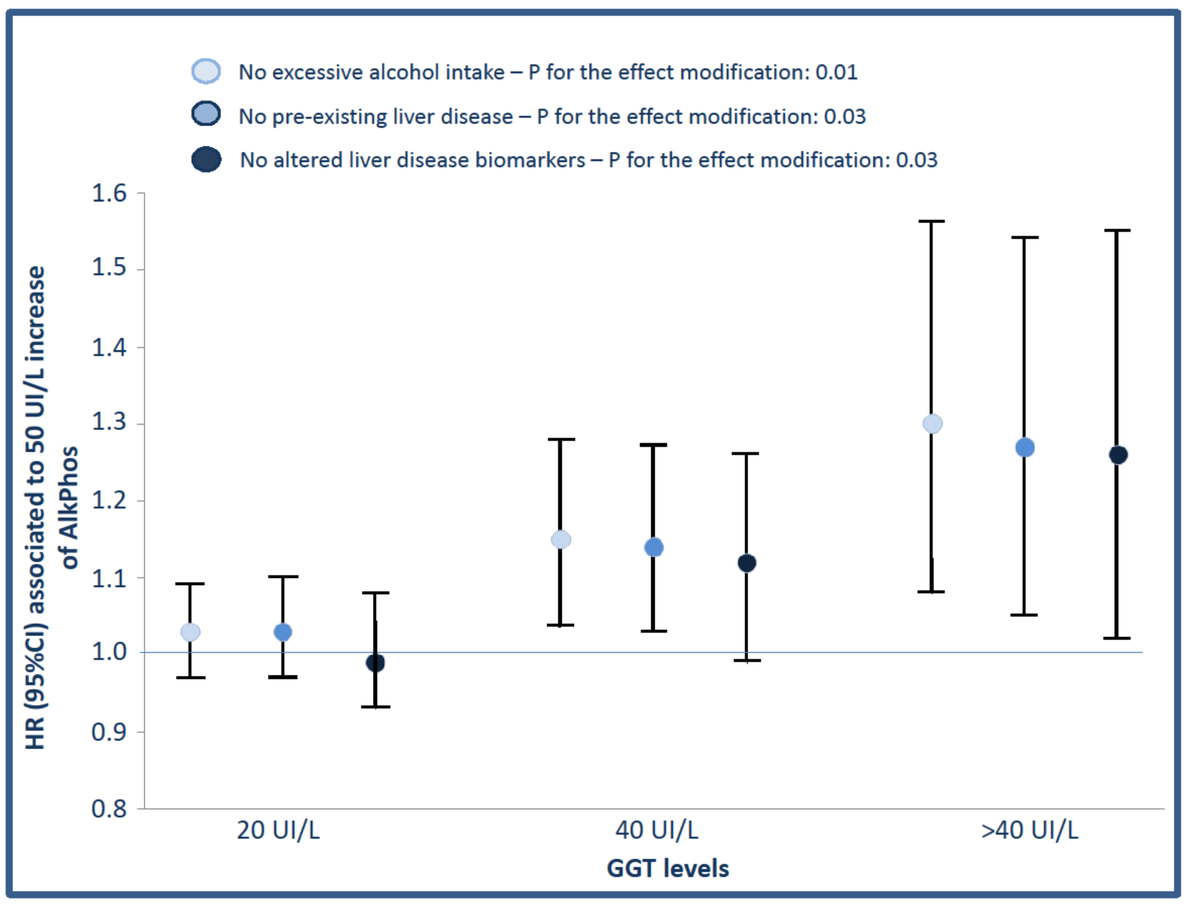


Fig. 1. Hazard ratio associated to AlkPhos levels and 95% CI showing the effect modification of GGT on all cause mortality.

Fig. 2. Hazard ratio associated to AlkPhos levels and 95% CI showing the effect modification of GGT on all cause mortality in sensitivity analyses excluding patients with excessive alcohol intake, pre-existing liver disease or altered liver disease biomarkers.



CONCLUSIONS

GGT amplifies the risk of death associated to high AlkPhos levels in dialysis patients. This observation is compatible with the hypothesis that oxidative stress is a strong modifier of the adverse biological effects of high AlkPhos in ESKD.

REFERENCES

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