Serum levels of the endoplasmic-reticulum-stress chaperone GRP78 are associated with inflammation, identify patients with coronary artery disease and predict mortality

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Introduction: Endoplasmic-reticulum-stress (ER Stress) and associated chaperones like the ER-Stress moderator GRP78 (glucose-regulated-protein, 78kDa) are involved in the pathogenesis of coronary artery disease (CAD). In addition to their intracellular effects, secretion and extracellular properties of chaperones, including GRP78, were recently described. In a recent study using proteomic data, we found coronary endothelial cells to secrete GRP78 into the extracellular space. Here, we investigated the significance of serum GRP78 in patients undergoing coronary angiography for suspected CAD.

Methods: Serum concentration of GRP78 was measured by ELISA in an all-comers cohort of 789 patients with clinical indication for coronary angiography. Samples were drawn from the arterial sheath. CAD was defined as >50% stenosis in any major epicardial coronary artery. Patients were stratified according to their clinical presentation (CCS: chronic coronary syndrome or ACS). Clinical endpoint was all-cause mortality after one year. Patients with malignant or active auto-immune diseases were excluded.

Results: Mean age was 70.8 ± 11.9 years and 65% of patients were male. 24% patients presented with acute coronary syndrome (ACS). CAD was found in 72.4% of patients. Mean GRP78 serum concentration was 2492 ng/ml. Increased levels of GRP78 (> median) were associated with diabetes (29.9% vs. 23.1%, p = 0.03), a higher BMI (28.9 kg/m² ± 7.1 vs. 27.0 kg/m² ± 6.0, p < 0.0001) and chronic kidney disease (CKD: 23.3% vs. 17.1%, p = 0.03). There was no difference regarding age or sex.

We further compared GRP78 levels to other biomarkers including WBC, Hemoglobin, Troponin, Creatinine, and Interleukin-6 (IL-6). There was no association between GRP78 levels and the mentioned biomarkers, except for a positive correlation between GRP78 and levels of Interleukin-6 (Pearson r = 0.14, p = 0.004).

GRP78 levels were increased in patients with CAD when compared to patients without CAD (2640 ng/ml vs. 2178 ng/ml, p = 0.013). Interestingly, GRP78 levels were lower in patients with ACS than in patients with CCS (2284 ng/ml vs. 2822 ng/ml, p = 0.018). There was no difference between NSTEMI and STEMI patients.

Finally, we assessed prognostic relevance of GRP78 in patients with CAD. Increased GRP78 levels were associated with lower occurrence of the clinical endpoint of one-year mortality (5.3% vs. 10.6% vs. p = 0.016). Increased GRP78 levels were associated with reduced one-year mortality (HR: 0.48 [95% CI: 0.25 - 0.92]). After adjusting for IL-6, age, sex, BMI, diabetes, CKD, and ACS, GRP78 remained an independent predictor of one-year mortality in patients with CAD.

Conclusion: GRP78 serum levels are generally elevated in patients with CAD but are downregulated during ACS. Reduced levels are associated with increased one-year mortality. These results support previous findings that GRP78 secretion is a protective mechanism in cardiovascular diseases.