Mutual effect modification between insulin-resistance and endothelial dysfunction in predicting incident heart failure in hypertensives

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Both type-2 diabetes mellitus and endothelial dysfunction are associated with heart failure (HF); in addition, a strong interplay between endothelial dysfunction and insulin-resistance status that precedes of many years the clinical appearance of type-2 diabetes mellitus, has been well-demonstrated. Thus, the aim of this study was to investigate whether endothelial dysfunction and insulin-resistance are independent predictors of incident HF and if exists a possible interaction between them.

For this study we selected 705 white never-treated hypertensive outpatients free from HF, type-2 diabetes mellitus, chronic kidney disease, previous cardiovascular events and other chronic diseases potentially impacting on HF development. Endothelium-dependent vasodilation was investigated by intra-arterial infusion of acetylcholine, and laboratory determinations were obtained by standard procedures. Insulin-resistance was evaluated by the homeostasis model assessment (HOMA). During the follow-up [median 117 months (range 31-211)], there were 223 new cases of HF (3.3 events/100 patient-years). Stratifying the study population in progressors and non-progressors, we observed that progressors were older and had a higher prevalence of females, baseline glucose, insulin, HOMA, creatinine, and hs-CRP mean values, while estimated glomerular filtration rate and endothelium-dependent vasodilation were lower. In the multiple Cox regression analysis, serum hs-CRP (HR=1.362, 95% CI=1.208-1.536), HOMA (HR=1.293, 95% CI=1.142-1.465), maximal ACh-stimulated FBF (100% of increase, HR=0.807, 95% CI=0.697-0.934) and e-GFR (10 ml/min/1.73m2 increase, HR=0.552, 95% CI=0.483-0.603) maintained an independent association with incident HF. The subsequent analysis demonstrated that HOMA and endothelial dysfunction interact between them in a competitive manner (HR=6.548, 95% CI=4.034-10.629), showing also a mutual effect modification. These interaction analyses revealed that, in crude and adjusted models, HOMA significantly modified the effect of acetylcholine-stimulated FBF on incident HF and, given the mutualistic nature of the effect modification, also acetylcholine-stimulated FBF significantly modified the effect of HOMA on HF development.

Our findings demonstrate that both endothelial dysfunction and HOMA are independent and strong predictors of incident HF in hypertensives; we also demonstrated that these two risk factors interact between them with a competitive mechanism.
Figure 1
Figure 2