ASSOCIATION OF CARDIOMETABOLIC PROTEINS WITH eGFR DECLINE IN OLDER ADULTS WITH ADVANCED CHRONIC KIDNEY DISEASE

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Background and Aims: Cardiovascular disease and advanced chronic kidney disease often coexist and share risk factors in older individuals. We investigated the association of cardiometabolic and cardiovascular proteins and pathways with decline in estimated glomerular filtration rate (eGFR).

Method: Two plasma protein panels (Olink® cardiometabolic T96 and cardiovascular II T96, Uppsala, Sweden) were analysed at the baseline visit of individuals enrolled in the prospective observational European QUALity (EQUAL) study of older people > 65 years with advanced CKD (incident eGFR < 20 ml/min/1.73m2). Generalised linear mixed effects models with a log link and random intercept and slope were used to determine annualised eGFR slope (CKD-EPI 2009 equation) using a complete case model. The model was executed in a "discovery" sample (Germany, United Kingdom and Poland) and positive results (< false discovery rate [FDR] of 5%) were tested in a Swedish "validation" sample using the same FDR criterion. The primary analysis was adjusted for baseline age, sex, country, diabetes mellitus status, primary renal disease, systolic blood pressure, urine albumin to creatinine ratio (ACR), and the use of renin-angiotensin aldosterone inhibitors and β-blockers. A sensitivity analysis was conducted to determine the effect of informative censoring on eGFR slope using a joint model.

Results: The discovery and validation samples had 254 subjects (median age 67 years, 41% female, median baseline eGFR 18 ml/min/1.73m2) and 247 (median age 75 years, 28% female and median baseline eGFR 18 ml/min/1.73m2) respectively with longer follow-up time for the validation sample (median 3.6 versus 2.6 years) primarily due to less kidney replacement therapy initiation (33% versus 37%) and fewer losses to follow up (5% versus 12%). Two of the 175 proteins showed more rapid eGFR decline per doubling in protein levels (Figure 1): Receptor-type tyrosine-protein phosphatase S [PTPRS] (~15%; 95% confidence interval [CI] –24 to −7%, pFDR = 0.01) and Insulin-like growth factor-binding protein 6 [IGFBP6] (~8%; 95% CI -12 to –3%, pFDR = 0.03) (Figure 2). Predicted slopes were similar across both samples and for the sensitivity analyses.

Conclusion: Receptor-type tyrosine-protein phosphatase S and Insulin-like growth factor-binding protein 6 were associated with more rapid CKD progression. Further research is needed to determine if these proteins are pathophysiologically linked to accelerated progression of CKD in older people or a secondary consequence of disturbances in protein sequestration or excretion.
Figure 1: Protein associations with eGFR (discovery estimates). Successfully validated proteins are labelled.

Figure 2: Slopes for successfully validated proteins (discovery estimates).