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Pathophysiological link between renal and cardiovascular disease in patients with type 2 diabetes mellitus: preliminary results from a proteomic study

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Background and Aims: Diabetic kidney disease (DKD) affects nearly 40% of people with diabetes and is the leading cause of chronic kidney disease (CKD). A high prevalence of cardiovascular disease (CVD) is known in this population. Indeed, DKD and CVD are often related and lead to worse outcomes in type 2 diabetes mellitus (T2D), i.e. cardiac fibrosis and CV events are frequently described in patients with DKD. However, specific associations and accurate prediction biomarkers for DKD and CVD progression in T2D are still lacking as various proteins may play a multi-mechanistic role. Lipocalin-2 (LCN2) is involved in several pathophysiological processes (inflammation, renal disease and cardiometabolic complications in CKD). Its leukocyte-chemoattractant effect has shown to reduce CVD in experimental models of cardiomyopathy when suppressed. Excess LCN2 in CKD is a determinant of disease progression, but also a potent mediator of cardiac injury in CKD. Insulin-like growth factor binding proteins (IGFBPs) also play an important role in cell homeostasis by regulating cell transcription, migration, and apoptosis. IGFBP-3 down-regulation has demonstrated to be a predictor of rapid renal progression in T2DM. On the other hand, IGFBP-6 increases when GFR drops, being involved in the pathophysiological process of CKD as an apoptosis-inducing protein. In this context, a proteomic-based approach would optimise the clinical utility of multiple plasma biomarkers. The aim was to identify proteins associated with DKD, cardiac fibrosis (estimated by the PICP biomarker), and the presence of a new CV event.

Method: A prospective cohort of 91 T2D patients, with a minimum follow-up of 3 years (mean: 4 years) was analysed. We evaluated the association between rates of change in GFR and PICP during follow-up (fold-change: end/initial) and their interaction with the development of a composite of cardiovascular (CV) events: CV death, stroke, ischaemic heart disease, atrial fibrillation, valvular heart disease and CV-related hospitalisation. In addition, ninety-two proteins were quantified in serum samples using a multiplex proximity extension assay with high-throughput protein detection technology (Olink proteomics, Cardiometabolic panel). Associations between variations in these proteins and changes in PICP and eGFR (all expressed as fold change from baseline) were assessed using linear regression analyses adjusted for their respective baseline values. All analyses were adjusted by multiple testing (Benjamini-Hochberg, FDR = 0.05%) using R software.

Results: Sixty-eight (74.7%) men and 23 (25.3%) women were included in the analysis. The mean age at baseline was 65.8 years, and the mean follow-up was 4 years (minimum 3 years). Sixteen cardiovascular events were recorded. An inverse association was observed between GFR and PICP (p = 0.003). Interaction analysis showed that this correlation occurred only in patients with incident CV events (p for interaction <0.001) (Fig. 1). By proteomic analysis (Fig. 2) several proteins were found to be significantly related to one of the three parameters studied (change in GFR, change in PICP and change with cardiovascular event), of which 3 proteins presented an overlap for all the parameters analysed: Lipocalin 2 (LCN2) and Insulin-like growth factor binding proteins 3 and 6 (IGFBP3 and IGFBP6). Interestingly, LCN2 and IGFBP6 were more highly expressed in patients with CV events whereas IGFBP3 was downregulated in these patients.

Conclusion: In patients with DKD, worsening ean function is associated with elevated circulating levels of the collagen synthesis biomarker PICP, particularly in those who developed at least one CV event. The link shown with LCN2, IGFBP-6 and IGFBP-3 shed light on possible multi-mechanistic pathways involved in DKD and narrow the scope towards a common pathway involving an interaction between pro-apoptotic and local inflammatory factors.
Figure 1:

Figure 2: