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PRO-INFLAMMATORY CYTOKINES IL-6 AND IL-17 DISPLAY A PARTICULAR MOLECULAR PATTERN IN ASSOCIATION WITH DYSREGULATED MIRNAS IN PATIENTS WITH TYPE 2 DIABETES MELLITUS IN THE EARLY STAGES OF DIABETIC KIDNEY DISEASE

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BACKGROUND AND AIMS: Glomerular injury and proximal tubule (PT) dysfunction have intricate mechanisms in diabetic kidney disease (DKD). Pro-inflammatory cytokines are involved in the initiation and progression of DKD through mediating the inflammatory response, both at glomerular and proximal tubular level. miRNAs are able to modulate cellular and biochemical functions, thus intervening in the pathogenesis of DKD.

The aim of the study, performed on patients with type 2 diabetes mellitus (DM), was to evaluate selective pro-inflammatory cytokines in relation to biomarkers of podocyte lesion and of PT dysfunction. Particular molecular pathways, such as specific miRNA profiles operating in this relation, have also been studied.

METHOD: A number of 126 patients with type 2 DM, staged by albuminuria [39 normoalbuminuric – urinary albumin/creatinine ratio UACR)<30mg/g; 45 microalbuminuric–UACR-30–300mg/g; 42 macroalbuminuric–UACR>300mg/g],

and 23 healthy control subjects were included in a cross-sectional study. All patients were evaluated concerning biomarkers of podocyte injury (nephrin, podocalyxin, synaptopodin) and of PT dysfunction [Kidney injury molecule-1(KIM-1), N-acetyl-beta-D-glucuronidase (NAG), alpha 1- microglobulin]. Also, serum and urinary levels of specific interleukins (IL-6, IL-17), serum cystatin C, and eGFR were determined. Serum and urinary miRNAs (miRNA-21, miRNA-124, miRNA-146a, miRNA-192) were assessed by RT-PCR.

RESULTS: The biomarkers of podocyte lesion and of PT dysfunction were increased, even in normoalbuminuric type 2 DM patients. Serum and urinary IL-6 and IL-17 showed increased levels in type 2 DM patients, across all groups studied. The model provided by univariable regression analysis showed that IL-6 and IL-17 correlated directly with biomarkers of podocyte injury (nephrin, podocalyxin, synaptopodin), of PT dysfunction (KIM-1, NAG, alpha 1-microglobulin), as well as with UACR. Negative correlations have been identified regarding eGFR.

In multivariable regression analysis, serum IL-6 correlated directly with synaptopodin, NAG, and negatively with eGFR ($p<0.00001$, $R2=0.805$); serum IL-17 correlated directly with synaptopodin, NAG, KIM-1, UACR, and negatively with eGFR ($p<0.00001$, $R2=0.941$); urinary IL-6 correlated directly with synaptopodin, NAG, and negatively with eGFR ($p<0.00001$, $R2=0.889$); urinary IL-17 correlated directly with synaptopodin, nephrin, NAG, and negatively with eGFR ($p<0.00001$, $R2=0.905$).

Also, important associations were found between specific interleukins and miRNAs. In univariable regression analysis, IL-6 and IL-17 correlated directly with miRNA-21 and miRNA-124, and negatively with miRNA-146a and miRNA-192. The models provided by multivariable regression analysis showed that urinary IL-6 correlated directly with urinary miRNA-21, and negatively with urinary miRNA-192 ($p<0.00001$, $R2=0.886$). Urinary IL-17 displayed direct correlations with urinary miRNA-21, and negative correlations with urinary miRNA-192 ($p<0.00001$, $R2=0.860$). Serum IL-6 correlated directly with serum miRNA-21, miRNA-124, and indirectly with serum miRNA-146a, miRNA-192 ($p<0.00001$, $R2=0.862$). Serum IL-17 showed direct correlations with serum miRNA-21, miRNA-124, and negative correlations with serum miRNA-192 ($p<0.00001$, $R2=0.745$).

CONCLUSION: In the early stages of DKD, there is an association of pro-inflammatory cytokines with specific miRNAs, and with biomarkers of podocyte injury and of PT dysfunction. IL-6 and IL-17, as well as dysregulated miRNA-21, miRNA-124, miRNA-146a, and miRNA-192 display a particular molecular pattern, in relation to complex mechanisms that can initiate and maintain the chronic inflammatory response in DKD. Routine detection of these interleukins may provide biomarkers to refine the diagnosis of early renal involvement in the course of type 2 DM, independently of albuminuria and level of renal function.