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Urinary annexin A3 and neutrophil gelatinase-associated lipocalin: Potential diagnostic biomarkers for diabetic nephropathy

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Diabetic nephropathy (DN) is one of the major complications of diabetes mellitus. Tubular lesions initially characterize DN before the glomerular injury. Therefore, albuminuria is not sufficient to diagnose DN. Urinary neutrophil gelatinase-associated lipocalin (*NGAL*) excretion is elevated in response to tubular injury. Annexin A3 (*ANXA3*) gene expression is found in mesangial cells of renal glomeruli and is linked to mesangial expansion. The aim of this study is to identify potential diagnostic urinary biomarkers for DN and their correlation with existing renal markers such as serum creatinine and estimated glomerular filtration rate. RNA extracted from urine samples (n = 82) including DN (n = 17), hypertensive nephropathy (n = 31), chronic kidney disease (CKD) with both diabetes and hypertension (n = 11), other cause of CKD (n = 13) and healthy controls (HC) (n = 10) were reverse transcribed and used for gene expression analysis using quantitative polymerase chain reactions. Gene expression of *ANXA3* and *NGAL* genes were analyzed against the reference gene, β2-microglobulin (*B2M*), using the relative quantification method. Fold changes (FC) of gene expression in DN, hypertensive nephropathy and other CKD study groups were calculated against HC. Log 2 normalized FC was used to study the significance level and correlation with existing serum markers. *NGAL* had greater than fourfold upregulation (FC = 9.83 ǂ 5.31) in DN patients compared with HC. The FC of *NGAL* in early and late DN was 11.68 ± 7.87 and 5.15 ± 3.07, respectively. Upregulation of the *ANXA3* gene was significantly high (p = 0.000), (FC = 782.91 ± 214.60) in DN compared to other chronic kidney diseases associated with hypertension and other causes. No significant correlation exists between the identified gene expression and existing serum markers (p > 0.05). *NGAL* has a good prognostic value for renal tubular injury-related biomarkers than glomerular-specific markers like albuminuria to diagnose DN and assess the disease progression. However, *ANXA3* could be a better biomarker for differential diagnosis of DN relative to the aetiology of CKD. The regulation of these genes and their related molecular pathways must be studied further in a large cohort for clinal validation.

Keywords: Annexin A3, diabetic nephropathy, Neutrophil Gelatinase-Associated lipocalin

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