# URINARY EXCRETION OF NEPHRIN, PODOCIN AND MINDIN AS EARLY MARKERS OF DIABETIC NEPHROPATHY (DN)

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## OBJECTIVES

Albuminuria (AU) level remains available noninvasive predictor of DN risk, regularly measured according to established guidelines. However, as shown by recent studies, both sensitivity and specificity of AU are not high enough for detecting the initial stage of DN. At the same time there is an exciting increase in our understanding that much of the early inciting events in DN stem from podocytes (Pds) pathology. Cytoskeletal Pds changes and foot process effacement are critically involved in the pathogenesis of DN.

**The aim of the study** was to assess urinary excretion of Pds proteins nephrin, podocin (an important slit diaphragm components) and mindin (integrin ligand for foot process fixation to the GBM and integrin ligand for inflammatory cell recruitment) in DM patients with different levels of AU and renal dysfunction, to clarify their significance as an early markers of DN.

## METHODS

74 DM pts were studied (type1 DM [T1DM] - 30, type2 DM [T2DM] - 44), including 41 pts with AU 10-30 mg/gCr (AU1), 13 pts with c AU 30-300 mg/gCr (AU2), 20 pts with proteinuria (PU). GFR>90 ml/min was revealed in 41 pts, GFR 90-60 ml/min – in 25 pts, GFR<60 ml/min – in 8 pts. Arterial hypertension (AH) was observed in 52 pts (70%), mainly in T2DM Urinary Pds biomarkers levels were measured by ELISA.

## RESULTS

High nephrinuria (NU), which not detecting in controls (> 5,84 ng/ml), and podocinuria (PdU) >1,73 ng/ml were revealed in 63% and 78% DM pts with AU1. The frequency of high NU and PdU increased gradually with AU growth, reaching maximum values (80 and 83%) in DN with PU. The mean NU level in overt DN was significantly higher than in AU1 and AU2 ($p<0,05$). Direct correlation was obtained between NU and AU ($R=0,47$ $p=0,03$), it was more strong in pts with AU2 ($R=0,947$ $p=0,01$). In pts with GFR<60 ml/min, regardless of DM type, there was direct relationship between the NU level and DM duration (fig.1). In DM duration less than 5 years NU correlated directly with HвA1c level (fig.2). These data reflect the key role of a hyperglycemia in podocytes dysfunction and emphasize the importance of glycemic control from the DM onset.

Potential role of mindin (as integrin ligand for foot process fixation to the GBM and integrin ligand for inflammatory cell recruitment) has been widely discussed in DN development (fig 3). The mean urinary mindin (Mnd) level in DM with AU1 has a tendency to increase compared to healthy; it increased significantly in pts with AU2 and PU and directly correlated with NU and PdU ($R=0,97$ $p<0,001$ and $R=0,984$ $p<0,001$). Correlation between urinary Mnd and PdU was detected even in short DM duration ($R= 0,998 < 0,001$). In DM course < 5years urinary Mnd correlated directly with HвA1C ($R=0,64$ $p=0,01$). NU and PdU in T1DM correlated directly with serum Cr level ($R=0,489$ $p=0,009$ and $R=0,468$ $p=0,02$) and indirectly with GFR ($R=-0,461$ $p=0,02$), emphasizing the role of Pds damage not only in glomerular permeability, but also in glomerulosclerosis formation. Systolic hypertension and NU correlated directly in T2DM pts ($R=0,53$ $p=0,029$), and strong correlation was obtained between urinary Mnd and arterial hypertension duration ($R=0,97$ $p=0,009$), reflecting also the hemodynamic mechanism of Pds injury in DM.

**Fig.1. Correlation between NU and DM duration**

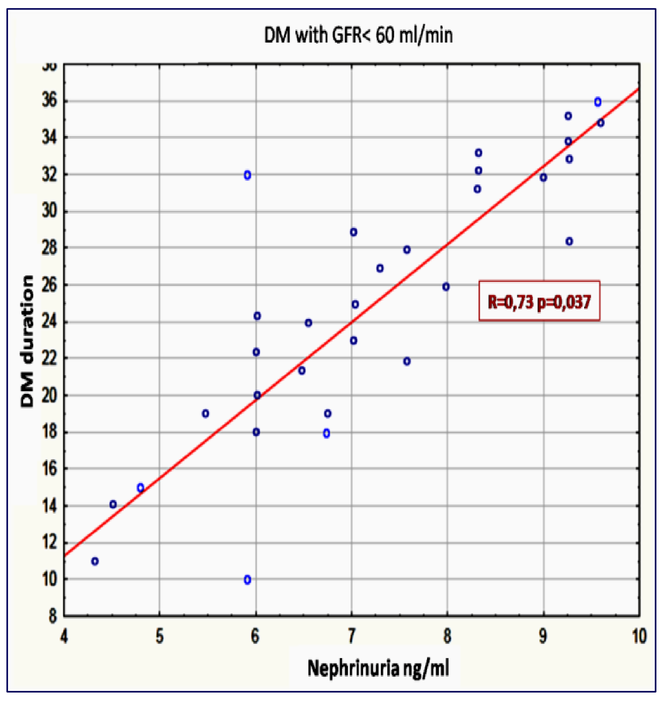



**Fig. 2. Correlation between NU and HвA1c level in DM pts**

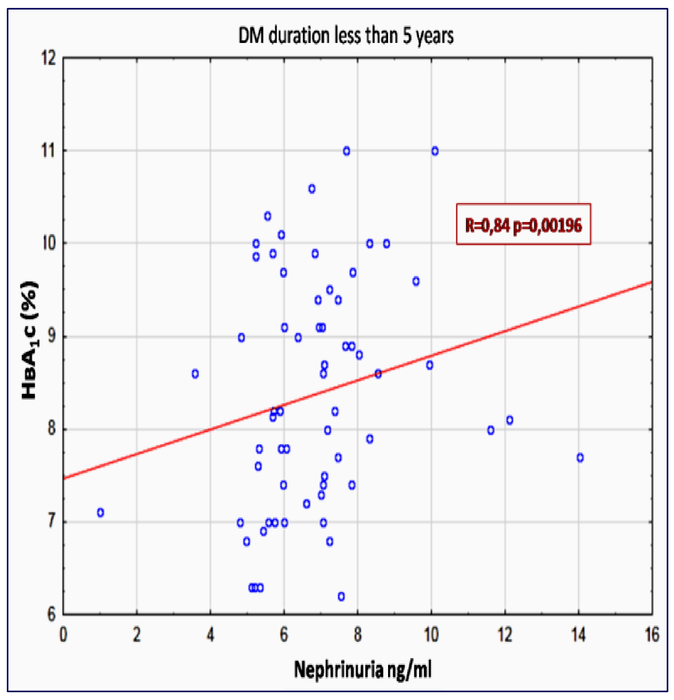
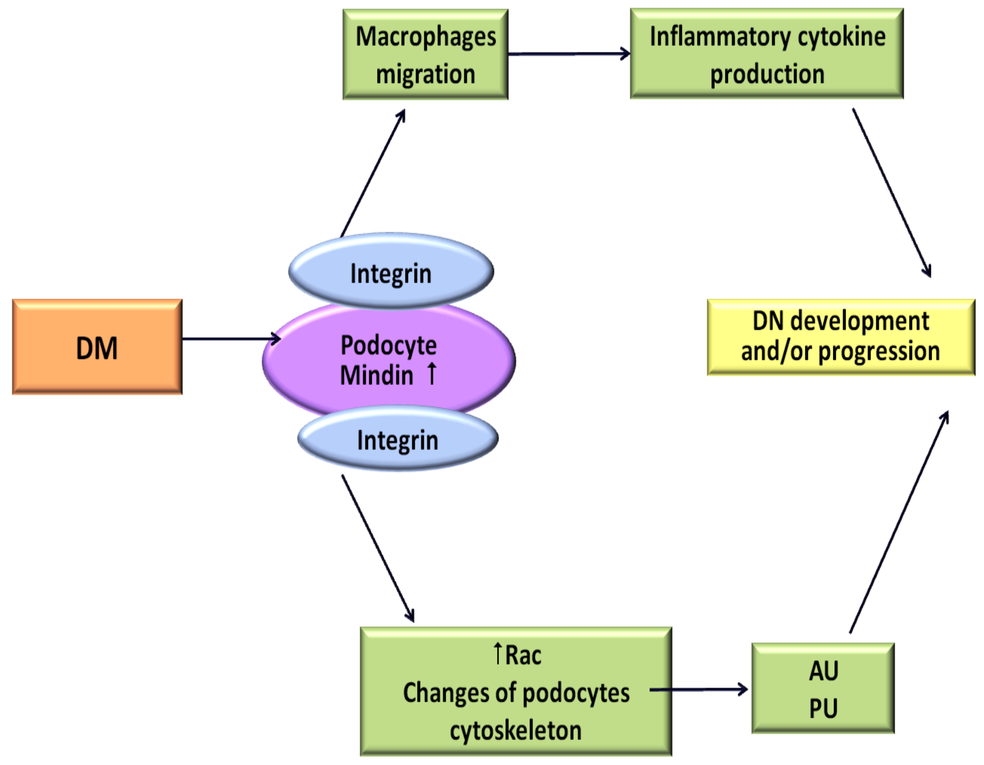



**Fig. 3. Potential role of mindin in DM**




## CONCLUSIONS

High urinary levels of podocytes damage markers reveal in many DM pts, preceding the development of clinically significant AU. The level of these indicators depends on DM duration, severity of glycemia and AH. Determination of of such urinary podocytes biomarkers as nephrin, podocin, mindin could be an useful tests for early identification and noninvasive monitoring of DN.


DOI: 10.3252/pso.eu.54ERA.2017