URINARY NEPHRIN AND ANGIOTENSIN CONVERTING ENZYME 2 EXCRETION - IMPORTANCE IN DIABETIC KIDNEY DIASEASE AND ITS PROGRESSION

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OBJECTIVES

It becomes increasingly recognized that functional and structural podocyte injury is an early and important event in diabetes associated kidney disease. Hyperglycemia, accumulation of advanced glycosilation end products and other metabolic alterations of diabetes may be responsible for podocyte injury. The latter can be quantified by increased urinary shedding of podocyte specific proteins such as nephrin. On the other hand, activation of the renin angiotensin system is considered a major component in the pathogenesis of diabetic nephropathy. The variant of the angiotensin conversing enzyme 2 (ACE2) cleaves angiotensin II into components with reduced proinflammatory and vasoactive potency and seems therefore to exert a renoprotective action. ACE2 is up-regulated in a counter-regulatory effort in diabetic associated kidney disease.
We aimed to determine for the first time to our knowledge the interrelation of urinary nephrin to urinary ACE 2 and to diabetes associated kidney disease in type 2 diabetic patients, as well as their importance as markers of progressive renal injury.

METHODS

We conducted an observational evaluation of type 2 diabetic patients. Routine laboratory evaluation; as well as nephrin and ACE 2 from a spot urine measurement (both also expressed as ratio to urinary creatinine) were obtained at baseline. A subset of patients was prospectively followed up for 3 years.

RESULTS

We included 75 patients. Characteristics of patients are presented in table 1. uNeph and u ACE2 were similar regardless of treatment with RAS blockers.
Albuminuric patients had higher uNeph (p=0.04) and somewhat higher $uACE_2$ (p=0.06), higher SBP and CRP than normoalbuminuric ones.

uNeph correlated to uACE2 (r=0.44, p<0.0001) and to UACR (r=0.25, p=0.032) – figure 1. In multivariate regression introducing parameters that are known to be related to DKD, $uACE_2$ (b=0.58, p<0.0001), Hb A1C (b=0.25, p=0.03), and LDL cholesterol (b=0.27, p-0.02), significantly predicted uNeph.
Using ROC curve a cut-off for uNeph of 451.63pg/ml was found. Patients with uNeph below this cut-off value had significantly lower uACE2 40.30(33.60-60.50) pg/mlversus 64.40(48.50-71.50) pg/ml p=0.0007. Logistic regression disclosed as significant predictor of uNeph above or below cut-off only $uACE_2$: OR=1.09; 95%CI(1.04-1.15), p=0.001.

Parameter	Value (n=75)
Age (years)	65.59±9.99
Male n(%)	48(64.0%)
Diabetes (years)	9(6-15)
BMI kg/m²	32.02±6.17
SBP(mmHg)	130(120-140)
DBP (mmHg)	80(70-80)
eGFR (ml/min)	82.44(55.96-95.65)
uACR (mg/g)	19.90(5.23-75.91)
Glycaemia(mg/dl)	143(126-178)
HbA1C (%)	7.50(6.65-8.96)
LDLC (mg/dl)	110.50±40.43
HDLC (mg/dl)	43.92±11.99
Trigl. (mg/dl)	143(104-212)
CRP (mg/dl)	0.34(0.18-0.67)
uNeph(pg/ml)	349.00±133.42
uNephCR(pg/g.)	5.47(3.55-7.57)
$uACE_2$(pg/ml)	45.50(36.35-62.60)
$uACE_2$CR (pg/g)	0.74(0.48-1.07)

Table 1: Characteristics of patients

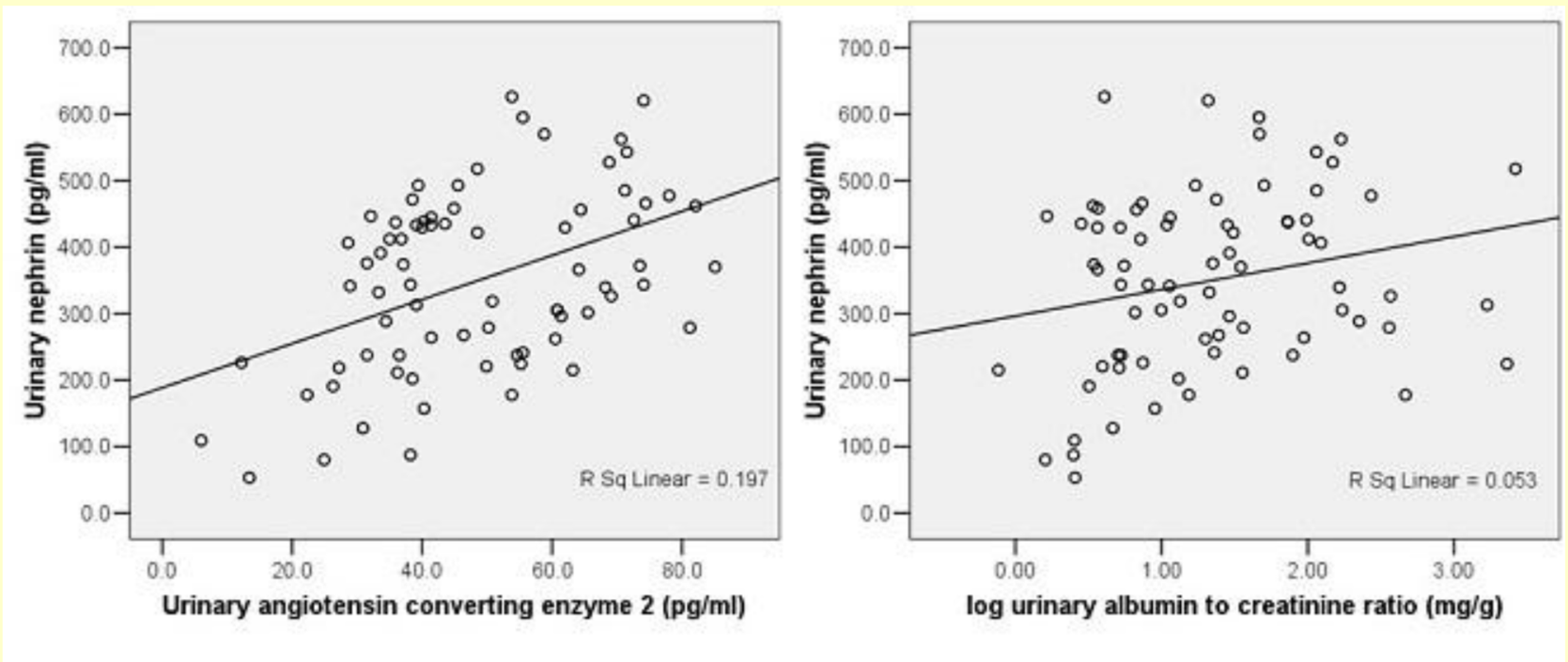

Figure 1: Correlation of uNeph to uACE2 and UACR

Fifty patients were followed up for 3 years. Mean decrease in eGFR (ΔGFR) was 2.50(-5.00-3.00) ml/min and mean increase in UACR was 4.34(-3.45-18.47)mg/g. Both nephrin to creatine ratio (r=-0.40, p=0.04) and ACE2 to creatinine ratio (r=-0.33, p=0.018) were related ΔGFR. – figure 2

DISCUSSIONS and CONCLUSIONS

Nephrin and ACE2 excretion are closely correlated in type 2 diabetes associated kidney disease and both predict decrease of eGFR over time. This might be explained by counter-regulatory up-regulation of ACE2 in early diabetic nephropathy which might have beneficial effects, as overexpression or administration of recombinant ACE2 ameliorates diabetic kidney injury in experimental settings. Human recombinant ACE2 has been synthetized and safely administrated to healthy volunteers, opening a potential therapeutic pathway. Nephrinuria might serve to identify patients who could benefit from this therapy.

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