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Predicting progression in ckd: Corin balances heart and renal systems

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OBJECTIVES

*B*Natriuretic peptides (NP) play a key role in regulation of salt and water balance and volume homeostasis. Once released, these peptides act on kidneys, blood vessels and adrenal glands, where they activate natriuretic peptide receptors (NPR), leading to natriuresis, diuresis and vasodilation, forming a negative feedback loop to reduce fluid volume and blood pressure (1,2). *In vitro* and *in vivo* studies demonstrated that both atrial (ANP) and brain (BNP) natriuretic peptides directly promote cardiovascular protective actions (3), as well as inhibit mesangial cell proliferation and renal fibrosis (4,5). Corin, a type II trans-membrane serine protease, is responsible for converting natriuretic peptide (pro-ANP) and pro-brain natriuretic peptide (pro-BNP) to active peptides (6,7).

It is primarily expressed in cardiomyocytes, but its mRNA has also been detected in renal tissue, especially in tubular, endothelial and perivascular cells, where it could be release into the circulation, due to membrane-bound form shedding (8).In particular, in renal epithelia, ANP mRNA was encountered together with corin expression in the proximal tubule, medullary thick ascending limb and medullary collecting duct, suggesting an immediate activation of pro-ANP and subsequent paracrine signalling (1). **Figure 1**

Clinical studies have examined circulating soluble corin in some diseases, such as heart failure, hypertension and preeclampsia. Impaired corin function were reported in patients who had hypertension and cardiac hypertrophy (9), as well as corin seems to play physiopathological roles in the pregnant uterus, promoting spiral artery remodelling and preventing gestational hypertension.

Moreover, in animal model, over-expression of corin has been linked to renal anti-fibrotic effects, through an increased intracellular cyclic guanosine monophosphate (cGMP) synthesis, inhibiting collagen synthesis and proliferation of fibroblasts.

To date, the association between corin and renal disease progression was not in-depth assessed.

Starting from these assumptions, the main aim was to examine the predictive and prognostic value of this protease for the progression of CKD.

METHODS

A prospective and observational study was designed, involving 189 non-dialysis patients referred to the outpatient clinic of our Nephrology and Dialysis Unit. Inclusion criteria were presence of CKD of stages 2-4 according to the National Kidney Foundation KDOQI guidelines and a stable renal function, defined as the absence of any transitory or permanent doubling in serum creatinine levels for at least 5 months before starting the study.

Patients with serum creatinine above 6 mg/dl and/or GFR < 15 ml/min, malignancy, liver, thyroid, or infectious diseases, severe proteinuria (> 3.5 g/d), inflammatory states, alterations in leukocyte count or formula and treatment with steroids or immunosuppressors, were excluded from the study. Moreover, patients with severe heart failure were also excluded, as well as patients with left ventricular ejection fraction < 50% or regional wall motion deficit assessed by echocardiography, due to the closely relationship between myocardial dysfunction and corin/NP system.

Furthermore, to limit confounding by cardiac dysfunction or volume overload, we enrolled clinically euvolemic CKD cohort without symptoms of cardiac disease. We measured circulating levels of BNP, hypothesizing that, in these patients, BNP can be shown to be relatively independent of GFR. All patients were considered eligible if BNP normal levels were detected. 50 healthy subjects (HS) were recruited as controls. Of the primary cohort of 189 patients, 160 could be followed prospectively over a period of 12 months. 29 patients (15%) were lost to follow-up because they moved or were not referred by their usual doctors to the study centre. Patients lost to follow-up had significantly better renal function.The study was approved by the local Ethic Committee, and all patients gave written informed consent.

Blood samples were drawn from all patients in fasting state in the morning during their regular visits. 24-h urine collection was also obtained in order to dose natriuria, albuminuria and proteinuria. Renal function measurements were performed using renal scintigraphy, with the administration of the radiopharmaceutical 99mTc-DTPA. Corin, measured using a commercial available ELISA kit (R&D Systems, Inc. Minneapolis) according to the manufacturer's instructions, was expressed as picograms per milliliter (pg/ml).

After the baseline assessments, patients were followed prospectively until the end of the observation period or the primary study endpoint was reached, defined as doubling of baseline serum creatinine, an accepted surrogate index of GFR slope (18), and/or the onset of end-stage renal disease (ESRD).

Statistical analyses were performed with NCSS for Windows (version 4.0), the MedCalc (version 11.0; MedCalc Software Acacialaan, Ostend, Belgium) software and the GraphPad Prisma.

For the analysis of corin as predictor of worsening of renal function, we performed univariate regression analysis with baseline corin as the independent variable and worsening of renal function (doubling of serum creatinine and/or ESRD) as dichotomic dependent variable. Subsequently, this association was adjusted for covariates that potentially could be confounders using multivariable regression models, built stepwise.

Receiver operating characteristics (ROC) analysis was employed to calculate the area under the curve for serum corin to find the best cut-off values capable of identifying CKD progression. Kaplan-Meier curves were generated to assess incidence of the progression of CKD in subjects with corin values above and below the optimal ROC-derived cut-off levels. Adjusted risk estimates for CKD worsening were calculated using univariate followed by multivariate Cox proportional hazard regression analysis.

RESULTS

Corin levels were higher in CKD patients than in healthy subjects (929.1 [575.1 to 1253.2] versus 678 [544-777.5] pg/ml, p<0.001), despite BNP levels did not differ in these two groups (18.7 [10-32.2] versus 12 [8-20.5] pg/ml, p>0.05). The associations between corin and left ventricular ejection fraction (b= -0.61,p=0.004), natriuria (b= -0.76,p=0.008), proteinuria (b=0.70,p=0.001), and pulmonary artery systolic pressure (b=0.56,p=0.01) were underlined by multiple regression model. During the follow-up, 41 patients (26%) reached the end-point. Patients with corin values above 1059 pg/ml experienced a significantly faster evolution to end-point, compared to patients with corin below the cut-off value indicated by ROC analysis.

Multivariable Cox regression analysis identified corin as a predictor of CKD progression (HR: 1.10; 95% CI: 1.06-1.16; p=0.001), independently of other potential confounders, including BNP.

Figure 2 Serum soluble corin levels in all enrolled patients and according to comorbiditiesA: While no differences were assessed in BNP levels between CKD and healthy subjects, in subject affected by chronic kidney disease high corin values have been detected. B: Diabetic patients and subjects with diabetic nephropathy were characterized by high corin levels, as well as observed in patients with positive history of myocardial infarction.

Figure 3 Receiver operating characteristics curves of serum corin considering renal disease progression as status variable.

The area under the curve for serum corin was 0.864 (95% CI: 0.80 to 0.91). The best cut-off value to predict decline of renal function was found to be 1059 pg/ml, with a sensitivity of 78 (95% CI: 62.4 to 89.4) and a specificity of 81.5 (95% CI: 73.4 to 88.0), whereas for proteinuria it was 905 mg/24h with a low sensitivity of 48.8 (95% CI: 32.9 to 64.9) and a valid specificity of 86.6 (95% CI: 79.1 to 92.1). The AUC for proteinuria was 0.719 (95% CI: 0.64 to 0.78) statistically different than those revealed for corin (p:0.02).

Figure 4 Kaplan-Meier survival curves of renal end-point in CKD patients with serum corin levels above and below the optimal receiver operating characteristics cut-off levels.

Patients with corin > 1059 pg/ml showed a significantly faster progression to endpoint

(log-rank test (c^2): 9.2; p: 0.002), with a hazard ratio of 0.35 (95% CI:0.1-0.6), with a mean follow-up time to progression of 5 months.

Figure 1

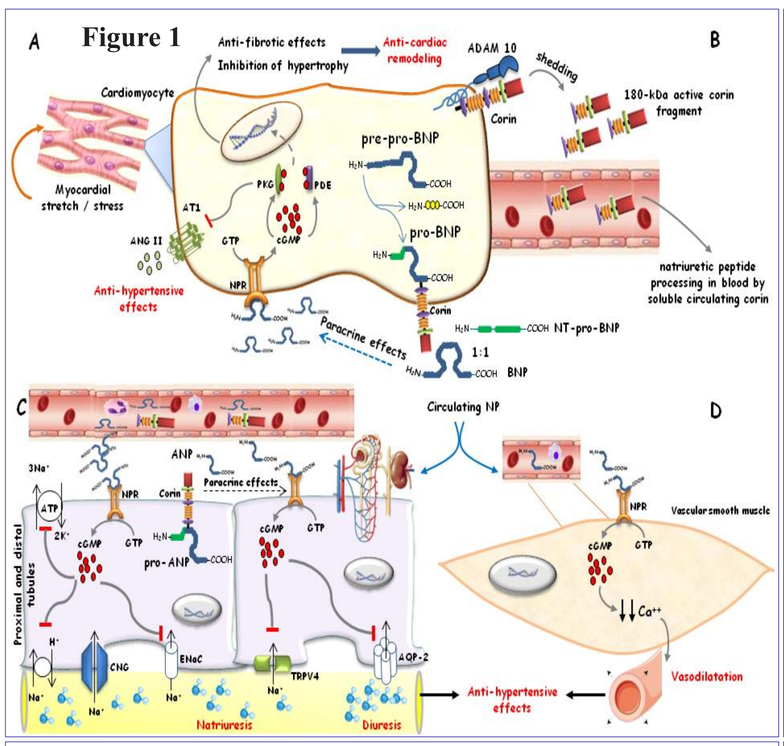


Figure 4

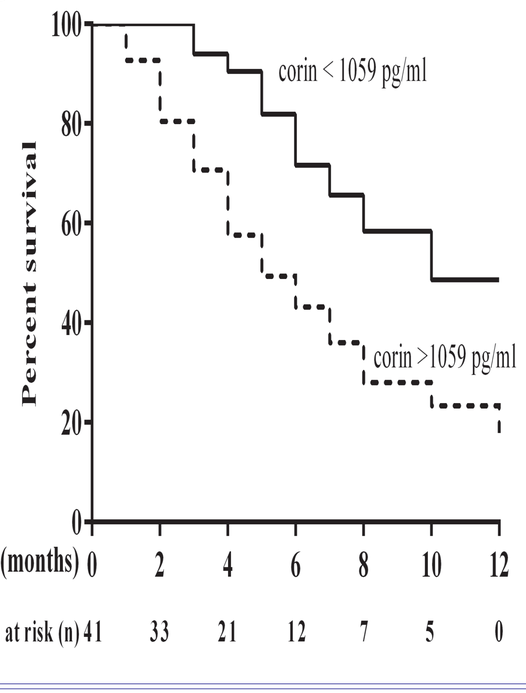


Figure 2

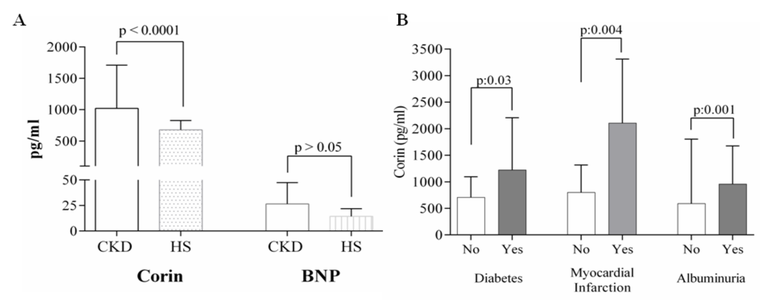
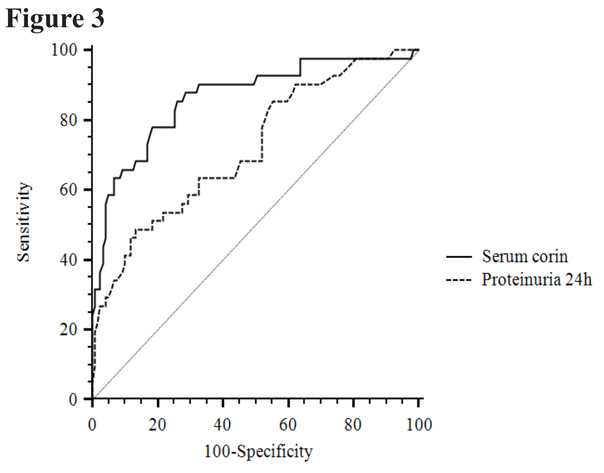


Figure 3



CONCLUSIONS

The findings from the present study clearly demonstrated that high levels of this protease were associated with accelerated progression of kidney disease. After adjustment for several factors, Corin emerged as an independent predictor of renal endpoints, providing prognostic information in addition to well-established risk markers, such as proteinuria, uric acid or markers of cardiac dysfunction. Moreover, BNP, whose values were similar in CKD and healthy subjects, did not influence these results, confirming that kidney dysfunction, alone, is not a major and unique contributor to increase its levels, as also revealed by several reports, in which low and/or normal BNP levels were observed in patients with reduced Gfr,

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