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Urinary neutrophil gelatinase associated lipocalin (NGAL), a marker of tubular damage, is increased in patients with chronic heart failure

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Abstract

Background
Renal impairment as measured by reduced glomerular filtration rate (GFR) and increased urinary albumin excretion (UAE) is prevalent in patients with chronic heart failure (CHF) and associated with reduced survival. The prevalence of structural tubular damage in CHF is unknown.

Methods and results
We investigated 90 CHF patients and 20 age and gender balanced healthy controls, and determined estimated GFR, UAE, N terminal pro brain natriuretic peptide (NT-proBNP) and urinary neutrophil gelatinase associated lipocalin (NGAL) as marker for tubular damage. CHF patients had significantly lower averaged estimated GFR (64 ± 17 vs 90 ± 12 mL/min/1.73m², P < 0.0001), but higher NT-proBNP and UAE levels (both P < 0.0001). Median urinary NGAL levels were markedly increased in CHF patients compared to controls (175 (70–346) vs 37 (6–58) μg/gCr, P < 0.0001). Both serum creatinine (r = 0.26, P = 0.006) and eGFR (r = -0.29, P = 0.002) were significantly associated with urinary NGAL levels as were NT-proBNP and UAE but to a lesser extent.

Conclusion
Renal impairment in CHF patients is not only characterised by decreased eGFR and increased UAE, but also by the presence of tubular damage, as measured by increased urinary NGAL concentrations.
Background

Renal dysfunction, as measured by decreased glomerular filtration rate (GFR), is common in chronic systolic heart failure (CHF) and associated with severely increased mortality and morbidity already apparent in the early stages of borderline renal dysfunction [1-3]. Even if GFR is only mildly impaired, increased urinary albumin excretion (UAE) levels, as a marker of early renal damage, are commonly observed in patients with CHF [4]. In primary renal disease, renal impairment is not only associated with decreased GFR and increased UAE, but also with the presence of structural tubular damage, as measured by increased urinary concentrations of specific tubular marker proteins [5-7]. One of these markers is neutrophil gelatinase associated lipocalin (NGAL), which has been shown to be highly increased in patients with acute and chronic renal injury in different clinical stages [5,8].

Aim

In the present study, we aimed to 1) investigate the prevalence of structural tubular damage as measured by urinary NGAL concentrations, 2) establish the relationship between urinary NGAL levels and estimated GFR, and 3) investigate the relationship between urinary NGAL levels and UAE, in patients with CHF.

Methods

In short, 90 outpatient CHF patients, aged ≥ 18 years, left ventricular ejection fraction (LVEF) < 45%, and clinically stable, were asked to participate. All patients were on angiotensin converting enzyme inhibitors and/or angiotensin II receptor blockers, and all medication had to be stable for at least 1 month. In addition, 20 healthy, age and gender matched controls were studied. All subjects gave informed consent to participate in the study, which was approved by the ethics review committee of the study centre. Baseline measurements included standard weight, height, systolic and diastolic blood pressure, serum creatinine, hemoglobin levels, N terminal-pro brain natriuretic peptide (NT-proBNP) and assessment of NYHA function class heart failure. LVEF was determined by nuclear ventriculography. Patients and controls collected 24-hours urine and urinary albumin excretion (UAE) was determined. Urinary creatinine was determined to correct for concentration of urine. Urinary NGAL was determined by means of a commercially available ELISA testkit from Antibody Shop (Gentofte, Denmark) and expressed as per gram urinary creatinine (μg/gCr). In brief, a monoclonal antibody against human NGAL, and biotinylated antibody against bound NGAL was used to detect NGAL in the urine samples. Horseradish peroxidase conjugated streptavidin was added, followed by color-forming peroxidase substrate containing tetramethylbenzidine. The color was then measured at 450 nm by a microtiter plate reader and compared with a standard curve. NGAL levels below the detection level were scored as 0.1 μg/gCr. Estimated GFR was calculated using the simplified modification of diet in renal disease formula (186.3 x serum creatinine^{ -1.154 } x age^{ -0.203 } (x 0.742 if female) (x 1.212 if black)) as validated in CHF patients [9].
Statistical analysis

Data are given as mean ± standard deviation when normally distributed, as median and interquartile range when skewed distributed. Differences between patients and controls were tested using Mann-Whitney U or students T testing where appropriate. Correlations were performed using Spearman’s correlation coefficients. Multivariate regression analysis was used to correct for eGFR when comparing patients with controls. All reported probability values are 2-tailed, and a P value < 0.05 was considered statistically significant. Statistical analyses were performed using SPSS, Chicago version 12.0.

Results

Clinical characteristics of patients and controls are summarized in Table 1. NGAL levels were highly elevated in patients with CHF (175(70–346) μg/gCr) compared to healthy controls (37 (6–58) μg/gCr, P < 0.0001) (Figure 1). Combining findings in CHF patients and controls, urinary NGAL levels were significantly related to eGFR (r = -0.29, P = 0.002) (Figure 2), serum creatinine (r = 0.26, P = 0.006), UAE levels (r = 0.33; P = 0.001) and NT-proBNP (r = 0.26, P = 0.007) (Figure 3). When adjusted for eGFR in multivariate analysis, CHF patients still had significantly higher urinary NGAL levels (P = 0.0004). Urinary NGAL levels were similar among different etiologies of heart failure, NYHA class and hemoglobin levels.

![Figure 1. NGAL and UAE levels in CHF patients versus controls. Shown are boxplots for urinary NGAL and UAE levels. Boxes display median (horizontal bars), interquartile ranges (lower and upper limits of boxes) and 5th and 95th percentiles (error bars). Abbreviations: CHF: chronic heart failure, NGAL: neutrophil gelatinase associated lipocalin, UAE: urinary albumin excretion.](image-url)
Conclusion

In the present study we show for the first time that structural tubular damage, as measured by increased urinary concentrations of NGAL, is highly prevalent in patients with CHF. Furthermore, across the spectrum of heart failure and healthy controls, urinary NGAL levels are not only associated with different indices of renal dysfunction, but also positively associated with increased levels of NT-proBNP.

NGAL is a 21 kD protein of the lipocalin family and is normally secreted in low amounts in lung, kidney, trachea, stomach and colon tissue [10]. NGAL levels are elevated in various...
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Figure 2. Relationship between eGFR and urinary NGAL levels. Abbreviations: CHF: chronic heart failure, eGFR: estimated glomerular filtration rate, NGAL: neutrophil gelatinase associated lipocalin.

Figure 3. Relationship between plasma NT-proBNP and urinary NGAL levels. Abbreviations: CHF: chronic heart failure, NGAL: neutrophil gelatinase associated lipocalin, NT-proBNP: N terminal-pro brain natriuretic peptide.
pathologic states, and possess bacteriostatic effects, by inhibition of iron-binding molecules that are important to certain bacteria. In renal failure both serum and urinary concentrations rise massively, and therefore (urinary) NGAL is thought to be a marker of tubular injury, an effect independent of its bacteriostatic properties [10].

NGAL has been associated with morphological changes and albuminuria in patients with primary renal disease, but never in patients with heart failure [5]. In CHF, reduced GFR is mainly dependent of reduced renal perfusion, which may serve as a hypoxic trigger for tubular damage [11,12]. In the chronic setting, patients with renal insufficiency due to IgA nephropathy had higher urinary NGAL levels compared to controls, and the urinary NGAL concentration also correlated strongly with the extent of tubulointerstitial injury [5].

Chronic renal hypoxia has not only been proposed as the final common pathway to end stage renal disease [12], but may also be the initiating trigger for a vicious circle between tubulointerstitial injury and chronic renal insufficiency [13]. This hypothesis may be one of the pathways by which chronic renal insufficiency may develop in patients with CHF.

Recently we hypothesized that also venous congestion might be a determinant of renal damage [14]. Plasma NT-proBNP levels were indeed correlated to NGAL levels, fitting this hypothesis, but may also be an expression of impaired cardiac systolic function leading to renal impairment.

NGAL has mainly been studied in the setting of acute renal failure. During cardiopulmonary bypass operation, patients who experienced acute renal dysfunction showed a marked in urinary NGAL levels, which preceded the increase in serum creatinine by a day [15,16]. In one single case of acute tubular necrosis due to heart failure induced hypotension, NGAL tubular expression was strongly increased [8].

Hence, measurements of NGAL may serve as a very early marker of worsening renal function, even preceding plasma serum creatinine rise. Urinary (or plasma) NGAL levels could therefore be used to adjust therapy, to anticipate and possibly prevent expected renal injury, even before a peak in serum creatinine occurs.

In conclusion, patients with CHF frequently suffer from a combination of reduced GFR, increased UAE and structural tubular damage. NGAL may serve as a novel non-invasive marker for (worsening) renal function in heart failure.
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Disclosures

None.
References


