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Neutrophil gelatinase-associated lipocalin (NGAL) correlations with cystatin C, serum creatinine and eGFR in patients with normal serum creatinine undergoing coronary angiography

Sir,

Neutrophil gelatinase-associated lipocalin (NGAL), a member of the lipocalin family, is readily excreted and detected in urine, due to its small molecular size (25 kDa) and resistance to degradation. NGAL is highly accumulated in the human kidney cortical tubules, blood and urine, after nephrotoxic and ischaemic injuries [1]. Thus, NGAL might represent an early, sensitive, non-invasive biomarker for acute renal injury [2], and urinary NGAL might serve as an early marker for ischaemic renal injury in children after cardiopulmonary bypass [3]. On the other hand, serum cystatin C was proposed as a new marker of glomerular filtration rate (GFR), even in chronic kidney disease [4]. Cystatin C has a low molecular weight (13 kDa) and is freely filtered and metabolized after tubular adsorption. Since interventional cardiologists are being asked more frequently to perform percutanous coronary intervention (PCI) on an increasing numbers of patients, contrast nephropathy is a more frequent and potentially serious complication of PCI. Since patients in invasive cardiology units are typically discharged within 24 h, rarely after 48 h, following PCI, it is extremely important to employ therapeutic approaches in the search for early detection markers of renal impairment. Therefore, we aimed to assess serum and urinary NGAL in relation to cystatin C, eGFR according to MDRD (81.04 ± 27.48 ml/min before PCI) and Cockcroft–Gault equations (69.85 ± 25.48 ml/min before PCI), and serum and urinary creatinine in 26 non-diabetic patients with normal serum creatinine, undergoing coronarography due to coronary artery disease. All the patients (mean age 63.4 ± 10.9 years, body mass index 29.1 ± 3.7 kg/m^2) were informed of the aim of the study and gave their consent; the protocol was approved by the local Ethics Committee. Duration of coronarography was 46.15 ± 16.36 min, volume of contrast agent administered 91.2 ± 25.4 ml (range 50–400 ml). All the patients were hypertensive, treated with statins and angiotensin-converting enzyme (ACE) inhibitors. Serum and urinary NGAL, serum cystatin C, and serum and urinary creatinine concentrations were evaluated before, and 2, 4, 8, 24 and 48 h after coronary angiography. NGAL was assessed using commercially available kits ELISA from ANTIBODYSHOP (Gentofte, Denmark). Serum cystatin C was measured using commercially available kits from Dade Behring. Data given were analysed using Statistica 6.0.PL. analysis of variance (ANOVA) or Kruskall–Wallis ANOVA for repeated measurements were used in statistical analysis with $P < 0.05$ considered statistically significant, when appropriate. We found a significant rise in serum NGAL after 2 and 4 h, and in urinary NGAL after 4 and 8 h after coronary angiography (Table 1). Creatinine clearance did not change significantly during 48 h (before PCI, 92 ± 26 ml/min; after 24 h, 84 ± 27 ml/min; after 48 h, 89 ± 28 ml/min). Serum and urinary NGAL returned to baseline values 48 h after the PCI. Serum cystatin C increased significantly 24 h after the coronary angiography and then decreased after 48 h, while serum and urinary creatinine remained unchanged. Before coronary angiography, serum NGAL was related significantly to serum creatinine (0.70, $P < 0.01$), urinary NGAL ($R = 0.40$, $P < 0.05$), age ($R = 0.41$, $P < 0.05$), eGFR by MDRD ($R = -0.50$, $P < 0.01$), Cockcroft–Gault ($R = -0.51$, $P < 0.01$) and cystatin C ($R = 0.63$, $P < 0.01$). Serum NGAL 2 h after coronary angiography correlated significantly with serum creatinine ($R = 0.65$, $P < 0.01$), time of coronary angiography ($R = 0.39$, $P < 0.05$), urinary NGAL ($R = 0.40$, $P < 0.05$), eGFR by MDRD ($R = -0.39$, $P < 0.01$), Cockcroft–Gault ($R = -0.40$, $P < 0.01$) and cystatin C ($R = 0.47$, $P < 0.01$). In our preliminary study on the small cohort of patients with normal serum creatinine, we found a significant rise in serum NGAL after 2 and 4 h and a significant rise in urinary NGAL after 4 and 8 h after coronary angiography. Cystatin C rose significantly 24 h after the procedure. Serum creatinine and creatinine clearance remained unchanged after procedure. When we defined contrast nephropathy as a 25% increase in cystatin-C from baseline values, then we calculated sensitivity and specificity of a respective 25% serum and urinary NGAL increase to detect this cystatin-C increase. We found 68% sensitivity and 76% specificity of serum and 80% sensitivity and 83% specificity of urinary NGAL increase.

Table 1. Kidney function assessed by serum and urinary NGAL, serum and urinary creatinine and cystatin C in 25 non-diabetic patients undergoing coronary angiography

	Before coronary angiography	2 h	4 h	8 h	24 h	48 h
Serum NGAL (ng/ml)	105.32 ± 67.54	129.82 ± 87.30*	138.40 ± 85.12*	122.76 ± 102.40	120.08 ± 95.16	107.89 ± 85.73
Urinary NGAL (ng/ml)	11.1 ± 15.81 (0.2–65.4)	11.8 ± 30.91 (0.2–98.2)	17.8 ± 34.48 (0.2–98.8)*	25.2 ± 48.21 (6.4–181.8)*	15.1 ± 44.71 (1.4–118.8)	12.7 ± 22.82 (0.2–98.2)
Cystatin C (mg/l)	1.69 ± 1.03	1.77 ± 1.03	1.76 ± 0.95	2.31 ± 1.67	2.85 ± 2.05**	1.79 ± 1.02
Creatinine (mg/dl)	1.12 ± 0.21	ND	ND	ND	1.19 ± 0.43	1.15 ± 0.21
Urinary creatinine (mg/dl)	107.00 ± 45.22	92.81 ± 44.69	79.03 ± 39.69	66.20 ± 36.06	114.93 ± 59.73	124.31 ± 42.92

*$P < 0.05$, **$P < 0.01$ *vs* baseline.
ND, not done.

This is the first study to examine prospectively a novel marker of acute renal injury in patients undergoing coronary angiography, as well as correlations between NGAL and other markers of kidney function: cystatin C, eGFR and serum creatinine. Volume of contrast agent was not related to urinary and serum NGAL and cystatin C. A similar correlation between time of the surgery and NGAL was reported by Mishra *et al*. [3]. Serum creatinine correlated significantly with both serum and urinary NGAL. It is interesting that a rise in serum NGAL was observed as early as 2 h after coronary angiography and lasted for 4 h. In urine, NGAL increased after 4 h and remained significantly elevated relative to baseline 8 h after the procedure. A similar pattern of changes was reported by Mishra *et al*. [3]. They found a rise in serum and urinary NGAL in samples taken as early as 2 h or at the first available sample after cardiopulmonary bypass in children who developed, as well as who never developed acute renal failure. In this population, a rise was smaller, but also significant. An earlier NGAL rise in serum, than in urine, in our study may be due to the fact that NGAL was released into the circulation probably secondary to inflammatory activation of neutrophils initiated by coronary angiography. Moreover, since NGAL is increased in atherosclerotic plaques [5], it might also be released into the circulation during the procedure. Patients with ischaemic heart disease often exhibit some degree of renal dysfunction due to concomitant diabetes, hypertension or congestive heart failure, despite normal serum creatinine [6]. Studies have suggested that serum cystatin C may have advantages over serum creatinine for estimating GFR, however, with some limitations [7]. We confirmed the findings of Rickli *et al*. [8] that the increase of cystatin C achieved a maximum at 24 h after the application of the contrast agent, and within 48 h, cystatin C decreased to the same level as before angiography. Since there are few reports on NGAL and kidney function, we decided to simultaneously assess NGAL, serum cystatin C, creatinine and eGFR and then to study their relationships. It should be stressed that NGAL correlated with both cystatin C and creatinine. The strength of our study is its prospective design, simultaneous measurement of urinary and serum NGAL as well as cystatin C. The limitations are, that this study is preliminary, single-centre, and on patients with normal serum creatinine, who did not develop contrast nephropathy. Our findings may have important implications for the clinical management of patients undergoing coronary angiography. The 'window of opportunity' is narrow in contrast nephropathy, and time is limited to introduce proper treatment after initiating insult, particularly when patients are discharged within 24 h after the procedure. Therefore, the search for a new biomarker of renal dysfunction continues. NGAL, due to its sensitivity and specificity, could be valuable in the detection of acute renal impairment.

Conflict of interest statement. None declared.

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