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1. Kittisupamongkol W. Not all that itches is uraemic pruritus. *Nephrol Dial Transplant* 2009; doi: 10.1093/ndt/gfp239
2. Pauli-Magnus C, Mikus G, Alscher DM *et al*. Naltrexone does not relieve uremic pruritus: results of a randomized, double-blind, placebo-controlled crossover study. *J Am Soc Nephrol* 2000; 11: 514–519
3. Neilly J, Martin A, Simpson N *et al*. Pruritus in diabetes mellitus: investigation of prevalence and correlation with diabetes control. *Diabetes Care* 1986; 9: 273–275
4. Weisshaar E, Mattered U, Mettang T. How do nephrologists in haemodialysis units consider the symptom of itch? *Nephrol Dial Transplant* 2009; 24: 1328–1330
5. Zucker I, Yosipovitch G, David M *et al*. Prevalence and characterization of uremic pruritus in patients undergoing hemodialysis: uremic pruritus is still a major problem for patients with end-stage renal disease. *J Am Acad Dermatol* 2003; 49: 842–846
6. Patel TS, Freedman BI, Yosipovitch G. An update on pruritus associated with CKD. *Am J Kidney Dis* 2007; 50: 11–20
7. Ständer S, Weisshaar E, Mettang T *et al*. Clinical classification of itch: a position paper of the International Forum for the Study of Itch. *Acta Derm Venereol* 2007; 87: 291–294

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Reduction in urinary excretion of neutrophil gelatinase-associated lipocalin by angiotensin receptor blockers in hypertensive patients

Sir,

We recently read a paper published by Bolignano *et al*. who investigated the association between urinary levels of neutrophil gelatinase-associated lipocalin (Ngal) and severity of renal disease in proteinuric patients [1]. Urinary Ngal is largely and rapidly increased during courses of acute kidney injury (AKI), making it especially useful for early diagnosis of AKI [2–5], but its clinical impact on chronic kidney disease (CKD) remains elusive. They studied non-diabetic patients having >1 g/day of proteinuria at least for 6 months and also healthy subjects, and reported that urinary Ngal concentrations were significantly associated with the extent of proteinuria, and inversely with the estimated glomerular filtration rate. The group also revealed in another study that the elevated urinary Ngal level was a predictor of CKD progression [6].

Our team has also evaluated the correlation between urinary Ngal levels and clinical parameters in CKD patients and observed similar findings. Since the response of urinary Ngal levels to treatment has not been analysed well, here we carried out a prospective observational study. We chose a cohort of 26 hypertensive patients having either

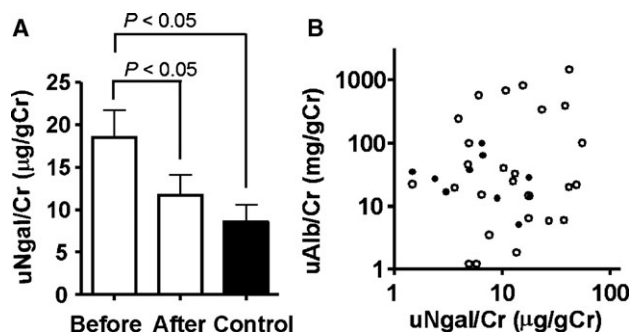


Fig. 1. Urinary Ngal and albumin levels in hypertensive patients having either obesity or diabetes. (A) Mean (\pm SEM) urinary Ngal/urinary creatinine ratios (uNgal/Cr) in patients before and 3 months after treatment with angiotensin receptor blockers, as well as in healthy controls. Comparison was carried out by paired and unpaired *t*-tests. (B) No significant correlation was observed between urinary Ngal and urinary albumin excretion (uAlb/Cr) before the treatment in patients with hypertension (open circles, $n = 26$), when analysed with or without healthy controls (closed circles, $n = 10$), by linear regression analysis.

diabetes ($n = 2$), obesity (15) or both (9), and treated them with angiotensin receptor blockers (ARBs). They included 15 males and 11 females who had ages of 55.5 ± 3.0 years (mean \pm SEM), body mass index of 32.8 ± 1.2 kg/m², serum creatinine of 0.82 ± 0.06 mg/dl and estimated glomerular filtration rate of 79.1 ± 6.5 ml/min/1.73 m² (calculated by a Japanese formula revised in year 2009 [7]). Ten healthy volunteers were also studied: 6 males and 4 females with a mean age of 55.7 years. Clinical parameters including urinary Ngal were examined before and 3 months after initiation of the treatment. Hypertension was defined as systolic blood pressure (BP) ≥ 140 , diastolic BP ≥ 90 mmHg or taking antihypertensive reagents. Diabetes was determined as blood HbA1c level $\geq 6.5\%$. Subjects with a body mass index ≥ 25 kg/m² were considered obese. Patients neither took any other inhibitors of the renin–angiotensin system, nor were given altered oral regimen during the course. ARBs were chosen from candesartan 12 mg, olmesartan 20 mg or telmisartan 40 mg by the treating physician's preference ($n = 14$, 7 or 5, respectively). The study was carried out in subjects followed at outpatient clinics of Kyoto University Hospital and Kyoto Medical Center, and was approved by ethical committees in those institutes. Patients gave written informed consent.

Before administration of ARBs, hypertensive patients had significantly elevated urinary Ngal levels as compared to healthy controls (Figure 1A). After 3 months of treatment, mean BP was reduced from $158 \pm 3/92 \pm 2$ to $143 \pm 2/82 \pm 2$ mmHg ($n = 26$, $P < 0.001$). All three ARBs similarly decreased systolic and diastolic BP by $\sim 10\%$ (supplementary Table S1). At the same time, urinary excretion of both Ngal and albumin was decreased by 36% (Figure 1A) and 46%, respectively. A similar trend was observed when patients were divided into ones having normoalbuminuria, microalbuminuria or macroalbuminuria ($n = 14$, 6 or 6, respectively; supplementary Table S2). Of note, urinary Ngal and albumin concentrations before ARB treatment were not significantly correlated with each other (Figure 1B, $P > 0.05$), suggesting that these two measurements may

reflect independent aspects of renal disorders, especially when the level of proteinuria is not very severe.

To our knowledge, this is the first report to show that short-term administration of ARBs significantly reduced urinary Ngal levels in human subjects. Consistently, we have recently observed that ARBs suppressed urinary excretion of Ngal in diabetic mice induced by streptozotocin (STZ) [8]. The concentrations of Ngal were much higher in STZ diabetic mice than human subjects investigated in this study, which may be explained by the difference in the extent of hyperglycaemia and by the species difference concerning Ngal protein metabolism. Furthermore, the treatment of nephrotic patients with steroids and other immune suppressants immediately reduced urinary Ngal excretion [8]. These findings warrant intensive research concerning usefulness of urinary Ngal as a monitoring marker of CKD.

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Conflict of interest statement. None declared.

Supplementary data

Supplementary data is available online at <http://ndt.oxfordjournals.org>.

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1. Bolignano D, Coppolino G, Campo S *et al.* Urinary neutrophil gelatinase-associated lipocalin (NGAL) is associated with severity of renal disease in proteinuric patients. *Nephrol Dial Transplant* 2008; 23: 414–416
2. Mori K, Lee HT, Rapoport D *et al.* Endocytic delivery of lipocalin-siderophore-iron complex rescues the kidney from ischemia-reperfusion injury. *J Clin Invest* 2005; 115: 610–621
3. Mishra J, Dent C, Tarabishi R *et al.* Neutrophil gelatinase-associated lipocalin (NGAL) as a biomarker for acute renal injury after cardiac surgery. *Lancet* 2005; 365: 1231–1238
4. Mori K, Nakao K. Neutrophil gelatinase-associated lipocalin as the real-time indicator of active kidney damage. *Kidney Int* 2007; 71: 967–970
5. Coca SG, Yalavarth R, Concato J *et al.* Biomarkers for the diagnosis and risk stratification of acute kidney injury: a systematic review. *Kidney Int* 2008; 73: 1008–1016
6. Bolignano D, Lacquaniti A, Coppolino G *et al.* Neutrophil gelatinase-associated lipocalin (NGAL) and progression of chronic kidney disease. *Clin J Am Soc Nephrol* 2009; 4: 337–344
7. Matsuo S, Imai E, Horio M *et al.* Revised equations for estimating GFR from serum creatinine in Japan. *Am J Kid Dis*, (2009 Epub)

8. Kuwabara T, Mori K, Mukoyama M *et al.* Urinary neutrophil gelatinase-associated lipocalin levels reflect damage to glomeruli, proximal tubules, and distal nephrons. *Kidney Int* 2009; 75: 285–294

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Reply

Sir,
 We have read with great interest the results published by Kasahara and co-workers, which confirm that NGAL is becoming more than a promising biomarker of acute renal injury.

Various human studies confirmed the utility of NGAL dosage for the stratification of AKI risk after procedures, potentially detrimental to the kidney. Moreover, it is demonstrated that NGAL plays a role in the onset and progression of chronic kidney disease [1].

Nevertheless, we think that the most interesting NGAL future application could be represented by the evaluation of this marker in response to different acute and chronic therapies. Recently, our group described a strong reduction in urinary NGAL levels in patients affected by steroid-resistant nephrotic syndrome treated with high doses of human immunoglobulins; this reduction was observed immediately after intravenous Ig administration and persisted even 24 h later [2].

If confirmed in different situations, these early variations in NGAL levels could help to predict the effectiveness of different therapeutical approaches, in order to personalize the treatment of nephrotic patients.

Kasahara and co-workers did not describe any relationship between NGAL urinary excretion and albuminuria. Nevertheless, in a recent study conducted on 56 diabetic patients classified according to glomerular damage (normo-, micro- and macroalbuminuria), NGAL levels directly correlated with the severity of the glomerular impairment and they were higher in normoalbuminuric patients than in controls [3]; these findings suggest a parallelism between tubular impairment and glomerular damage and a potential role for NGAL as a marker of diabetic nephropathy even earlier than microalbuminuria.

Enlarging the group of patients affected by arterial hypertension enrolled in the study, we wonder if Kasahara *et al.* may extend their observations also to this pathologic condition, which significantly involves the renal tubule.

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1. Bolignano D, Lacquaniti A, Coppolino G *et al.* Neutrophil gelatinase-associated lipocalin (NGAL) and progression of chronic kidney disease. *Clin J Am Soc Nephrol* 2009; 4: 337–344