


**doi**:10.1093/ndt/gfl381

**Advance Access publication 19 August 2006**

**Albininuria is an independent predictor of decreased serum erythropoietin levels in type 2 diabetic patients**

Sir,

Anaemia occurs more commonly in patients with diabetic nephropathy than those with non-diabetic renal diseases [1]. Reduced erythropoietin (EPO) production has been implicated as a predominant cause of anaemia in patients with diabetic nephropathy [1,2]. EPO is produced in peritubular fibroblasts in the renal cortex [3]; therefore, tubulointerstitial damage in diabetic nephropathy may contribute to EPO deficiency. Although previous studies demonstrated that decreased haemoglobin is associated with both reduced glomerular filtration rate (GFR) and increased albuminuria in diabetes [1,2], information is scarce regarding the independent effects of these parameters on serum EPO levels in diabetic patients with nephropathy. We, therefore, conducted this cross-sectional study to determine factors that contribute to decreased EPO levels in type 2 diabetic patients with albuminuria.

Adult type 2 diabetic patients with clinical albuminuria were recruited from the outpatient clinic of the Diabetes Centre, Tokyo Women’s Medical University Hospital, in Tokyo, Japan. Subjects were excluded if they had been treated with dialysis, and had received recombinant human EPO or oral/intravenous iron. At a regular visit, patients provided a first morning urine specimen. Non-fasting blood was drawn to determine serum EPO concentration as well as routine laboratory tests. Serum and urinary EPO levels were measured by radioimmunoassay, with a detection limit of 5.0 mU/ml. Urinary EPO levels <5.0 mU/ml were treated as 4.0 mU/ml. Albumin-to-creatinine ratio (ACR) was calculated from urinary albumin and creatinine concentrations; clinical albuminuria was defined as an ACR ≥300 mg/g Cr. Glomerular filtration rate (GFR) was estimated using the Modification of Diet in Renal Disease Study group equation, refitted for Japanese individuals [4]. To determine which parameters are associated with serum EPO levels, simple correlational analysis and multivariate regression analyses with stepwise selection procedure were performed. For univariate correlation analyses, the Spearman’s correlation coefficient ($R_s$) was calculated. For multiple regression analysis, age, sex, haemoglobin A1C, urinary ACR, estimated GFR (GFR), and the usage of ACE inhibitors and ARBs were included as covariates; serum EPO, eGFR and urinary ACR were logarithmically transformed to improve normality. A P-value <0.05 was considered statistically significant.

We studied a total of 269 type 2 diabetic patients with clinical albuminuria, 71 women and 198 men, with a mean (±SD) age of 61 ± 12 years. Mean serum creatinine was 1.91 ± 1.42 mg/dl (range: 0.38–10.15) and blood haemoglobin was 11.9 ± 2.0 g/dl (8.0–17.3). Geometric mean eGFR, urinary ACR and serum EPO were 31.5 ml/min/1.73 m² (4.6–100.3), 1400.3 mg/g Cr (300–11213.9), and 21.9 mU/ml (8.8–85.3). Among 269 patients, 81 patients were treated with an angiotensin-converting enzyme (ACE) inhibitor, 140 with an angiotensin receptor blocker (ARB), 150 with a diuretic and 55 with other antihypertensives. In univariate correlational analyses, serum EPO correlated positively with age ($R_s = 0.204$, $P < 0.001$) and inversely with ACR ($R_s = −0.188$, $P = 0.002$). There was no significant correlation between serum EPO and eGFR ($R_s = 0.107$, $P = 0.080$) or blood haemoglobin ($R_s = 0.052$, $P = 0.398$). In the multiple regression analysis, age and logarithmic ACR remained in the model as variables significantly associated with logarithmic serum EPO, with the standardized partial regression coefficient of 0.198 ($P = 0.002$) for age and −0.127 ($P = 0.049$) for logarithmic ACR; the association between logarithmic eGFR and serum EPO was marginal (standardized partial regression coefficient: 0.109, $P = 0.087$). Urinary EPO was undetectable in 75% of patients. There was no significant correlation between urinary EPO and ACR ($R_s = 0.0143$, $P = 0.834$).

In this cross-sectional study, we demonstrate for the first time that lower serum EPO levels was independently associated with increased albuminuria but not with reduced GFR in diabetic patients. In glomerular diseases, increased protein filtration through the glomeruli, including filtration of cytotoxic cytokines, causes tubulointerstitial injury. We hypothesize that glomerular–proteinuria-induced tubulointerstitial damage, and the consequent reduced number of EPO-producing peritubular fibroblasts, may be responsible for decreased serum EPO levels, irrespective of GFR levels.

Another possibility for the decreased EPO levels may be due to increased glomerular filtration of EPO [5], which has a molecular weight of 30-400. Our present data do not support this hypothesis, as there was no relationship between urinary EPO and albuminuria, in accordance with an earlier study of children with nephrotic syndrome [6]. However, direct measurement of urinary EPO may be problematic due to conformational changes in EPO epitope following glomerular filtration.

In conclusion, we found that increased albuminuria was independently associated with decreased serum EPO levels in patients with type 2 diabetes regardless of GFR. Reduced EPO production of peritubular cells is most likely associated with lower EPO levels. Urinary loss of EPO should be determined by more sophisticated methods.

**Conflict of interest statement.** None declared.

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Unusual adult-onset manifestation of an attenuated Bartter’s syndrome type IV renal phenotype caused by a mutation in BSND

Sir,

Bartter’s syndrome (BS) comprises a range of overlapping autosomal recessive renal salt-losing phenotypes, characterized by hypocalaemic metabolic alkalosis. The antenatal BS autosomal recessive renal salt-losing phenotypes, characterized by hypocalaemic metabolic alkalosis. The antenatal BS comprises a range of overlapping categories, including the classic BS caused by mutations in the BSND gene [1]. This gene encodes barttin, an essential β-subunit for ClC-Ka and ClC-Kb chloride channels in basolateral membranes of renal tubular epithelia and inner ear [2]. BS type IV presents with life-threatening neonatal volume depletion accompanied by hypocaemia [3,4]. Chronic renal failure frequently develops during infancy [1,3], although this finding is not uniformly reported [4], but persistent hypercalciuria and nephrocalcinosis are unusual findings.

Herein we report a deaf daughter of consanguineous parents, who was referred to our nephrology unit for the first time at the age of 20, because of refractory hypocaemia. The patient was born by vaginal delivery, and although the mother had a large amount of amniotic fluid on ultrasound examination during pregnancy, the postnatal period was unremarkable until the 2nd year of life, when parents noticed hearing loss and she was diagnosed with congenital hearing loss. The same mutation was also described, bilateral nephrocalcinosis, given the absence of hypercalciuria, were reported. The same mutation was also described, in homozygosity, in two additional Spanish kindreds, with affected individuals presenting polyhydramnios, premature birth and salt loss, although not as severe as usually reported for BS type IV [6]. Since the co-expression of p.G47R barttin and CIC-Ka resulted in a Cl− current reduction to the same extent as those observed for other missense mutations [2], we can hypothesize that this allele enables barttin to retain some residual function with CIC-Kb, therefore conditioning a milder phenotype. In addition, the better long-term GFR preservation possibly allows for the filtered calcium to be excreted more efficiently as those observed for other phenotypes.