requisites are actually present in children, this does not imply that this is the best way to ‘physiologically’ interpret GFR values. We would favour GFR percentiles as it has been nicely proposed by Piepsz et al. [3,5].

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RAAS blockade in combination with diuretic therapy increases urine excretion, which in turn increases drinking and thus reduces erythropoietin and proteinuria

Dear Sir,

In the recent article by Slagman et al. [1] published in March 2010 (Nephrol Dial Transplant issue), the renin–angiotensin–aldosterone system (RAAS) blocker losartan (LOS), with and without a diuretic, was used to examine—in a randomized, double-blind, placebo-controlled, crossover design—erythropoietin (EPO), haemoglobin and proteinuria in chronic kidney disease patients with preserved renal function on either a low or high salt diet. Although the conclusion is that addition of a diuretic to LOS treatment is effective in decreasing EPO via a reduction in renal oxygen requirement, there are several components of the study that merit comment. The authors note that EPO levels are already inappropriately low to begin with which would indicate that they may have been lowered by the stimulatory effect of angiotensin on EPO [2]. This could indicate that there were perhaps lowered levels of plasma angiotensin which would beg the question as to why LOS was used in the first place. The effect of the low or high salt diet is barely mentioned.

I have suggested previously that one of the actions of antagonism of the RAAS is to increase urine production which would have the effect of increasing fluid intake via drinking [3]. LOS alone decreased proteinuria and plasma haemoglobin concentrations which could have been due to a dilutional effect from the resulting increased blood volume. Addition of a diuretic, which would have increased urine output, and thus stimulated fluid intake, further enhanced the action of LOS, especially in the case of EPO, which could once again suggest a possible dilutional action. An increased fluid intake has been suggested as the mechanism for reduced microalbuminuria in diabetical patients treated with RAAS blockers [4].

Under normal physiological circumstances, chronic hypoxia, as well as hypovolaemia, leads to the activation of the RAAS [5]. Thus, there could be a functional link between hypovolaemia, tissue perfusion and tissue hypoxia. Angiotensin has a role in the regulation of erythropoietin production as part of the signals of the feedback loop of blood volume regulation [2]. This would imply that, with hypovolaemia, there could also be hypoxia. Thus, with increased fluid intake, blood volume would be restored, at least partially, thus leading to decreased RAAS activation and decreased EPO release.

In conclusion, it could be that hypovolaemia induces sub-chronic metabolic dysfunction via hypoxia-induced mitochondrial dysfunction [5] through lowered tissue perfusion, and thus lowered oxygen supply which would activate EPO production. It would, thus, be of interest to study RAAS antagonist-induced drinking behaviour of patients with chronic kidney disease and preserved renal function, in order to correlate appropriately the impact of fluid intake with the decreases in blood parameters (EPO) and proteinuria.

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Reply

Dear Sir,

We thank Dr Thornton for his interest in our work. We share his interest in the diuretic effects of RAAS blockade, and actually were among the first to describe this more than 20 years ago [1]. With RAAS blockade, after an initial period of negative sodium and water balance, steady state is restored at a lower extracellular volume with restoration of urine volumes towards baseline.

In the current study [2], data were obtained after 6 weeks of treatment, i.e. during steady state. Steady-state urine volumes were higher during high sodium intake, but were unchanged by losartan and/or hydrochlorothiazide (Figure 1). Dr Thornton suggests that haemodilution may be present and may account for changes in haemoglobin and erythropoietin, but no signs of haemodilution were present in our study. Actually, all data pointed towards haemoconcentration as apparent from increased plasma levels of creatinine, urea, uric acid, albumin and renin, and decreased body weight and blood pressure [3]. Thus, the reduction of erythropoietin and haemoglobin by hydrochlorothiazide added to losartan in our proteinuric renal patients with preserved renal function occurred despite the simultaneous presence of haemoconcentration, suggesting that the reduction of absolute erythropoietin and haemoglobin levels may even be underestimated. In line with animal studies [4,5] we hypothesize that erythropoietin reduction by hydrochlorothiazide is caused by a decrease in renal oxygen requirement, which is the main stimulus for erythropoietin production, due to the inhibition of active tubular sodium reabsorption.

Furthermore, Dr Thornton points to the tight relationship between oral fluid intake and urine concentration, at least during steady state, which should be accounted for when measuring proteinuria. We fully agree on this issue and consistently assessed proteinuria in 24-h collections of urine, with proteinuria reported as protein excretion per 24 h (gram per 24 h) as well as protein:creatinine ratio (milligram per milligram) [3]. This minimizes the risk of underestimation of proteinuria in comparison with spot urine analysis and makes it possible to correct for collecting errors.

To conclude, erythropoietin and haemoglobin levels were reduced by hydrochlorothiazide added to losartan in our study population, without signs of haemodilution.

Conflict of interest statement. None declared.

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![Figure 1](image-url)