Letter and Reply

Advance Access publication 19 April 2012

The elusive erythropoietin receptor

Elliott et al. [1] have shown that erythropoietin receptor (EpoR) protein is low to undetectable in human renal cells and other tissues with no detectable EpoR on cell surfaces. This result was obtained by western blotting with an EpoR-specific monoclonal rabbit antibody (A82) and measurement of the binding of radiolabelled recombinant human Epo ($^{125}\text{I}$$\text{rHuEpo})$. RHuEpo did not induce intracellular signalling or proliferation of renal cell lines. EpoR and $\text{Jak2}$ knockdown had no effect on viability of renal and other non-haematopoietic cell lines. The expected 59-kDa EpoR was apparent with cultured erythroid cells, whereas no 59-kDa EpoR was detected in any other human tissue including kidney, brain, heart, liver, lung and colon among others. These findings are in contrast to previous studies with non-specific anti-EpoR antibodies, and they call into question the hypothesis that cells from renal tissues—and other non-haematopoietic tissues—express functional EpoR and that Epo is a pleiotropic cytoprotective factor.

However, the findings carry weight with respect to an open question regarding the long-term administration of rHuEpo or other erythropoiesis-stimulating agents (ESAs) to patients with chronic kidney disease (CKD), namely whether this therapy could impact on the development of malignancies. The EpoR promoter lacks a TATA box, which is characteristic of a ubiquitously expressed gene. EpoR messenger RNA is present at low basal levels in non-erythroid tissues, but it is questionable whether this is translated into functional EpoR protein integrated in the membrane. Some preclinical studies have suggested that tumour cells are responsive to Epo [2], and in cancer patients, there is concern that the therapy with ESAs may affect tumour growth and/or mortality [3]. Noteworthily, Elliott et al. [1] investigated several different renal and non-renal tumour cell lines, and none of these presented with measurable Epo-R protein or responded to Epo. This finding is further evidence against a direct tumour-promoting effect of ESAs. In regard to the possibility that Epo might promote tumour angiogenesis through mobilizing bone marrow-derived endothelial progenitor cells in CKD patients, it is noteworthy that long-term ESA treatment did not affect endothelial markers in patients on haemodialysis [4]. Taken together, there is little evidence to assume that ESAs directly or indirectly stimulate tumour growth in CKD patients.

Foley et al. [5] argued that if ESAs truly predispose to malignancy in haemodialysis patients, cancer-specific mortality rates should rise in parallel with rising ESA doses (which more than tripled in the USA since ESAs were introduced). The authors performed a retrospective incident cohort study including 873 493 US patients aged ≥20 years who initiated haemodialysis between 1995 and 2005. The study has shown that yearly cancer mortality rates were static throughout the observation period of 10 years, even though ESA doses escalated dramatically. Furthermore, the authors observed modest declines in overall and cardiovascular mortality, which militates against the reasoning that ESAs lead to death exclusively through cardiovascular disease [5].

Conflict of interest statement. The author has received honoraria for consultations and educational lectures from several pharmaceutical companies marketing ESAs.

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doi: 10.1093/ndt/gfs086

Advance Access publication 26 April 2012

Outcome of the living kidney donor

Sir,

In a recent paper, the outcome of the living kidney donor was discussed. Obese donors were discussed separately and the authors stated their worries for the nephrological prognosis of the donor because of the possibility of hypertension and proteinuria [1]. We wish to point out that several centres are therefore sceptical to accept an obese kidney donor, which has led to the policy of mandatory weight loss prior to donation.

We evaluated this practice in the 63 living donors who donated in the University Medical Centre Utrecht in 2009 and 2010. Weight at initial presentation, time of donation and a year after donation was measured. Forty-eight per
cent of donors managed to lose weight prior to donation, while 73% of them regained weight after the donation. Fifty-one per cent of the patients weighed even more a year after donation than at the start of the screening [2]. Of 10 patients with a body mass index (BMI) >30 kg/m² at presentation, 8 regained weight after the operation and 4 eventually weighed more compared to pre-screening.

In our series, weight loss prior to donation was not maintained at 1 year post-donation. A possible explanation for the weight gain after donation is that donors revert to the lifestyle they had before they considered kidney donation. Additionally, emotional arguments (to indulge lack of physical activity and nutritionally unfavourable habits as a reward for donation) may also play a role in the process.

Since weight loss is not maintained, one can question if the prerequisite to lower predonation BMI to <30 kg/m² is useful. Our relatively small series emphasizes the need for further studies to establish the risk of obesity in kidney donation as pointed out by Delanaye et al. [1].

Conflict of interest statement. None declared.

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doi: 10.1093/ndt/gfs101

Advance Access publication 3 May 2012

Cardiovascular assessment of patients with advanced kidney disease

Sir,

We read with interest the article by Galvao De Lima et al. [1]. The role of myocardial scintigraphy in cardiovascular (CV) risk assessment of patients with end-stage renal disease on the waiting list for transplantation is evaluated. This relatively large study highlights the complexity in identifying patients who may benefit from coronary angiography and revascularization.

There were a number of patients who were defined as being high or very high risk (28% and 15%, respectively) based on risk assessment. Half of those who were considered high risk and all patients who were considered very high risk had pre-existing CV disease. Similarly, 13% of patients considered high risk and 19% of patients considered very high risk had a history of myocardial infarction. Yet, only a minority of them had previous coronary intervention (6% in each group). Coronary angiography with a view to revascularization in the high-risk patient groups may have been beneficial in preventing further CV events. The presence of significant coronary artery disease may be predicted based on clinical risk. In a prospective study of over 300 haemodialysis patients, the prevalence of significant coronary artery disease increased with the number of clinical predictors (diabetes, age >50 years or evidence of CV disease) from 26% in patients with no risk factors to 100% in patients with all three risk factors. Similarly, the incidence of fatal/non-fatal major adverse cardiac events increased 2-, 4- and 6-fold in those with diabetes, peripheral artery disease or previous myocardial infarction, respectively [2].

Almost a third of all patients on the renal transplant waiting list may have coronary lesions amenable to revascularization [3]. This proportion may be even greater if limited to patients considered high or very high risk. Among wait-listed patients with significant CV risk factors (diabetes, age >50 years or clinical evidence of CV disease) undergoing coronary angiography, significant coronary artery disease may be found in almost half of the patients [2].

Admittedly, not all patients with a positive myocardial scintigraphy will have coronary lesions amenable to revascularization due to the fact that CV disease includes a spectrum of pathologies including sudden death, myocardial infarction and malignant arrhythmias. Sudden cardiac death accounts for ∼60% of this [4]. Myocardial scintigraphy and other investigations to diagnose atherosclerotic disease may therefore be less sensitive in some patients with chronic kidney disease, who may be prone to non-atherosclerotic CV disease. The impact of myocardial microvascular disease on major CV adverse events will be investigated in the MICROCARD study, the results of which are eagerly awaited [5]. The challenge that lies ahead is in identifying an integrative approach to cardiac investigations that is most likely to yield a practical approach to the management of an individual patient.

Conflict of interest statement. None declared.