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# Anemia management and chronic renal failure progression

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**Anemia management and chronic renal failure progression.** Analysis of the biologic effects of erythropoietin and pathophysiology of chronic kidney diseases (CKD) suggests that treatment with erythropoiesis-stimulating agents (ESA) could slow the progression of CKD. By decreasing hypoxia and oxidative stress, it could prevent the development of interstitial fibrosis and the destruction of tubular cells. It could have direct protective effects on tubular cells through its antiapoptotic properties. It could help maintain the integrity of the interstitial capillary network through its effects on endothelial cells. Thus, suggesting that correcting anemia with ESA could slow the progression of CKD is biologically plausible.

In patients with CKD, three small prospective studies and a retrospective study have suggested that treatment with ESA may have protective effects. Post-hoc analysis of the Reduction in Endpoints in Noninsulin-dependent Diabetes Mellitus with the Angiotensin II Antagonist Losartan study has also shown that anemia was an independent risk factor for progression of nephropathy in patients with type 2 diabetes. In addition, a large clinical trial, which had to be stopped prematurely because of labeling change for subcutaneous administration of epoetin alfa, suggests that complete normalization of hemoglobin levels is safe in CKD patients not on dialysis and without severe cardiovascular disease. Thus, it seems reasonable to advocate starting a large randomized, prospective study to determine if normalization of hemoglobin concentration can effectively slow the progression of CKD.

Renal failure results in considerable increase of cardiovascular morbidity and mortality, and is associated with decreased quality of life and heavy costs from renal replacement therapies. Furthermore, in the 1990s, the incidence of end-stage renal disease has been relentlessly increasing at an annual rate of about 6% to 8% in most European countries and even more rapidly in the United States [1]. Slowing the progression of renal failure thus appears to be a major therapeutic challenge. Besides treatment of the underlying disease, the main therapeutic tools that are available are optimal control of blood pressure, use of angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, and strict glycemic control in patients with diabetes mellitus [1]. The efficacy of these therapies is limited, however, and there is a clear need for additional treatments. Among the therapeutic interventions that could slow the progression of chronic kidney disease (CKD) is correction of anemia through administration of erythropoiesis-stimulating agents (ESA).

**Key words:** anemia, chronic kidney disease, progression, erythropoietin.



## BIOLOGIC EFFECTS OF TREATMENT WITH ESA

The most obvious benefit of treatment with ESA is an increase in red blood cell concentration, which is responsible for increased oxygen delivery to tissues and reduction of hypoxia. However, administration of ESA has other effects, including protection against oxidative stress and apoptosis, and possibly stimulation of angiogenesis.

Erythrocytes represent a major antioxidant component of blood [2]. Their antioxidant effects are mediated through enzymes such as superoxide dismutase, catalase, and glutathione peroxidase, and through cellular proteins that are devoided of enzymatic activity but can react with reactive oxygen species, such as low-molecular weight proteins of the erythrocyte membrane, vitamin E, vitamin C, or coenzyme Q. Furthermore, glutathione reductase can regenerate reduced glutathione from its oxidized form, using reduced nicotinamide adenine dinucleotide phosphate produced through the pentose phosphate pathway.

The ability of erythropoietin to promote survival of erythroid progenitors via the binding to its receptor has been established for a long time. However, recent studies have shown that erythropoietin receptors are also expressed in a variety of non-hematopoietic cells, such as neuronal cells, cardiomyocytes, vascular cells, and renal tubular cells, and that the binding of erythropoietin to these receptors can have antiapoptotic effects [3]. Protection against apoptosis appears to be mediated by different pathways, including (*1*) activation of the transcription of genes encoding antiapoptotic molecules such as Bcl-$x_L$, XIAP, or c-IAP2; (*2*) inhibition of the transcription of genes encoding proapoptotic molecules such as Fas ligand or Bim; (*3*) activation of protein kinase B/Akt through the phosphatidylinositol 3-kinase pathway; and (*4*) induction of heat shock protein 70 (Fig. 1). In agreement with these data, acute administration of relatively large doses of erythropoietin can dramatically decrease the consequences of experimental injuries of neuronal cells,

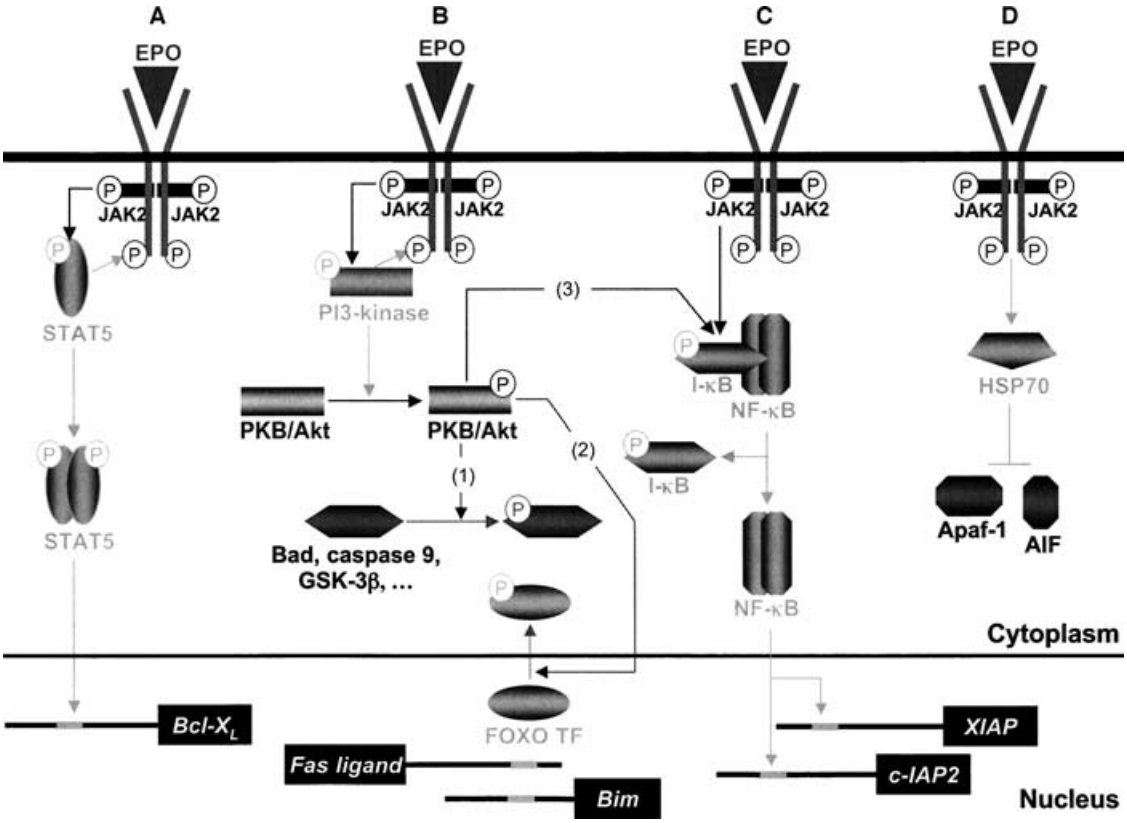


**Fig. 1. Schematic representation of the pathways by which the binding of EPO to its receptor can inhibit apoptosis.** Binding of EPO induces: (*A*) phosphorylation of the STAT5 transcription factor that will then homodimerize, translocate into the nucleus, and activate target genes encoding antiapoptotic molecules such as Bcl-$X_L$; (*B*) phosphorylation of phosphatidylinositol 3-kinase (PI-3 kinase) that, in turn, phosphorylates protein kinase B (PKB)/Akt, which then phosphorylates (1) proapoptotic molecules such as Bad, caspase 9, or glycogen synthase kinase-3β (GSK-3β), leading to their inactivation, (2) FOXO transcription factors (FOXO TF), inducing their retention into the cytoplasm, and thus preventing activation of target genes such as *Fas ligand* or *Bim*, (3) I-κB, leading to the activation of the transcription factor nuclear factor-κB; (*C*) phosphorylation of I-κB, which allows the release of the transcription factor nuclear factor-κB, its translocation into the nucleus and activation of target genes encoding antiapoptotic molecules such as XIAP and c-IAP2; and (*D*) activation of heat shock protein 70 (Hsp70), which binds to and inactivates proapoptotic molecules such as apoptosis protease activating factor-1 (Apaf-1) and apoptosis-inducing factor (AIF). Reprinted from [3] with permission.

transient or permanent occlusion of a coronary artery, or renal ischemia-reperfusion injury [3]. For example, pretreatment of animals with recombinant human erythropoietin at a dose ranging from 300 to 5000 IU/kg can reduce renal dysfunction and morphologic damage after transient clamping of renal artery [4–8]. These protective effects appear to be mostly mediated by a decrease of apoptotic cell death [4, 6].

Analyses of knock-out mice have shown that the binding of erythropoietin to its receptors is required for normal development of the heart and brain [9, 10], but also for normal angiogenesis [11], demonstrating that physiologic doses of erythropoietin can have proangiogenic effects. These data are in agreement with in vivo data obtained with chick embryo chorioallantoic membrane, and with in vitro experiments performed with cultured endothelial cells that have outlined the proangiogenic effects of erythropoietin [12, 13]. Recently, Bahlmann et al have shown that low doses of darbepoetin alfa, which did not increase hematocrit levels, had protective effects in rats undergoing subtotal nephrectomy [14]. Interestingly, in this model, treatment with ESA prevented the loss of peritubular capillaries. Because the Akt/protein kinase B pathway was activated, ESA may act by inhibiting the apoptosis of endothelial cells.

Experiments performed with neuronal cells have also shown that the binding of recombinant erythropoietin to its receptors can protect against oxidative stress [15]. It activates nuclear factor-κB which, in turn, enhances the expression of genes encoding proteins such as superoxide dismutase that have potent antioxidant properties. However, it is not known whether erythropoietin can have similar antioxidant properties in other cell types.

## BIOLOGIC LINKS BETWEEN TREATMENT WITH ESA AND PROGRESSION OF CKD

During the course of CKD, nephron destruction is caused by direct effects of the underlying disease on glomerular, tubular, or vascular structures, and also two vicious circles triggered by reduction in nephron number (Fig. 2). One links nephron loss with glomerulosclerosis

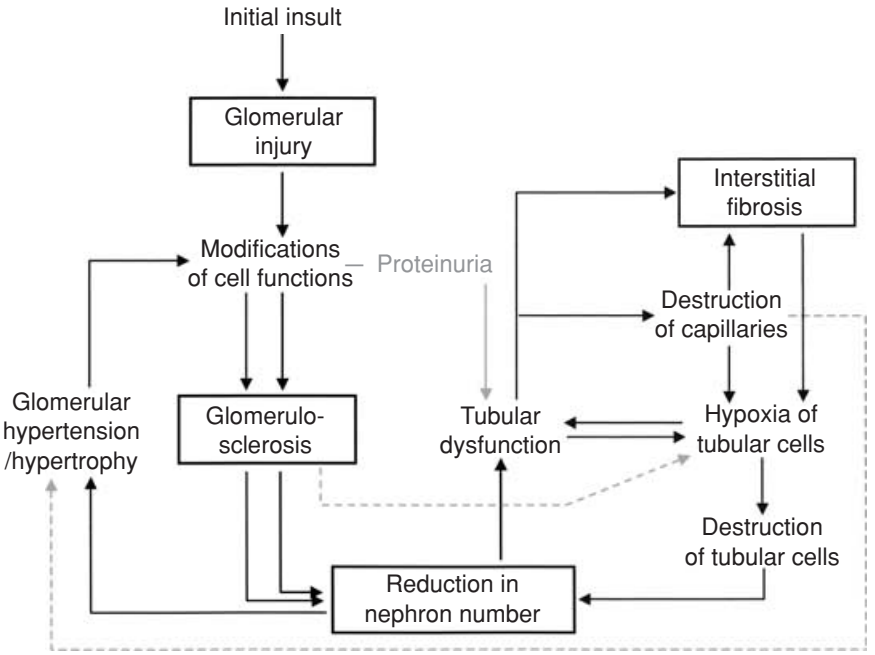


**Fig. 2. Schematic representation of the mechanisms responsible for nephron loss in patients with glomerular disease.** An initial glomerular insult is responsible for alterations of glomerular cell functions, leading to glomerulosclerosis and thus reduction in nephron number. Reduced nephron number induces an increase in glomerular capillary pressure and/or glomerular volume, which leads to further glomerular damage. Reduced nephron number is also associated with tubular dysfunction. The modifications of tubular cell functions are responsible for interstitial fibrosis and destruction of peritubular capillaries, which leads to tubular destruction. Destruction of interstitial capillaries may also increase glomerular capillary pressure and thus enhance glomerular damage. Similarly, glomerulosclerosis damages glomerular capillaries and enhances tubular hypoxia. Proteinuria enhances tubular dysfunction and thus interstitial fibrosis.

and glomerular destruction. The other links reduction in nephron number with interstitial fibrosis and tubular damage.

The glomerular vicious circle has been highlighted by pioneer work performed in Brenner's laboratory more than 20 years ago [16]. Experimental studies performed in rats undergoing subtotal nephrectomy have shown that nephron loss increases capillary pressure and flow in the remaining glomeruli and induces hypertrophy of these glomeruli which, in turn, leads to podocyte injury, overproduction of extracellular matrix by mesangial cells, and glomerulosclerosis [16]. Human sequential studies of renal biopsies obtained from few patients who had an important reduction of their renal mass have also shown that a decrease in nephron number can be responsible for the development of glomerulosclerosis [17].

Two series of observations derived from careful analyses of renal biopsies have suggested that reduction in nephron number is responsible for the development of interstitial fibrosis, and that the corresponding interstitial lesions play a key role in the progression of CKD. First, during the course of many renal diseases, there is a striking correlation between renal function and severity of interstitial fibrosis [18, 19]. Second, the extent of interstitial fibrosis is the best histologic prognostic marker of most renal diseases, including glomerular and vascular diseases [20–23]. As pointed out by Fine and Johnson, hypoxia probably plays a central role in this process, favoring both the production of extracellular matrix and nephron loss [24, 25]. In patients with reduced nephron number, hypoxia of tubular cells is favored by (*1*) an increase of oxygen consumption by tubular cells of the remaining nephrons; (*2*) a decrease in the number of interstitial capillaries [26]; and (*3*) an accumulation of extracellular matrix between interstitial capillaries and tubular cells, which hampers oxygen diffusion. In turn, hypoxia appears to have at least three consequences. First, it stimulates the production of profibrotic molecules, such as transforming growth factor-β or endothelin-1, by tubular cells, as well as the synthesis of extracellular matrix by these cells [27, 28]. Second, it directly enhances the production of extracellular matrix by fibroblastic cells [29]. Third, it ultimately leads to a destruction of tubules, with formation of so-called "atubular glomeruli." The importance of tubular destruction in the progression of CKD has been highlighted by analysis of various experimental models of CKD as well as by careful analyses of renal biopsies [30]. For example, after subtotal nephrectomy, progression of renal failure appears to be due much more to tubular destruction with formation of atubular glomeruli than to glomerulosclerosis [31]. In patients with renal failure, increased oxygen consumption by the remaining nephrons favors hypoxia, but it also enhances the production of reactive oxygen species, which could play a role in progression of CKD. Oxidative stress has been shown to induce the release of proinflammatory and profibrotic molecules, such as monocyte chemotactic protein-1 and transforming growth factor-β1, to directly enhance the production of extracellular matrix by fibroblastic cells and favor cell death [32–36]. Its role in CKD progression is supported by experiments showing that, in vivo, treatment of rats with antioxidants can protect against the development of interstitial fibrosis, whereas deprivation of antioxidants has opposite effects [32, 37].

Analysis of the mechanisms of progression of CKD shows that treatment with ESA could exert protective

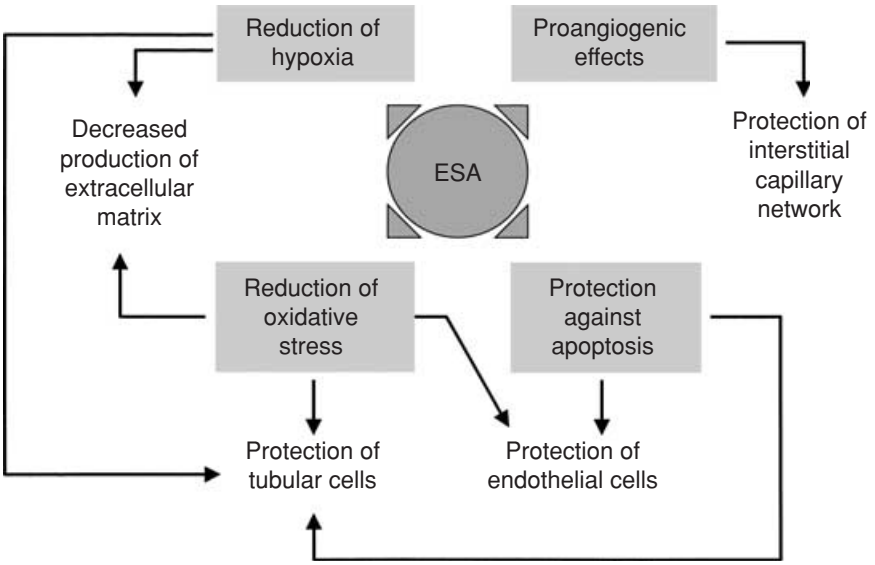


**Fig. 3. Schematic representation of the potential links between treatment with ESA and nephroprotection.** Treatment with ESA will reduce hypoxia and oxidative stress and possibly have proangiogenic and antiapoptotic effects. This will lead, in turn, to decreased production of extracellular matrix, protection of interstitial capillary network, and protection of tubular cells and interstitial cells.

effects at different levels (Fig. 3). It could (*1*) slow the development of interstitial fibrosis as well as the destruction of tubular cells by decreasing hypoxia and oxidative stress through correction of anemia; (*2*) have direct protective effects on tubular cells; and (*3*) help maintain the integrity of the interstitial capillary network. Thus, suggesting that correcting anemia with ESA could slow the progression of CKD is biologically plausible.

## CLINICAL STUDIES SUGGESTING THAT TREATMENT WITH ESA MAY SLOW THE PROGRESSION OF RENAL FAILURE

The fact that correcting anemia does not accelerate the progression of CKD has been shown by different clinical studies performed in the early 1990s, and it is not questioned anymore. Nevertheless, the question of whether it slows the progression of renal failure remains an open one. So far, this hypothesis is mostly supported by three prospective clinical studies including a limited number of patients [38–40].

The first study, which was published in 1994, included 83 patients with severely impaired renal function [mean measured glomerular filtration rate (GFR) 10 mL/min] and severe anemia (mean hematocrit, 26.8%) [38]. After a two-month stabilization period, 40 patients were randomly assigned not to receive epoetin and 43 to receive epoetin in order for their hematocrit to reach 35%. The patients were followed up for 48 weeks. No beneficial effect of epoetin could be demonstrated by simply comparing renal survival or GFR decrease between the two groups of patients. Nevertheless, when data were analyzed only after the hematocrit levels of the patients included in the epoetin group had reached the target values (i.e., after week 16), the rate of GFR decline was three times slower in the treated group than in the control group ($-0.13 \pm 0.35$ mL/min/month vs. $-0.39 \pm 0.65$ mL/min/month, $P = 0.05$).

The second study, which was published in 1997, included 73 patients with severe anemia (mean hematocrit, 27.4%) and renal failure (mean creatinine clearance, 18.2 mL/min) [39]. After an eight-week stabilization period, the patients were randomly assigned to receive or not receive epoetin. Thirty-one patients were left untreated. Forty-two patients received epoetin to increase their hematocrit to 33% to 35%. Follow-up was at 36 weeks. During this period, creatinine doubled in about 52% of patients in the treated group and in more than 90% of patients in the control group ($P < 0.0005$). Furthermore, while 64% of patients in the control group required dialysis, only 33% of those in the epoetin group had to start dialysis ($P < 0.005$).

The third study was published in 2004 [40]. Eighty-eight patients with nondiabetic nephropathy, proteinuria of less than 2 g/day, and hemoglobin concentration between 9 g/dL and 11.6 g/dL were randomly allocated to early or late treatment with ESA. Patients included in the former group received epoetin to increase their hemoglobin concentration above 13 g/dL. Those included in the latter group did not receive epoetin until their hemoglobin concentration decreased below 9 g/dL. Treatment with an angiotensin-converting enzyme inhibitor was not permitted during the study. After a median follow-up of 22.5 months, significantly more patients reached a combined end point of doubling of serum creatinine, end-stage renal disease, or death in the early treatment group (13 vs. 23, $P < 0.01$). Similarly, significantly less patients reached a combined end point of end-stage renal disease or death in the early treatment group (13 vs. 22, $P = 0.01$).

In addition to these prospective randomized studies, a retrospective and noncontrolled study also suggested that treatment with ESA may slow the progression of

renal failure [41]. In this study, the authors compared 20 patients with CKD who were treated with epoetin with 43 patients who had a similar degree of renal failure but who were less anemic and, thus, did not receive epoetin. The rate of decline of creatinine clearance did not change over time in the control group, whereas in the treated group, it was significantly slower after epoetin treatment had been started ($-0.36 \pm 0.16$ mL/min/1.73 $m^2$/month vs. $-0.26 \pm 0.15$ mL/min/1.73 $m^2$/month, $P < 0.05$). Although this study has many limitations, it suggests that treatment with ESA could have protective effects that are not mediated by correction of anemia.

A post-hoc analysis of the Reduction in Endpoints in Noninsulin-dependent Diabetes Mellitus with the Angiotensin II Antagonist Losartan study also supports the possibility that correction of anemia may slow the progression of CKD [42]. A total of 1513 type 2 diabetes patients with nephropathy were included in this double-blind, randomized trial designed to test the renoprotective properties of losartan. Multivariate analysis showed that, in this population, anemia was an independent risk factor of progression, together with the levels of serum creatinine, proteinuria, and serum albumin.

In 2001, the Effect of Early Correction of Anaemia on the Progression of Chronic Kidney Disease study was initiated to define the effects of complete correction of anemia with epoetin alfa on progression of CKD. The main inclusion criteria were an estimated GFR between 60 and 25 mL/min, and hemoglobin levels below 13 g/dL for men and 12.5 g/dL for women. Patients included in this study were randomly assigned to early treatment with epoetin alfa to achieve high hemoglobin targets (13–15 g/dL), or to conventional treatment with no administration of epoetin as long as hemoglobin levels were above 11 g/dL. Unfortunately, the study was terminated early because of labeling change for subcutaneous administration of epoetin alfa. Only 391 patients were included, and mean follow-up was only 7.4 months in the high hemoglobin group and 8.3 months in the low hemoglobin group. Measured GFR decline was numerically, but not statistically, significantly lower in the high hemoglobin group (0.058 vs. 0.081 mL/min/1.73$m^2$/month). Importantly, adverse events rates were similar between the two groups, and neither epoetin dosage nor hemoglobin level was associated with cardiovascular adverse events or death.

## CONCLUSION

The hypothesis that correction of anemia with ESA may slow the progression of renal failure is biologically plausible, and preliminary results issued from few clinical studies suggest that it is worth being tested in a large prospective study. In our opinion, such a study should include patients with moderate anemia, treated according to current guidelines, and randomly assigned to receive treatment with ESA to normalize their hemoglobin levels. The Effect of Early Correction of Anaemia on the Progression of Chronic Kidney Disease study has shown that such a study is feasible.

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