Hyperparathyroidism and Anemia in Uremic Subjects: A Combined Therapeutic Approach

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Abstract. Several factors are involved in conditioning renal anemia, and a critical role is attributed to parathyroid hormone (PTH) oversecretion, which has some direct effects on endogenous erythropoietin (EPO) synthesis, bone marrow erythroid progenitors, and red cell survival. Indirect effects are mainly based on the induction of bone marrow fibrosis. Indirect evidence of the role of PTH is based on the observation that parathyroidectomy, when performed in uremic patients, is often followed by restoration of the hematocrit. The interpretations of such positive results are based on the observation of the restored bone marrow space after operation and also in a rise of immunoreactive EPO serum concentrations observed in the first weeks after gland removal. Another field of clinical interest is the possible beneficial effects of vitamin D therapy in controlling PTH secretion, which in turn determines an improvement of anemia of uremic subjects. Several uncontrolled studies confirmed this possibility, indicating that patients who respond to calcitriol or its analogs also show an increase of their hemoglobin levels. Thus, a combined therapeutic approach to PTH oversecretion and anemia is possible by intravenous calcitriol or parathyroidectomy pointing to the possible reversibility of bone marrow fibrosis, which is a common feature of secondary hyperparathyroidism. The increased sensitivity to EPO therapy can also induce a successful reduction of its dosage, thus allowing an interesting reduction of costs.

One of the most important steps in improving the quality of life in patients on who are regular dialysis treatment (RDT) is represented by the use of recombinant human erythropoietin (EPO), which became routine in the 1980s (1). However, the individual response to EPO administration in uremia is variable; most of the patients (>90%) are responders; a minority, however, seems to respond poorly, requiring larger amount of hormone; a few others do not respond at all.

An inadequate response to EPO therapy is defined as failure to reach or maintain a target hemoglobin concentration within 4 to 6 wk of treatment, in the presence of adequate iron stores, when a dose of 300 units/kg per wk is administered subcutaneously (2). Needless to say, when a patient requires >15,000 units/wk or more (considering a patient of 70 kg body weight, it means 214 units/kg per wk), the costs of treatment also substantially increase. It is therefore obvious that, in these cases, the identification of the mechanism of such EPO resistance represents a priority.

The main factors up to now recognized as responsible for EPO resistance are listed in Table 1. As expected, the most common cause in conditioning EPO resistance is the absolute or functional iron deficiency. In this short review, however, the attention is focused on the possible role of parathyroid hormone (PTH) oversecretion, which is a very common comorbid situation among uremic patients on RDT.

**PTH Toxicity on Red Blood Cell Production**

Whether excessive parathyroid activity per se causes anemia and resistance to EPO remains controversial. The potential mechanisms include a direct effect of PTH on endogenous EPO synthesis, on bone marrow erythroid progenitors, and on red blood cell survival (accelerated hemolysis). An indirect effect through the induction of bone marrow fibrosis also has been proposed (3).

**EPO Synthesis**

The group from the Necker Hospital in Paris evaluated plasma EPO levels 2 wk after parathyroidectomy in a group of patients who presented severe hyperparathyroidism. The plasma levels reached a concentration >10-fold greater (and in some cases even 50-fold greater) than normal values (4). Another group of investigators confirmed the same findings but only during the first 24 h after parathyroidectomy (5). Both of these studies suggest a direct inhibitory effect of PTH on the already reduced EPO levels to which the hypocalcemic state also could contribute.

**Inhibition of Bone Marrow Erythroid Progenitors**

Early in vitro studies (6) showed that intact PTH in concentrations comparable to those found in the blood of uremic patients was able to induce a profound inhibition of the mouse bone marrow burst-forming units-erythroid (BFU-E). In serum-free cultures of fetal mouse liver cells, Dunn and Trent (7) showed an inhibition of heme synthesis at higher bovine PTH levels that was not observed at low bovine 1 to 84 PTH.
response to EPO therapy. Indeed, the most dramatic improvement of anemia and a concomitant reduction of EPO doses have been reported in several patients after parathyroidectomy.

A representative case report was published by Goicoechea et al. (12): the described patient on RDT showed a progressive increase of PTH levels along with a progressive decrease of Ht levels down to 25% despite periodic blood transfusions and increased doses of EPO up to 240 units/kg per wk. After parathyroidectomy, PTH dropped from 768 to 19 pg/ml and Ht rose progressively and reached levels of 30 to 40% in a few weeks, and EPO requirement was reduced by 50%. Blood transfusions were no longer necessary, whereas ferritin values, which were maintained at >100 to 150 μg/L, remained unchanged. In this case, a six-old increase of the weekly dose of EPO was not successful in restoring the hematocrit to its previous level; only parathyroidectomy succeeded in improving the patient’s Ht and in minimizing EPO needs.

**Effect of Parathyroidectomy**

The first reports on the positive effects of parathyroidectomy in ameliorating anemic status of uremic patients appeared more than two decades ago. Zingraff et al. (13) observed an increase in Ht (from 24.4 to 30.9%) in 18 patients 6 to 9 mo after surgery. They were also able to show, in a subset of five patients, a correlation between the amount of marrow fibrosis and the improvement of anemia after parathyroidectomy. In three of them, Ht strikingly improved (from 22.7 to 31.3%), whereas marrow fibrosis decreased significantly (from 19.3 to 7.2%, expressed as percentage of total marrow space); in two patients who showed only moderate fibrosis at the time of operation, Ht had only a mild improvement (from 25.5 to 28%).

In 1979, Barbour (14) described 14 patients who had chronic renal failure and were submitted to parathyroidectomy. Those who showed a rise of Ht also had a higher degree of bone marrow fibrosis. Because responders and nonresponders had similar PTH plasma levels, the authors concluded that the PTH negative role in conditioning anemia is mediated by marrow fibrosis. More recently, Goicoechea et al. (15) described seven patients who showed an increase of their Ht (from 28 to 35%), along with reduced EPO needs (from 136 to 94 units/kg per wk), 6 mo after parathyroid surgical removal.

Mandolfo et al. (16) also evaluated retrospectively the effect of parathyroidectomy in a cohort of 39 patients. Surgery improved anemia in all, but the improvement in the subset of patients who received EPO was further emphasized by a concomitant 30 to 40% reduction of the weekly administered amount. Conversely, these authors also performed bone biopsies in 20 patients, and, in this subset, they found no correlation between marrow fibrosis and anemia before and after surgery. Coen et al. (17) also confirmed the positive effect of parathyroidectomy on anemia in a group of 45 dialysis patients.

**Table 1. Factors involved in r-HuEPO poor responsiveness in patients with renal anemia**

<table>
<thead>
<tr>
<th>Condition</th>
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<tbody>
<tr>
<td>Iron deficiency</td>
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<tr>
<td>Inflammatory states</td>
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<td>Infections</td>
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<tr>
<td>Malignancy</td>
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<td>Aluminium overload</td>
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<td>Secondary hyperparathyroidism</td>
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<tr>
<td>Malnutrition</td>
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<tr>
<td>Uncontrolled uremic state</td>
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<tr>
<td>Blood loss</td>
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<tr>
<td>Bone marrow dysfunction</td>
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<tr>
<td>B12/folate deficiency</td>
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<td>Interference with immunosuppressive or chemotherapeutic agents</td>
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concentration. However, McGonigle et al. (8) were not able to demonstrate any major effect on erythroid progenitor cell growth in the presence of EPO. More recently, Komatsuda et al. (9) also found no evidence that PTH itself (even at the concentration of 5000 pg/ml) can inhibit hematopoietic progenitor cell growth.

Taken together, these studies that deal with inhibition of erythropoiesis indicate conflicting data; however, other mechanisms, such as shortened red blood cell survival time as a result of increased osmotic fragility, PTH-induced reduction in platelet aggregability, and the PTH-induced bone marrow fibrosis, were also investigated.

**PTH and Bone Marrow Fibrosis**

More than a quarter of a century ago, Brikmann et al. (10) showed that an excess of PTH could induce a marrow fibrosis with a concomitant reduction of space for erythropoiesis. Two decades later, this hypothesis was confirmed by Rao et al. (11), who evaluated the response to EPO therapy in a group of 18 uremic patients on RDT, following them for 1 to 3 yr. He showed that in the poor-response group (seven patients), the mean EPO dose required to maintain the target hematocrit (Ht) of 35% was dramatically higher in comparison with the good-response group (176 versus 56 units/kg 3 times a week). All patients were submitted to bone biopsy. Histomorphometry showed that osteoid volume, surface, and thickness and also aluminum content were similar in the two groups. In contrast, the mean serum PTH levels (880 ± 648 versus 266 ± 322 pg/ml) and the degree of bone marrow fibrosis (15.6 ± 16.4% versus 1.1 ± 1.1%) were significantly greater in the poor-response group. The authors concluded that the severity of secondary hyperparathyroidism and the extent of bone marrow fibrosis increase the EPO dose required to maintain adequate response.

**PTH, Anemia, and Response to EPO: Clinical Studies**

Conflicting data have been reported so far in understanding the actual role of hyperparathyroidism in conditioning the anemia in patients with renal failure and were submitted to parathyroidectomy. Those who showed a rise of Ht also had a higher degree of bone marrow fibrosis. Because responders and nonresponders had similar PTH plasma levels, the authors concluded that the PTH negative role in conditioning anemia is mediated by marrow fibrosis. More recently, Goicoechea et al. (15) described seven patients who showed an increase of their Ht (from 28 to 35%), along with reduced EPO needs (from 136 to 94 units/kg per wk), 6 mo after parathyroid surgical removal.

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**Serum EPO Levels after Parathyroidectomy**

Another area of scientific interest is the direct effect of parathyroidectomy on serum immunoreactive EPO (iEPO) levels. Two interesting studies appeared during the last decade:
Table 2. Serum EPO levels after parathyroidec tomy

<table>
<thead>
<tr>
<th>Hyperparathyroidism (N = 23)</th>
<th>iEPO Serum Levels (mU/mL)</th>
<th>Reticulocyte Count (n/mm³)</th>
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<tbody>
<tr>
<td>Before PTX</td>
<td>23.1 ± 4.8</td>
<td>61,000 ± 13,317</td>
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<tr>
<td>Day 7, after PTX</td>
<td>28.2 ± 5.0</td>
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<tr>
<td>Day 14, after PTX</td>
<td>245 ± 125</td>
<td>86,533 ± 13,462</td>
</tr>
<tr>
<td>12 mo after PTX (in 4 pts)</td>
<td>37.0 ± 8.4</td>
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<tr>
<td>24 mo after PTX (in 4 pts)</td>
<td>31.8 ± 13.5</td>
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PTX, parathyroidec tomy.
Adapted from Urena et al. (18).

Urena et al. (18) described the follow-up after surgery in patients who had primary (n = 16) and secondary (n = 23) hyperparathyroidism. The results related to the latter group are summarized in Table 2.

This study shows an increase in serum iEPO concentration in the immediate follow-up after surgical correction of hyperparathyroidism in patients on RDT, whereas such an increase was not observed after parathyroid adenoma removal in patients who had primary hyperparathyroidism. The same results were observed in a smaller study by Washio et al. (19), who showed an iEPO increase after parathyroidec tomy in 10 patients on RDT (from 48.4 ± 17.8 mU/ml to 103.3 ± 34.7 and 163.4 ± 50.2 mU/ml, respectively, at 6 and 12 h after parathyroidec tomy). Both studies indicate that reduction of ionized calcium could play some role in the elevation of iEPO plasma levels.

**Suppression of Secondary Hyperparathyroidism with Active Vitamin D Compounds: Its Effects on Anemia of Uremic Patients**

On a theoretical basis, surgical and medical suppression of PTH oversecretion should have similar effects on the anemia observed in dialysis patients. Several studies confirm this hypothesis, although most of them are noncontrolled studies.

Argilès et al. (20) treated seven patients who had severe hyperparathyroidism with intravenous alfalcacidol (6 to 14 μg/wk with a follow-up of 4 mo) and observed a clear improvement in controlling PTH secretion (from 1193 ± 207 to 489 ± 166 pg/ml). Concomitantly, the hemoglobin levels increased significantly from 10.8 ± 1.1 to 12.1 ± 1.0% at the end of the observation. In addition, three of the four patients who received EPO could decrease the dose and eventually withdraw the drug. Although it was an uncontrolled study and therefore of limited value, these data support the hypothesis of a possible reduction of bone marrow fibrosis or a direct effect of vitamin D metabolites on normal cell differentiation.

Llach et al. (21) evaluated 31 patients who had severe hyperparathyroidism and were treated with intravenous calcitriol for 30 mo. Along with a dramatic decrease of intact PTH from 1650 ± 175 to 225 ± 31 pg/ml, there was a gradual decrease—by 80%—of EPO administration needed to maintain patients in the Ht range of 30 to 36%.

Albitar et al. (22) described 40 patients who all had severe hyperparathyroidism and were treated for 6 mo with high doses of alfalcacidol: of them, 20 were considered responders, whereas 20 patients were not and therefore were candidate for parathyroidec tomy. Data from this study are presented in Table 3. It was concluded that only the patients who responded to alfalcacidol, in terms of PTH secretion, also presented a better control of the anemic status despite a reduced EPO administration.

More recently, Goicoechea et al. (23) investigated the effects of a 12-mo treatment with intravenous calcitriol (mean dose 6 μg/wk) in a group of 28 hemodialysis patients who presented various degrees of hyperparathyroidism (from moderate to severe). Epoetin and iron doses were adjusted during the study period to maintain the Ht levels >30% and ferritin levels >150 ng/ml. Their data, summarized in Table 4, indicate that besides controlling PTH secretion in the majority of the uremic patients, intravenous calcitriol is able to improve anemia and to decrease EPO needs.

In conclusion, a combined therapeutic approach to PTH oversecretion and anemia of patients on RDT can be achieved by intravenous calcitriol or parathyroidec tomy, thus indicating the possible reversibility of bone marrow fibrosis, which is a common feature of secondary hyperparathyroidism. However, a direct effect of calcitriol on hematopoiesis cannot be excluded and needs further investigation.

In addition, it should be kept in mind that any progressive hyperparathyroidism carries a progressive resistance of bone marrow to respond to EPO treatment. It is therefore obvious that the early control of PTH secretion is crucial for preventing

Table 3. Effect of alfalcacidol treatment in 40 patients with severe hyperparathyroidism

<table>
<thead>
<tr>
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<th>Responders (N = 20)</th>
<th>Nonresponders (N = 20)</th>
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<tr>
<td>Intact PTH (basal values; pg/ml)</td>
<td>741 ± 190</td>
<td>1269 ± 154</td>
</tr>
<tr>
<td>Intact PTH (6 mo after; pg/ml)</td>
<td>164 ± 72</td>
<td>974 ± 161</td>
</tr>
<tr>
<td>Hemoglobin (basal values; g/dl)</td>
<td>9.16 ± 0.90</td>
<td>8.74 ± 0.54</td>
</tr>
<tr>
<td>Hemoglobin (6 mo after; g/dl)</td>
<td>10.54 ± 0.68</td>
<td>8.97 ± 1.02</td>
</tr>
<tr>
<td>Epoietin dose (basal amount; units/kg per wk)</td>
<td>142 ± 62</td>
<td>156 ± 52</td>
</tr>
<tr>
<td>Epoietin dose (6 mo after; units/kg per wk)</td>
<td>54 ± 43</td>
<td>172 ± 57</td>
</tr>
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PTX, parathyroid hormone.
Adapted from Albitar et al. (22).
metabolic bone disease and also the worsening of anemic status. This statement is even more convincing if we consider the huge costs that the use of erythropoiesis-stimulating proteins implies. An effective management of calcium-phosphate balance with a combination of adequate dialysis regimen, dietary restrictions, and phosphate binders therefore should be a major objective in the early phase of treatment of uremic patients.

References