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Review

Association of secondary hyperparathyroidism with anemia in patients with end-stage renal disease; a review on current knowledge

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Abstract

End-stage renal disease (ESRD) is one of the most common life-threatening diseases and anemia is a known common and important complication of ESRD which can develop well before the onset of uremic symptoms. Anemia among patients with ESRD is principally due to reduced renal erythropoietin (EPO) production and if left untreated is associated with several abnormalities including deterioration in cardiac function and debilitating symptoms and is also associated with an increased risk of hospitalization, hospital length of stay and mortality among these patients. Secondary hyperparathyroidism (SHPT) is also a common and unrecognized complication of ESRD which is caused by several changes including hypocalcemia, diminished 1,25-dihydroxyvitamin D levels, hyperphosphatemia, a decrease in the activation of the calcium-sensing receptor in the parathyroid gland, and skeletal resistance to the calcemic effect of PTH. There are several forms of renal osteodystrophy, including osteitis fibrosa cystica and mixed osteodystrophy which are largely induced by SHPT. In addition to the renal bone disease, several studies have suggested a significant relationship between SHPT and anemia in ESRD patients. The present article summarizes some of these observations including pathophysiologic mechanisms of anemia due to SHPT, relationship between serum PTH levels and the degree of bone marrow fibrosis and the possible beneficial effect of surgical and medical intervention of SHPT on anemia among these patients.

Keywords: End-stage renal disease, Bone marrow fibrosis, Secondary hyperparathyroidism, Anemia

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Introduction

End-stage renal disease (ESRD) is defined as permanent and irreversible loss of renal function requiring renal replacement therapy including hemodialysis, peritoneal dialysis, and kidney transplantation. It is one of the most common life-threatening diseases with significant complication and the number of patients accepted for renal replacement therapy increases each year and imposes a major social and economic burden on developed and developing countries (1-8).

Materials and Methods

For this review, we used a variety of sources by searching through PubMed/Medline, Scopus, EMBASE, EBSCO and directory of open access journals (DOAJ). The search was conducted, using combination of the following key words and or their equivalents such as end-stage renal disease, bone marrow fibrosis, secondary hyperparathyroidism and anemia.

Anemia in end-stage renal disease

Anemia is a known common and important complication of ESRD and it can develop well before the onset of uremic symptoms due to ESRD. According to the NHANES survey, the prevalence of anemia increased from 1% at an estimated glomerular filtration rate (GFR) of 60 ml/min to 9% at an estimated GFR of 30 ml/min and to 33% to 67% at an estimated GFR of 15 ml/min (9). Anemia among patients with ESRD is principally due to reduced renal erythropoietin (EPO) production and, to a lesser degree, to shortened red cell survival and decreased responsiveness to the hormone because of iron deficiency, vitamin deficiencies, infection and inflammation. Anemia of ESRD, if left untreated is associated with several abnormalities including deterioration in cardiac function and debilitating symptoms, such as fatigue, weakness, anorexia, and sleep disturbances. It is also associated with an increased risk of hospitalization, hospital length of stay and mortality among these patients principally due to cardiac disease and stroke (10,11).

The most common therapeutic option for the anemia of ESRD is EPO stimulating agents (ESAs), which became routine in the 1980s, because they have substantially reduced the need for red cell transfusions and therefore the

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Implication for health policy/practice/research/medical education

In addition to the renal bone disease, several studies have suggested a significant relationship between secondary hyperparathyroidism (SHPT) and anemia in end-stage renal disease (ESRD) patients. The present article summarizes some of these observations including pathophysiologic mechanisms of anemia due to SHPT, relationship between serum PTH levels and the degree of bone marrow fibrosis and the possible beneficial effect of surgical and medical intervention of SHPT on anemia among these patients.

risk for transfusion-related complications (10-14).

Although, the administration of ESAs is particularly attractive, however some patients are relatively resistant to ESAs and it may be an important clinical observation since a poor response to ESAs therapy and need to higher dose of ESAs may be associated with increased mortality among these patients (15-17). The most common factors that may be responsible for resistance to ESAs is absolute iron deficiency, which may be due to external blood losses and/or exhaustion of iron stores (18,19). The evaluation for other causes of resistance to ESAs is also very important especially when ESA resistance occurs in iron replete patients. These include secondary hyperparathyroidism (SHPT), occult malignancy, and the presence of a failed kidney transplant or an occult infection (19-24).

From the above causes of resistance to ESAs, SHPT is a common and unfortunately often unrecognized complication of ESRD which caused by several changes that occur in bone and mineral metabolism as a result of decreased kidney function (20). The major factors responsible for stimulating parathyroid gland function in renal failure are hypocalcemia, diminished 1,25-dihydroxyvitamin D levels, hyperphosphatemia, a decrease in the activation of the calcium-sensing receptor in the parathyroid gland, and skeletal resistance to the calcemic effect of PTH (25-27). More recently it is also suggested that fibroblast growth factor-23, which increases among chronic kidney disease patients possibly as a consequence of hyperphosphatemia, can suppress 1,25-dihydroxyvitamin D synthesis and induce hyperparathyroidism (28).

Although SHPT is frequently asymptomatic, however there are several forms of renal osteodystrophy, including osteitis fibrosa cystica and mixed osteodystrophy which are largely developed by the direct result of increased parathyroid hormone (PTH) levels (29-32).

In addition to the renal bone disease, several studies have suggested a significant relationship between SHPT and anemia in ESRD patients (33-37). The present article summarizes some of these observations about this issue including pathophysiologic mechanisms of anemia due to SHPT, relationship between serum PTH levels and the degree of bone marrow fibrosis and the possible beneficial effect of surgical and medical intervention of SHPT on anemia among these patients.

The reverse relationship between SHPT and anemia in uremic patients

Normochromic and normocytic anemia has been recognized as a complication of severe primary hyperparathyroidism (33). Therefore it is suggested that if the severe primary hyperparathyroidism can induce anemia in patients with normal renal function, the extremely high levels of PTH usually observed in SHPT may also be able to induce anemia among ESRD patients. In consistence with this hypothesis, there are several studies which have suggested a reverse correlation between SHPT and anemia in uremic patients (34-42).

For example, the cross-sectional study by Chutia et al which was carried out among ESRD patients admitted in hemodialysis (HD) unit of North East Indira Gandhi Institute of Health and Medical Science is a study on this issue. They analyzed the effect of SHPT on aggravating the anemia and relationship between intact PTH and hemoglobin level among 63 ESRD patients (31 men and 32 women). The result of study demonstrated a significant and a reverse relationship between PTH and hemoglobin levels among these patients. In addition, there was no association between intact PTH and serum ferritin in this study which indicated that the anemia which has observed among these patients is not due to iron deficiency states (34). In the other article, Baradaran et al investigated the role of SHPT in the severity of anemia among 36 ESRD patients (20 men and 16 women) undergoing regular HD. Similar to the result of Chutia et al study, the result of this study also showed a reverse relationship between intact PTH and hemoglobin level as well as between intact PTH and hematocrit and between alkaline phosphatase and hemoglobin level among these patients. In the end of the study, they suggested that SHPT per se can intensify anemia and contribute to the severity of this complication (35).

Bashardoost has also evaluated the relationship between hemoglobin and intact PTH levels among 26 ESRD patients (16 men and 10 women) undergo in maintenance HD and also showed a reverse relationship between PTH and hemoglobin levels among these patients. Although, the result of Bashardoost study is limited because, he did not evaluate other common cause of anemia including iron state among these patients; however the result of this article is also consistent with the results of above studies (36).

The possible pathophysiologic mechanisms of anemia due to SHPT

Bone marrow fibrosis

Pathophysiologic mechanisms of anemia due to SHPT are unclear. However a variety of mechanisms have been postulated for the possible causes of anemia due to SHPT. It is suggested that the severe bone marrow fibrosis with a concomitant reduction of space for erythrogenesis is an important cause of anemia among these patients (37,38, 43,44).

This hypothesis is firstly suggested by Brickmann et al

study in approximately four decades ago who showed that an excess of PTH could induce a bone marrow fibrosis among uremic patients (37).

Two decades ago, the results of Brickmann et al study supported by Rao et al study who evaluated the relation between the erythropoietic response to EPO and SHPT among 18 ESRD patients undergoing HD. According to the erythropoietic response to EPO, Rao et al divided their patients to good-response and poor-response groups. All patients were submitted to bone biopsy in the study. In seven patients who were named as the poor-response group, the mean dose of EPO required to maintain the target hematocrit was 174 ± 33 units/kg intravenously 3 times a week and it was 56 ± 18 units/kg in other 11 patients who were named as the good-response group. The results of the study and bone biopsy showed that in the ESRD patients with poor-response to EPO, the mean serum PTH levels, the percentages of osteoclastic and eroded bone surfaces, and the degree of bone marrow fibrosis are significantly greater compared to the ESRD patients with good-response (38).

The results of Zingraff et al (43) and Barbour (44) studies are also consistent with this hypothesis and are strongly suggested that PTH by causing bone marrow fibrosis and a concomitant reduction of space for erythrogenesis, contribute to anemia among patients with ESRD.

Red blood cell osmotic fragility in ESRD patients

In addition to severe bone marrow fibrosis as a possible mechanism of anemia due to SHPT, there is also evidence that the PTH is probably a major factor influencing RBC osmotic fragility and inducing a short erythrocyte life span among ESRD patients. RBC osmotic fragility is the resistance of RBC hemolysis to osmotic changes (39,45).

Wu et al compared the RBC osmotic fragility among 57 ESRD patients undergoing maintenance HD and 19 healthy volunteers as a control group. The results of study showed that the median osmotic fragility was significantly greater in hemodialyzed patients compared to control group. In addition the osmotic fragility was also higher among ESRD patients who had an intact PTH level >100 pg/ml and there was a significantly correlation between median osmotic fragility and intact PTH level. Therefore they concluded that PTH is probably a major factor influencing RBC osmotic fragility and a cause of shortened red cell survival among ESRD patients (39).

The results of Akmal et al study is also suggested that PTH increases RBC osmotic fragility and induces their hemolysis among animals with chronic renal failure (45). They were compared RBC survival in six normal dogs, six animals with chronic renal failure and SHPT and six thyroparathyroidectomized dogs with comparable degree and duration of chronic renal failure and showed that RBC survival is not different among normal and thyroparathyroidectomized dogs but significantly lower in animals with chronic renal failure and SHPT. Therefore Akmal et al concluded that SHPT and no other complication of renal failure is responsible for the shortened RBC survival among uremic dogs (45).

The beneficial effect of parathyroidectomy on anemia in ESRD patients

The results of above studies suggested a reverse association between SHPT and anemia in ESRD patients. In addition to these studies, there are several articles which have investigated the possible beneficial effect of parathyroidectomy on anemia in uremic patients (43-51).

The first studies about the possible influence of parathyroidectomy on anemia in uremic patients have released in more than 3 decades ago by Zingraff et al in 1978 and Barbour in 1079 (43,44). Zingraff et al evaluated the beneficial effect of subtotal parathyroidectomy on the severity of the anemia in 18 ESRD patients undergoing long-term HD and observed a significant increase of mean hematocrit value (from 24.4% to 30.9%), red blood cell (RBC) count, and hemoglobin level 6 to 9 months after surgery. By serial bone biopsies, they were also able to suggest, in a subset of five patients, a relationship between the amount of marrow fibrosis and the improvement of anemia after subtotal parathyroidectomy (43).

In Barbour study, the effect of parathyroidectomy on the 14 patients with chronic renal failure has described. He showed an increase in hemoglobin level among seven of these patients. However, other seven patients did not show an increase in hemoglobin level. Those who responded to parathyroidectomy also had a higher degree of bone marrow fibrosis compared to non-responders. Therefore the author concluded that the PTH may contribute to anemia in renal failure by causing marrow fibrosis among these patients (43).

Approximately two decades later in 1996, the beneficial effect of parathyroidectomy on anemia in uremic patients has also reported by Goicoechea et al who evaluated seven uremic patients after parathyroid surgical removal. They showed an increase in hematocrit value (from 28% to 35%), along with reduced EPO needs from 136 to 94 units/kg per week 6 months after parathyroidectomy (46).

The results of Mandolfo et al study who evaluated the effect of parathyroidectomy in a cohort of 39 patients are also consistent with the results of above studies. Parathyroidectomy improved anemia in all of these patients. However, there was no correlation between bone marrow fibrosis and anemia before and after surgery in this study (47).

In a multicenter study, Coen et al evaluated the long-term results of parathyroidectomy on anemia in 45 ESRD patients with SHPT and observed an increase in hemoglobin level despite a reduction of administered EPO after parathyroidectomy (48).

More recently, Chow et al and Trunzo et al have also investigated the beneficial effect of parathyroidectomy on anemia in uremic patients and confirmed the positive effect of surgery on anemia among these patients (49,50).

The results of Trunzo et al study showed that EPO dos-

ing requirement significantly are decreased after parathyroidectomy from 10086 ± 1721 to 3514 ± 620 units/week. In addition, Trunzo et al proposed that ESRD patients who have SHPT and refractory anemia should be considered as a secondary indication for surgical parathyroidectomy (50).

However, as mentioned in the next section, this type of anemia is also responsive to medical treatment of SHPT and therefore, controversy exists regarding this issue and it seems that resistant anemia alone should not be considered as an independent indication for surgical intervention (52).

The beneficial effect of medical intervention of SHPT on anemia in ESRD patients

The results of above studies confirmed a beneficial effect of surgical parathyroidectomy on anemia in uremic patients. More recently, some authors have evaluated the impact of the correction of SHPT by medical intervention on anemia among these patients (53,54).

For example Lin et al evaluated 37 chronic hemodialysis patients in two groups: patients with SHPT and patients without SHPT. Furthermore, they used calcitriol which is an active vitamin D analog for the treatment of SHPT and then according to the response of SHPT to calcitriol therapy, they divided the patients into responders and no responder's patients. The results of this study showed that SHPT usually associated with more severe anemia similar to the results of the above studies. In addition, they were also able to show that the hematocrit level is significantly increased and the dose of EPO requirement is significantly decreased among responding patients. They concluded that calcitriol therapy has a beneficial effect on anemia in ESRD patients with SHPT (53).

In the other study, Mpio et al evaluated the impact of the correction of SHPT by cinacalcet which is a new calcimimetic drug on the anemia among 22 ESRD patients with severe SHPT. Cinacalcet which is now considered as a pharmacological parathyroidectomy, increases the sensitivity of the calcium sensing receptors to calcium. ESRD patients who had intact PTH level above 800 pg/ml were included in this study. The results of the study showed that the cinacalcet can significantly decrease level of PTH, serum phosphate and serum calcium-phosphorus product. They also able to show that cinacalcet can significantly increase the hemoglobin level without important change of the median weekly administered EPO doses in the majority of patients (54).

Conclusion

SHPT is a common and unrecognized complication of ESRD which is caused by several changes including hypocalcemia, diminished 1,25-dihydroxyvitamin D levels, hyperphosphatemia, a decrease in the activation of the calcium-sensing receptor in the parathyroid gland, and skeletal resistance to the calcemic effect of PTH.

Anemia is also an important complication of ESRD and is associated with an increased risk of mortality among these patients principally due to cardiac disease and stroke.

There are several studies which have suggested a reverse correlation between SHPT and anemia in uremic patients. Although, mechanisms of anemia due to SHPT are unclear, it is suggested that the severe bone marrow fibrosis with a concomitant reduction of space for erythrogenesis is an important cause of anemia among these patients.

There is also evidence that the PTH increases RBC osmotic fragility and induces short erythrocyte life span among ESRD patients.

There are also several studies which have confirmed the beneficial effect of surgical parathyroidectomy on anemia in uremic patients. More recently, some studies have also showed the beneficial effect of correction of SHPT by medical intervention on anemia among these patients. According to these studies, cinacalcet which is a new calcimimetic drug and calcitriol which is an active vitamin D analogs can significantly decrease the level of PTH and increase the Hb level without important change of the median weekly administered EPO doses in the majority of ESRD patients with SHPT.

Authors' contribution

SSBM and MRT prepared the primary draft. HS and SSBM conducted searching the data. Editing the final manuscript done by MRT and SSBM.

Conflicts of interest

None to be declared.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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