Renal Replacement Therapy

CASE REPORT

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Possible role of cardiovascular stress induced by the volume load as a cause of anemia in hemodialysis patients: a case of a maintenance hemodialysis patient with a literature review

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Abstract

Background Although a deficiency in erythropoietin relative to decreased hemoglobin levels is presumed to be the predominant cause of renal anemia, other factors may also exist that are not fully understood.

Case presentation A 58-year-old man with pyelonephritis who had been on hemodialysis for 18 years presented a gradually decreasing serum creatinine level, possibly due to voluntary dietary restrictions, accompanied by a gradual increase in the cardiothoracic ratio from 48% to 56%. Concomitantly, his hemoglobin level decreased gradually from 14.5 to 8.7 g/dL by 6 months. Although he had no symptoms of heart failure and his left ventricular ejection fraction was 66.3%, which was almost identical to his condition 2 years prior, a drastic reduction in posthemodialysis body weight from 71.0 to 68.6 kg in 9 days was performed without apparent intrahemodialysis hypotension. His cardiothoracic ratio and serum prehemodialysis N-terminal pro-brain natriuretic peptide level decreased steeply, from 56% to 49% by 2 weeks and from 6139 to 647 pg/mL by 8 weeks, followed by a gradual increase in his hemoglobin level from 8.7 to 15.1 g/dL by 3 months. The patient was administered 50 mg/day sodium ferrous citrate but no erythropoietin-stimulating agents or hypoxia-inducible factor prolyl hydroxylase inhibitors. Although a modest increase in the serum protein level was observed immediately after the rapid reduction in posthemodialysis body weight, the patient's hemoglobin level increased markedly and gradually, suggesting an improvement in anemia rather than hemoconcentration.

Conclusions Cardiovascular stress induced by the volume load is one of the causes of anemia in hemodialysis patients.

Keywords Anemia, Chronic kidney disease, Hemodialysis, Cardiovascular stress, Volume load, Heart failure, Erythropoietin

Background

In chronic kidney disease (CKD) and dialysis patients, anemia is common, especially in those on hemodialysis [1, 2]. Renal anemia is defined as anemia that becomes apparent when the amount of erythropoietin (EPO) produced in the kidneys is insufficient to compensate for the

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decrease in the hemoglobin level, and the administration of erythropoietin stimulating agents (ESAs) has become the mainstay of anemia treatment in these populations [3, 4]. However, the suppression of erythropoiesis, shortened red blood cell lifespan, and disorders of iron metabolism also influence renal anemia; these factors are not yet fully understood [3].

In CKD and dialysis patients, heart failure and cardiovascular disease are major causes of death [5, 6]. Like these populations, patients with heart failure commonly have anemia, which is associated with an increased risk of mortality [7]. Despite sufficient renal function to produce EPO, anemia in heart failure patients is characterized by a low EPO concentration [8], and similar to the cause of renal anemia, the cause of anemia in heart failure patients might be multifactorial [9] and not fully understood.

Given that the majority of hemodialysis patients experience cardiovascular stress caused by volume overload due to insufficient urinary volume and water removal during hemodialysis and that this volume overload can cause heart failure, it is speculated that dialysis patients can present both renal anemia and anemia in heart failure.

Here, I present the clinical course of a patient on maintenance hemodialysis who presented with exacerbation of anemia and improved remarkably after water removal via hemodialysis; additionally, I consider the involvement of cardiovascular stress induced by the volume load as a cause of anemia in hemodialysis patients.

Case presentation

Case

A 58-year-old man with pyelonephritis who had been on hemodialysis for 18 years and was in fairly good condition during this time presented with a gradual decrease in hemoglobin levels from 14.5 to 8.7 g/dL by 6 months, accompanied by a gradual increase in the cardiothoracic ratio from 48% to 56% and a gradual decrease in the serum creatinine level from 19.33 to 15.76 mg/dL, possibly due to voluntary dietary restrictions. During this period, his prehemodialysis N-terminal pro-brain natriuretic peptide (NT-proBNP) level increased from 715 to 6139 pg/mL. Ultrasound cardiography revealed fairly good cardiac function; his left ventricular ejection fraction was 66.3%, there was no valvular heart disease, which was almost identical to the condition 2 years prior, and fecal occult blood was not detected. The serum iron, ferritin, and transferrin saturation levels were 83 μg/dL, 158.2 ng/mL, and 35.3%, respectively. His dry weight decreased drastically after water removal via hemodialysis, from 71.0 to 68.6 kg in 9 days. As shown in Fig. 1, water removal was followed by a prompt decrease in the cardiothoracic ratio from 56% to 49% within 2 weeks and a decrease in the serum prehemodialysis NT-proBNP level from 6139 to 647 pg/mL within 8 weeks. His serum protein level increased rapidly from 7.3 to 8.3 g/dL immediately after water removal and was less than 8 g/dL thereafter. In contrast, his hemoglobin level increased gradually from 8.7 to 15.1 g/dL over 3 months and remained at the same level thereafter. During this period, he was administered 50 mg/day sodium ferrous citrate but no ESAs or hypoxia-inducible factor prolyl hydroxylase inhibitor. His serum EPO concentration was approximately 5 mIU/mL when the hemoglobin level was stable between 13 and 15 g/dL and was 8.9 mIU/mL as his anemia improved.

Discussion

Anemia is common in CKD and dialysis patients [1, 2]. Heart failure is one of the major causes of death in these populations, and anemia is also common in patients with heart failure [7]. Anemia management has improved dramatically due to the introduction of ESAs [10]. However, patient prognosis is not necessarily satisfactory. An increase in the hemoglobin level to approximately 13 g/dL following ESA administration results in an increase in cardiovascular morbidity [11], end-stage renal disease [12], or risk of stroke [13] in CKD patients, and inferior patient survival in hemodialysis patients [14]. Moreover, thromboembolic adverse events are increased in patients with heart failure with this hemoglobin level following ESA administration [15]. Supraphysiological EPO concentrations could be harmful for patients [16]. However, since insufficient EPO production relative to hemoglobin levels is the cause of anemia in these populations [3, 4, 8, 17], these discouraging results are puzzling. Moreover, evaluation of this agent in renal anemia and anemia in heart failure patients is not the same; ESA administration is recommended for renal anemia [3, 4] but not for anemia in heart failure [18]. Therefore, we may have to modify our understanding of anemia in these populations.

Based on the findings of the present case, anemia in CKD and hemodialysis patients, especially the involvement of anemia due to cardiovascular stress induced by the volume load, will be discussed in the following order: renal anemia and innate EPO production, possible influence of cardiovascular stress induced by the volume load on anemia in dialysis patients, anemia in heart failure patients, and possible coexistence of renal anemia and anemia of heart failure in CKD and dialysis patients.

Renal anemia and innate EPO production

Although EPO production is insufficient relative to hemoglobin levels in CKD and dialysis patients [3, 4, 17], the serum innate EPO concentration is maintained within

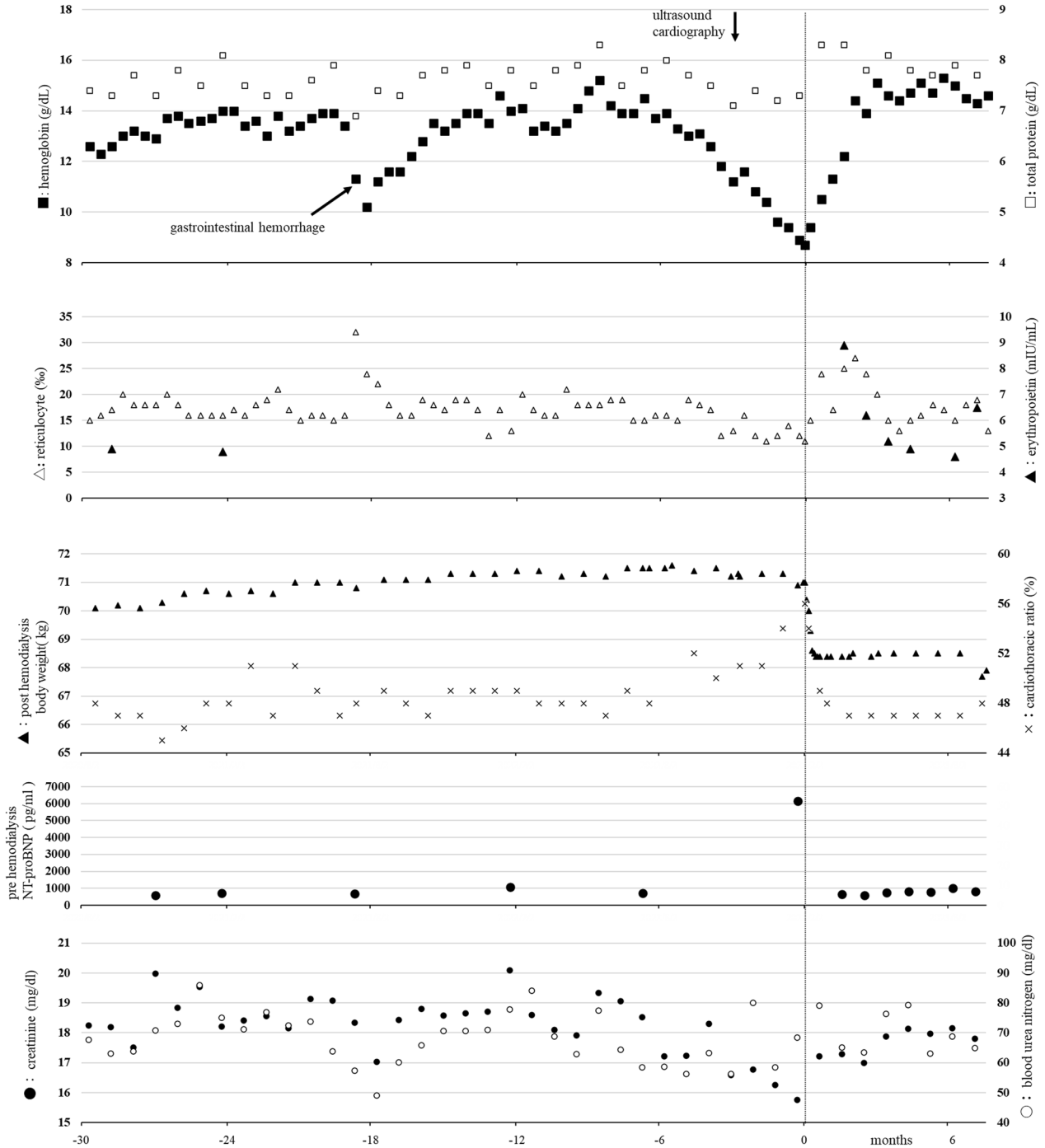

Fig. 1 Changes in the serum creatinine, blood urea nitrogen, total protein, hemoglobin, reticulocyte, erythropoietin and prehemodialysis N-terminal pro-brain natriuretic peptide levels, body weight, and cardiothoracic ratio of a 58-year-old man receiving maintenance hemodialysis

or above the normal range in hemodialysis patients [19]. Additionally, although the response of EPO production to a decrease in hemoglobin level declines as CKD progresses, it is still observed in CKD stage 5 patients [20]. Posttransplant erythrocytosis, which is defined as a hematocrit level greater than 51%, is reported to occur in 10–15% of kidney graft recipients, and a prompt reduction in the EPO level and correction of erythrocytosis have been observed after the surgical removal of both native kidneys [21], suggesting that native kidneys in

end-stage CKD patients have the potential for substantial EPO production. In hemodialysis patients, not only the potential of EPO production but also the regulation of EPO production and erythropoiesis is recognized. The serum EPO concentration and reticulocyte ratio decrease following transfusion and increase following hemorrhage, respectively [22]. Figure 2 shows the correlation between the serum EPO concentration and hemoglobin level in hemodialysis patients treated without ESA or hypoxia-inducible factor prolyl hydroxylase inhibitor for more than 6 months and with oral iron administration in our clinic; 58 blood samples from 28 patients were analyzed. Although the correlation was weaker than that observed in the nonrenal anemia population [17], there was a negative correlation between the serum EPO concentration and hemoglobin.

Given that the decrease in hemoglobin level in renal anemia patients is usually slower than that following bleeding, it is unlikely that prompt and significant increases in innate EPO production and erythropoiesis are needed for the recovery of hemoglobin levels. Additionally, as shown in the present case and Fig. 2, in hemodialysis patients without anemia, the serum EPO concentrations are almost identical to those of the general population [23], suggesting that hemoglobin levels could be maintained with relatively low serum EPO concentrations in hemodialysis patients. Thus, the cause of renal anemia cannot be ascribed solely to insufficient EPO production.

Uremia itself is the cause of anemia, whose mechanisms include not only relative EPO deficiency and inhibition of erythropoiesis [24, 25] but also a shortened red blood cell lifespan. Before the era of hemodialysis and the availability of ESA therapy, Loge et al. followed up on the clinical course of anemic CKD patients and investigated the changes in red blood cell lifespan [26]. Red blood cells from normal individuals that were transfused into CKD patients disappeared at an accelerated rate in CKD patients with azotemia progression; however, the lifespan of transfused red blood cells was normal when the patient's azotemia was stable. Additionally, when red blood cells from CKD patients were transfused into normal subjects, the lifespan of the red blood cells was normal, irrespective of whether the azotemia in the CKD patients was progressing or stable. Although this was a report from more than 70 years ago and the accuracy and ethical problems of the study are not known, these results are impressive when considering the cause of renal anemia. The lifespan of red blood cells can change according to uremic status, and a change in uremic level rather than absolute uremic level could be an important factor in renal anemia.

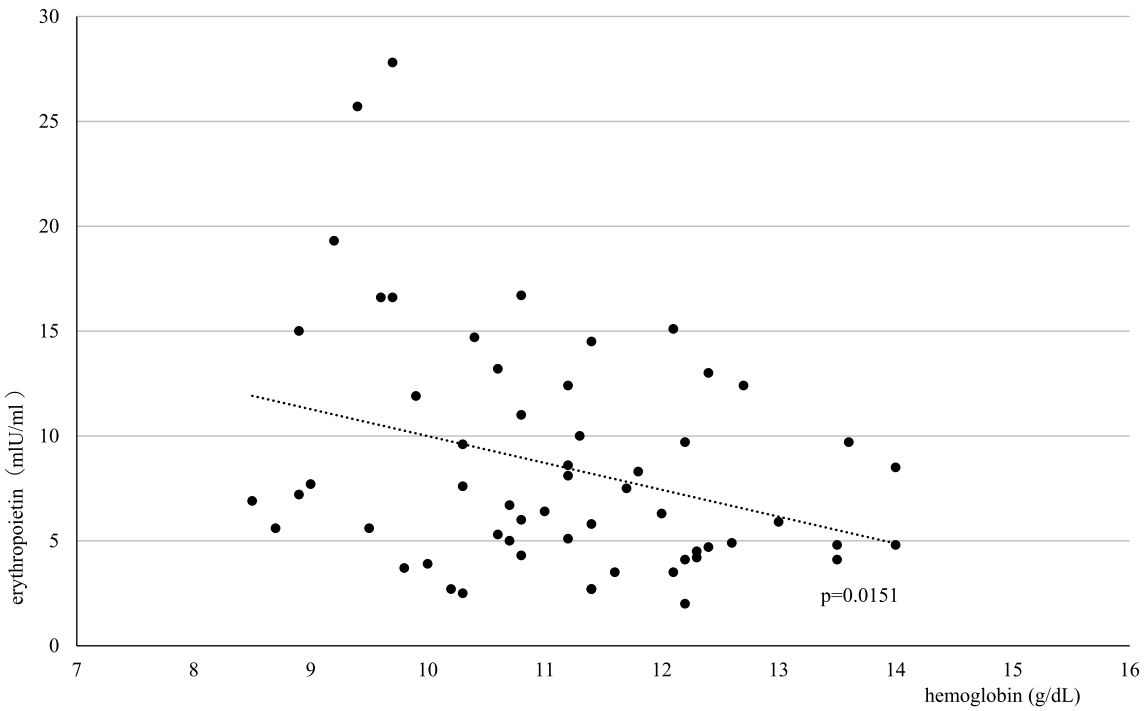

Fig. 2 Correlation between serum erythropoietin and hemoglobin levels in hemodialysis patients. Fifty-eight blood samples were collected from 28 patients ($p=0.0151$)

Possible influence of cardiovascular stress induced by the volume load on anemia in dialysis patients

Although uremia is an important cause of renal anemia, the cause of the exacerbation of anemia in the present case cannot be ascribed to uremia because the patient was a maintenance hemodialysis patient and his anemia was exacerbated without an exacerbation of uremia. Although inflammation is also one of the causes of anemia in CKD and hemodialysis patients [27, 28], the C-reactive protein levels in the present patient were consistently less than 0.2 mg/dL. A rapid reduction in body weight after water removal should be avoided to prevent intradialytic hypotension and the formation of intravascular thrombi. However, the body weight was reduced rapidly by water removal because it was certain that a substantial excessive water volume existed. Consequently, following the rapid decreases in the prehemodialysis NT-proBNP level and cardiothoracic ratio, the anemia status improved significantly without a significant increase in the serum protein level. These findings suggest an improvement in anemia rather than hemoconcentration, which may be due to the reduction in cardiovascular stress induced by the volume load.

The cardiothoracic ratio is one of the indicators of body fluid control in hemodialysis patients [29]. The cardiothoracic ratio is influenced by the intravascular blood volume; thus, a change in the cardiothoracic ratio reflects a change in cardiovascular stress induced by the volume load. Figure 3 shows the correlation between the cardiothoracic ratio and hemoglobin level in a 48-year-old man with diabetic kidney disease treated with hemodialysis for 10 years without ESA administration or hypoxia-inducible factor prolyl hydroxylase inhibitor therapy. There was an inverse correlation between the cardiothoracic ratio and the hemoglobin level. Such a correlation was not detected between the cardiothoracic ratio and total protein level. This finding suggests that the change in the hemoglobin level did not reflect hemoconcentration or hemodilution but rather reflected the anemia status according to the change in cardiovascular stress induced by the volume load.

Although the underlying mechanisms are not known, these results suggest that cardiovascular stress induced by the volume load can be the cause of anemia. This could be one of the major causes of anemia in CKD and dialysis patients because, in these patients with insufficient urination volume, some degree of cardiovascular stress induced by the volume load is common.

Anemia in heart failure patients

In addition to CKD and dialysis, anemia is also common in patients with heart failure [7]. The cause of anemia in heart failure might be multifactorial and not fully understood; possibilities include iron deficiency, decreased EPO production due to renal dysfunction caused by structural renal disease, inflammation, the use of angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, bleeding, cachexia, and fluid retention [9]. In the present case, except for fluid retention, none of the above factors seemed to exacerbate anemia because iron deficiency, bleeding, appetite loss, and apparent exacerbation of inflammation were not observed, and an angiotensin-converting enzyme inhibitor or an angiotensin II receptor blocker was not used. Regarding the possibility of decreased EPO production, the serum EPO concentrations were consistently less than 5 mIU/mL even when anemia was not detected. The patient in the present study was an anuric hemodialysis

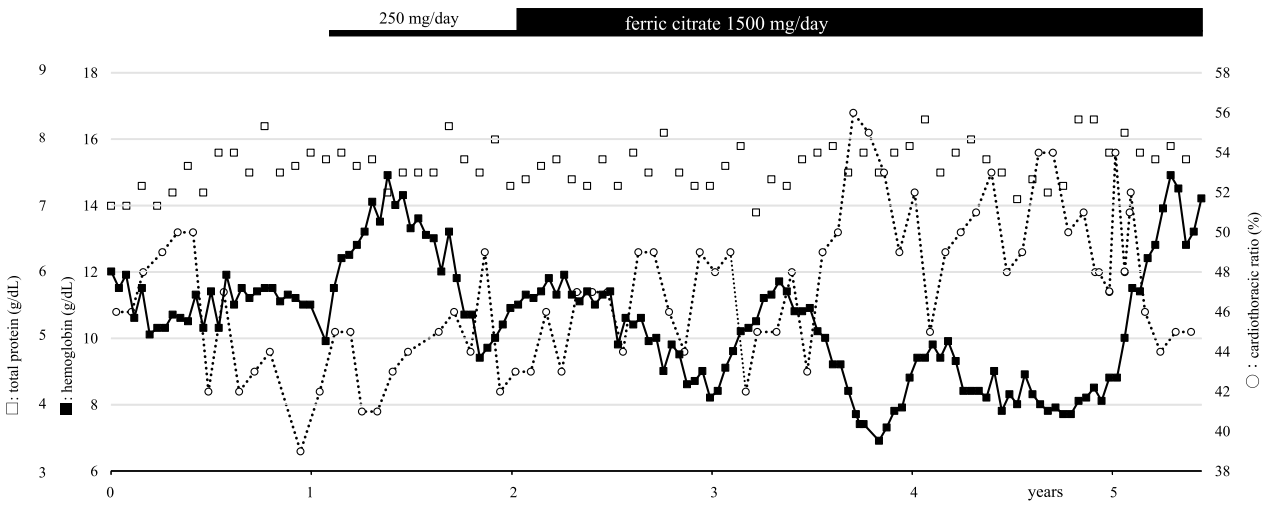

Fig. 3 Changes in total protein, hemoglobin, and the cardiothoracic ratio in a 48-year-old male hemodialysis patient

patient and a further decline in kidney function, which may have influenced EPO production, was unlikely, although hemodilution by fluid retention is thought to be a possible mechanism of anemia in heart failure [9]. In the present case, as mentioned above, the main cause of the significant increase in the hemoglobin level after the drastic decrease in dry weight cannot be ascribed to hemoconcentration; therefore, hemodilution was not the main cause of anemia. Thus, none of the proposed potential mechanisms for anemia in heart failure apply to the cause of the exacerbation of anemia in the present case and strongly suggest the possibility of cardiovascular stress induced by the volume load as a cause of anemia.

The hypothesis derived from the present case is that "cardiovascular stress induced by the volume load is one of the causes of anemia in hemodialysis patients"; this hypothesis may be inconsistent with the finding that heart failure can increase the EPO level in hemodialysis patients [30]. In the present case, the serum EPO concentration was greater during the improvement in anemia than during the period when the hemoglobin level was stable between 13 and 15 g/dL. Although the EPO concentration during the exacerbation of anemia was not investigated, the reticulocyte level was stable or slightly decreased. This suggests that, rather than only the suppression of erythropoiesis, which includes hyporesponsiveness to EPO, a shortened red blood cell lifespan was one of the causes of the exacerbation of anemia. Additionally, the somewhat suppressed reticulocyte levels observed during the progression of anemia with an increase in the cardiothoracic ratio contrast with the acute increase in reticulocyte level when the hemoglobin level decreases suddenly due to gastrointestinal hemorrhage. This suggests the possibility that anemia caused by the cardiovascular stress induced by the volume load is an adaptation to cardiovascular stress. Again, the underlying mechanisms are not known.

Recently, new promising cardioprotective agents, such as sodium–glucose cotransporter inhibitors and sacubitril/valsartan, have emerged [31, 32]. In addition to its cardioprotective effect, the use of sodium–glucose cotransporter inhibitors is associated with a modest increase in hematocrit levels [33, 34]. Similarly, with the use of sacubitril/valsartan, hemoglobin decreases less and the incidence of new anemia is lower than that with enalapril [35]. We recently reported an improvement in anemia after the administration of sacubitril/valsartan, and this improvement was accompanied by a decrease in the cardiothoracic ratio and the serum prehemodialysis NT-proBNP level in hemodialysis patients, which was not explained by hemoconcentration [36]. In addition to glycosuria and natriuresis by sodium–glucose cotransporter inhibitors and natriuresis by sacubitril/valsartan, sacubitril/valsartan may promote a shift in fluid from the intravascular space to the extravascular space and result in a decrease in intravascular volume regardless of kidney function [36, 37]. Although changes in iron metabolism and EPO production are possible mechanisms underlying the improvement in anemia induced by the administration of these agents [32–34], these changes are still not fully understood. I believe that relieving cardiac stress induced by volume overload is also a possible mechanism underlying the beneficial effect of these agents on anemia.

Anemia in heart failure patients is associated with cardiovascular death or hospitalization [7]. Thus, if anemia is a mediator rather than just a marker of poor outcomes, correcting anemia could be an important and novel therapeutic approach for improving long-term outcomes in patients with heart failure [38]. However, in the Reduction of Events with Darbepoetin alfa in Heart Failure (RED-HF) trial, treatment with darbepoetin alfa did not improve clinical outcomes in patients with systolic heart failure or mild-to-moderate anemia [15], suggesting that anemia itself is likely not a mediator of poor outcomes but rather a marker of heart failure severity [9]. According to the "2022 AHA/ACC/HFSA Guidelines for the Management of Heart Failure," ESA therapy is not recommended for the treatment of anemia in heart failure patients [17].

Possible coexistence of renal anemia and anemia in heart failure in CKD and dialysis patients

Cardiorenal syndrome is a spectrum of disorders of the kidneys and heart in which loss of function in one organ contributes to reduced function in the other organ, and in this syndrome, anemia is frequently recognized [39]. Although the mechanisms of renal anemia and anemia in heart failure may not be the same, given that heart failure is not infrequent in CKD and dialysis patients, the coexistence of renal anemia and anemia in heart failure is also not infrequent, and it is difficult to distinguish renal anemia from anemia in heart failure in these populations. Thus, it is possible that the so-called "renal anemia" in CKD and dialysis patients is not a pure renal anemia; it has factors of both renal anemia and anemia in heart failure and, as one of the mechanisms of the latter anemia, cardiovascular stress induced by the volume load may be included.

Except for the drastic change in body weight by water removal, the current case is not rare. When treating end-stage CKD and hemodialysis patients, we sometimes encounter exacerbation of anemia; bleeding, iron deficiency, or hematopoietic disorders are unlikely causes. In such cases, we usually perform dose adjustments to ESAs or hypoxia-inducible factor prolyl hydroxylase inhibitors.

In many cases, anemia is improved by these management practices, and we recognize that this improvement in renal anemia can be achieved by adjusting the dose of these agents. However, before performing these management practices, we should consider the possibility of cardiovascular stress due to volume overload. In patients with substantial excessive body fluid, as a strategy to improve anemia, removal of body fluid via a reduction in dry weight may be helpful. Additionally, for CKD patients, in addition to the administration of diuretics, sodium–glucose cotransporter inhibitors and sacubitril/valsartan may be promising choices.

Given that ~80% of hemodialysis patients have cardiac disease [40], renal anemia and anemia in heart failure may coexist frequently in hemodialysis patients, Although ESA administration is recommended for renal anemia [3, 4] but not for anemia in heart failure [18], it seems impractical that the strategies for treating these two anemia types differ. Compared with that in anemia in heart failure patients [35], the hemoglobin level in CKD and dialysis patients sometimes drops to severe levels, and ESA or some kind of hypoxia-inducible factor prolyl hydroxylase inhibitor is necessary to manage the extremely low hemoglobin level. Nonetheless, before using these agents, we should consider the influence of cardiovascular stress induced by the volume load as a possible factor in anemia and try to reduce cardiovascular stress.

Conclusions

The primary cause of renal anemia may not necessarily be reduced EPO production relative to a decreased hemoglobin level, which is likely more complicated. Cardiovascular stress induced by the volume load may have a substantial influence on anemia and prognosis in CKD and hemodialysis patients. To improve the prognosis of these populations, not only an approach targeting hemoglobin levels by ESA administration but also other points of view should be taken into consideration for the management of anemia.

Abbreviations

CKD	Chronic kidney disease
EPO	Erythropoietin
ESA	Erythropoietin-stimulating agent
NT-proBNP	N-terminal pro-brain natriuretic peptide

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Author contributions

SD contributed to the writing of the manuscript. The author has read and approved the final manuscript.

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Availability of data and materials

The datasets generated during the current study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee at the facility in which the studies were conducted and with the 1964 Helsinki Declaration guidelines and its later amendments or comparable ethical standards.

Consent for publication

Informed consent for publication was obtained from the individual participants included in the study.

Competing interests

The author declares that he has no competing interests.

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