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Abstract

There is a continuing increase in the prevalence of chronic kidney disease (CKD) and cardiovascular disease (CVD) with the aging of the population. Anemia is also frequently seen in both conditions, and the triad of anemia, CKD and CVD is known as the cardio-renal anemia (CRA) syndrome. The three conditions contribute to a vicious circle, in which each of them is capable of causing or being caused by another. Anemia itself can further deteriorate cardiac and renal functions and make the patients resistant to conventional CKD or CVD therapy. Thus, correction of anemia plays a crucial role in the prevention of the progression of both CKD and CVD. It has widely been accepted that the treatment of anemia with erythropoiesis-stimulating agents (ESAs) improves patients' quality of life and mortality, but recent randomized controlled studies have shown that targeting at higher hemoglobin levels in CKD patients increases the risks for CVD and end-stage renal disease. The reasons for these unexpected results are still obscure, and further studies are required to elucidate the precise mechanisms and to determine an appropriate hemoglobin level in patients with CRA syndrome.

Key Words: chronic kidney disease (CKD), cardiovascular disease (CVD), anemia, cardio-renal anemia (CRA) syndrome, erythropoiesis-stimulating agents (ESAs)

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Introduction

It is well known that chronic kidney disease (CKD) is common and that its prevalence is steadily increasing.[1] In Japan, CKD prevalence with reduced renal function has been estimated to be in excess of 18% of the population.[2] High prevalence of CKD may in part be explained by the current definition and classification of CKD based on the presence of persistent microalbuminuria and a low estimated glomerular filtration rate (GFR), since both markers have been shown to be associated with clinical as well as subclinical atherosclerosis in the elderly.[3] This leads to the concern that CKD is likely to reflect one of the manifestations of overt and subclinical atherosclerosis and cardiovascular disease (CVD).[4]

There are many studies demonstrating that CKD substantially increases the risks of death, cardiovascular events, and hospitalization in a large community-based population.[5-7] These findings highlight the importance of early detection and prevention of CKD. Anemia is known to be one of the most common and morbid complications of CKD, [8] causing unpleasant symptoms and increasing cardiovascular events. Strong associations between CKD, CVD and anemia are called the cardio-renal anemia (CRA) syndrome.[9] In this review, we summarize the concept of CRA syndrome and its management.

The CRA syndrome

There is no doubt that disorders such as diabetes mellitus, hypertension and glomerulonephritis are important and common risk factors for progressive CKD and end-stage renal disease (ESRD) requiring dialysis. In addition to their direct effects on the kidneys, these disorders can accelerate renal damage by causing ischemic, metabolic and hypertensive cardiac damage and by resulting anemia. On the other hand, many patients with CVD are also accompanied by CKD and anemia and these co-morbid conditions can further worsen CVD.[10] The triad of CKD, CVD and anemia is known as the CRA syndrome and interacts as a vicious circle so as to cause or worsen each other (Fig. 1). In this circle, CKD can cause CVD and anemia, CVD can cause CKD and anemia, and anemia can worsen CKD and CVD.

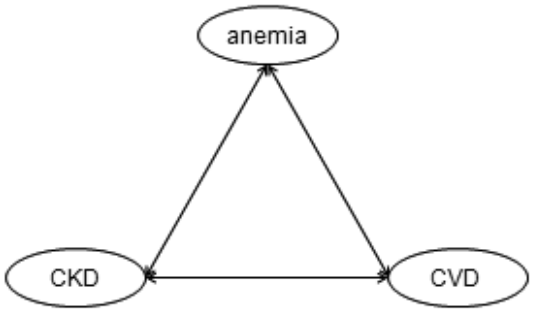

Fig. 1. The vicious circle involved in CRA syndrome
CKD: chronic kidney disease, CVD: cardiovascular disease, CRA syndrome: cardio-renal anemia syndrome

The importance of these interactions between CKD, CVD and anemia has been demonstrated by the study conducted in a large sample of the Medicare population in the USA (Table 1).[11] As shown in Table1, each of CKD, congestive heart failure which is mainly caused by CVD, and anemia increases 2-3 times the risks of death and ESRD, and these risks in patients with three conditions are markedly higher than those without morbid conditions. The interactions between CKD, CVD and anemia are probably mediated by many factors such as hypertension, volume overload, renin-angiotensin-aldosterone (RAA) system, sympathetic nerve activity, dyslipidemia, oxidative stress, inflammatory cytokines, malnutrition and other factors (Table 2).

Table 1. Two-year mortality and the risk for ESRD in a 5% sample of the Medicare population in the USA

	Two-year mortality (%)	Two-year risk for ESRD (%)
No CKD, CHF or anemia	7.7	0.1
Anemia	16.6	0.2
CKD	16.4	2.6
CKD and anemia	27.3	5.4
CHF	26.1	0.2
CHF and anemia	34.6	0.3
CKD and CHF	38.4	3.5
CKD, CHF and anemia	45.6	5.9

ESRD: end-stage renal disease, CKD: chronic kidney disease, CHF: congestive heart failure. Reprinted from Gilbertson D et al.[11]

Table 2. Possible mechanisms involved in CRA syndrome

traditional factors	Nontraditional factors
Older age	Albuminuria
Male sex	Volume overload
Hypertension	Renin-angiotensin-aldosterone system
Diabetes	Sympathetic nervous system
Smoking	Oxidative stress
Dyslipidemia	Inflammation
Physical inactivity	Malnutrition
Menopause	Thrombogenic factors
Family history of CVD	Nitric oxide/endothelin imbalance
	Homocysteine

Adapted from Sarnak MJ et al.[12]

These factors not only act together to cause damage but further stimulate each other.

CVD and anemia in CKD patients

CKD is now recognized as an important contributor to both ESRD and CVD. An American Heart Association statement published in 2003 has recommended that patients with CKD should be considered as members of the highest risk group for subsequent cardiovascular events.[12] Several large prospective studies have reported that CVD risk is independently associated with CKD markers, e.g. elevated serum creatinine, low estimated GFR and microalbuminuria.[7, 13] An independent, graded association has also been observed between a reduced estimated GFR and the risk of death, cardiovascular events, and hospitalization in a large, community-based population.[5] The adjusted hazard ratio for cardiovascular events is increased inversely as the estimated GFR decreases. In the general Medicare population, it has been indicated that CVD is twice as common and advances at a significantly higher rate in CKD patients, when compared with non-CKD group.[14]

Anemia is the most common and functionally important complication of CKD. It causes fatigue and dyspnea and reduces the quality of life. It has been well recognized that a reduced erythropoietin production by the kidneys resulting from renal damage is the most important contributor to the anemia in CKD patients. Recently, several studies have shown that anemia is an independent risk factor for the progression of CKD.[15, 16] Renal vasoconstriction and ischemia resulting from anemia, and the direct effects of RAA system and renal sympathetic nerve activity on renal tissue may cause renal fibrosis and further deterioration of renal function.[17] Anemia is also one of the serious risk factors causing the higher prevalence of CVD in patients with CKD. The strong association between anemia and CVD has been found in CKD patients.[8]

CKD and anemia in CVD patients

CVD can be an important risk factor for the prevalence of CKD as suggested by a large prospective study of hypertensive patients followed over 15 years.[18] The presence of CVD was the independent predictive risk factor for advancing to ESRD. The high prevalence of CKD in CVD patients and the increase in its severity in consonance with the progression of CVD have also been supported by other studies.[19] Another recent study has shown that patients with CKD and CVD progress to ESRD at a more rapid rate than those without CVD.[20] Impaired renal function observed in CVD patients has generally been attributed to both cardiovascular and hemodynamic effects.

It has been suggested that anemia is also frequently seen in CVD patients. There is a very wide variation in prevalence of anemia in CVD patients from 10-25% in some studies [21] to 40-60% in others.[22] The differences in prevalence in the various studies may result from the different definitions of anemia used and the different populations studied. Anemia in CVD patients is associated with higher mortality, increased hospitalization and a greater severity of CVD compared to non-anemic CVD patients.[23] Inverse relationship between the severity of CVD and hemoglobin level has also been noted by other researchers.[24] According to studies, this association has been found to be independent of other factors such as CKD, and CKD and anemia seem to be additive in increasing the severity of CVD.[22] Anemia in CVD patients has been assumed to be ascribed primarily to the associated CKD. However, it is unlikely that CKD is the sole explanation for the anemia in CVD, since anemia is also associated in CVD patients with normal renal function. Malnutrition and inflammatory cytokines including tumor necrosis factor-alpha and interleukin 6 have been proposed as other possible causes for anemia in CVD patients.[25]

Management of CRA syndrome

In CRA syndrome, anemia plays a key role in worsening of both CKD and CVD. Although early detection and optimal treatment of CKD or CVD are important to prevent the prevalence and progression of the disease, it appears that the maximum effects cannot be achieved by aggressive therapy for CKD or CVD alone without anemia correction. In the PRESAM study carried out in Europe and other countries, routine treatment of anemia with erythropoiesis-stimulating agents (ESAs) in pre-dialysis CKD patients has been associated with a reduced incidence of hospitalization for CVD and an inhibitory effect on the progression to ESRD.[26]

Similarly, it has been suggested that the intensive and early treatment of CVD in combination with anemia correction can prevent the worsening not only of CVD but of CKD as well.[27)]

ESAs have become a hallmark of anemia therapy since the first ESA, recombinant human erythropoietin (rHuEPO) that mimics the naturally occurring molecule in function, was introduced in the 1980s.[28)] The availability of rHuEPO led to extensive improvement in anemia and to a reduction in the need for blood transfusion in CKD patients. In addition, numerous studies have indicated that the rHuEPO therapy results in improvements in the patients' quality of life and the outcomes.[29)] As a result, rHuEPO treatment has become a standard management for dialysis patients, and has also been approved for anemia correction in pre-dialysis CKD patients.

The rHuEPO treatment was highly effective, but because of the short half-life of the molecule at approximately 6 to 8 h, new ESAs with improved characteristics have been developed in the recent two decades. Hyperglycosylated erythropoietin analogue has been introduced as a novel erythropoiesis stimulating protein with a 3-fold longer half-life compared to traditional rHuEPO.[30)] More recently, continuous erythropoietin receptor activator and erythropoietin-mimetic peptide with a chemical structure unrelated to naive erythropoietin have also become available or are under development as new ESAs with enhanced biological activity and prolonged half-life.[31)]

Although ESAs have been widely accepted for the treatment of anemia associated with CKD, optimal hemoglobin levels have not yet been established. A number of small studies conducted in the late 1980s supported the concept that higher hemoglobin concentrations are beneficial. However, recent randomized controlled trials have failed to confirm this concept and have found a strong tendency for increased mortality and other risks in the group of higher hemoglobin target.[32, 33)] It is difficult to provide reasonable interpretations of these findings, but some possibilities such as potential hemoconcentration, increased whole blood viscosity, instability in hemoglobin concentrations and higher exposure to ESAs have been proposed.[34)] Apart from these confounded results, there is a substantial body of evidence indicating the usefulness of anemia correction with ESAs for the prevention of prevalence and progression of both CKD and CVD. Further studies are needed to demonstrate the optimal anemia management in patients with CRA syndrome.

References

1) Coresh J, Selvin E, Stevens LA, Manzi J, Kusek JW et al. Prevalence of chronic kidney disease in the United States. JAMA 298: 2038-2047, 2007.
2) Imai E, Horio M, Iseki K, Yamagata K, Watanabe T et al. Prevalence of chronic kidney disease (CKD) in the Japanese general population predicted by the MDRD equation modified by a Japanese coefficient. Clin Exp Nephrol 11: 156-163, 2007.
3) Weir MR. Microalbuminuria and cardiovascular disease. Clin J Am Soc Nephrol 2: 581-590, 2007.
4) El Nahas M. Cardio-kidney-damage: a unifying concept. Kidney Int 78: 14-18, 2010.
5) Go AS, Chertow GM, FanD, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med 351: 1296-1305, 2004.
6) Weiner DE, Tighiouart H, Amin MG, Stark PC, MacLeod B et al. Chronic kidney disease as a risk factor for cardiovascular disease and all-cause mortality: a pooled analysis of community-based studies. J Am Soc Nephrol 15: 1307-1315, 2004.
7) Coresh J, Astor B, Sarnak MJ. Evidence for increased cardiovascular disease risk in patients with chronic kidney disease. Curr Opin Nephrol Hypertens 13: 73-81, 2004.
8) Kazmi WH, Kausz AT, Khan S, Abichandani R, Ruthazer R et al. Anemia: an early complication of chronic renal insufficiency. Am J Kidney Dis 38: 803-812, 2001.
9) Silverberg DS, Wexler D, Blum M, Wollman Y, Iaina A. The cardio-renal anaemia syndrome: does it exist? Nephrol Dial Transplant 18 (Suppl 8): Ⅷ 7-12, 2003.
10) McClellan WM, Langston RD, Presley R. Medicare patients with cardiovascular disease have a high prevalence of chronic kidney disease and a high rate of progression to end-stage renal disease. J Am Soc Nephrol 15: 1912-1919, 2004.
11) Gilbertson D, Li S, Murray AM, Herzog CA, Collins AJ. Competing risks of death vs ESRD in Medicare beneficiaries age 65+ with chronic

kidney disease, CHF and anemia. J Am Soc Nephrol 13: SA848, 2002.
12) Sarnak MJ, Levey AS, Schoolwerth AC, Coresh J, Culleton B et al. Kidney disease as a risk factor for development of cardiovascular disease: a statement from the American Heart Association Councils on kidney in cardiovascular disease, high blood pressure research, clinical cardiology, and epidemiology and prevention. Circulation 108: 2154-2169, 2003.
13) Manjunath G, Tighiouart H, Ibrahim H, MacLeod B, Salem DN et al. Level of kidney function as a risk factor for atherosclerotic cardiovascular outcomes in the community. J Am Coll Cardiol 41: 47-55, 2003.
14) Collins AJ, Li S, Gilbertson D, Liu J, Chen SC et al. Chronic kidney disease and cardiovascular disease in the Medicare population. Kidney Int 64: S24-31, 2003.
15) Keane WF, Brenner BM, De Zeeuw D, Grunfeld JP, McGill J et al. The risk of developing end-stage renal disease in patients with type 2 diabetes and nephropathy: The RENAAL study. Kidney Int 63: 1499-1507, 2003.
16) Mohanram A, Zhang Z, Shahinfar S, Keane WF, Brenner BM et al. Anemia and end-stage renal disease in patients with type 2 diabetes and nephropathy. Kidney Int 66: 1131-1138, 2004.
17) Nangaku M. Chronic hypoxia and tubulointerstitial injury: a final common pathway to end-stage renal failure. J Am Soc Nephrol 17: 17-25, 2006.
18) Perry HM, Miller JP, Fornoff JR, Baty JD, Sambhi MP et al. Early predictors of 15-year end-stage renal disease in hypertensive patients. Hypertension 25: 587-594, 1995.
19) Dries DL, Exner DV, Domanski MJ, Greenberg B, Stevenson LW. The prognostic implications of renal insufficiency in asymptomatic and symptomatic patients with left ventricular systolic dysfunction. J Am Coll Cardiol 35: 681-689, 2000.
20) Levin A, Djurdjev O, Barrett B, Burgess E, Carlisle E et al. Cardiovascular disease in patients with chronic kidney disease: getting to the heart of the matter. Am J Kidney Dis 38: 1398-1407, 2001.
21) Ezekowitz JA, McAlister FA, Armstrong PW. Anemia is common in heart failure and is associated with poor outcomes. Circulation 107: 223-225, 2003.
22) McClellan WM, Flanders WD, Langston RD, Jurkovitz C, Presley R. Anemia and renal insufficiency are independent risk factors for death among patients with congestive heart failure admitted to community hospitals: a population-based study. J Am Soc Nephrol 13: 1928-1936, 2002.
23) Silverberg DS, Wexler D, Blum M, Iaina A. The cardio renal anemia syndrome: correcting anemia in patients with resistant congestive heart failure can improve both cardiac and renal function and reduces hospitalization. Clin Nephrol 60 (Suppl 1): S93-102, 2003.
24) Horwich TB, Fonarow GC, Hamilton MA, MacLellan WR, Borenstein J. Anemia is associated with worse symptoms, greater impairment in functional capacity and a significant increase in mortality in patients with advanced heart failure. J Am Coll Cardiol 38: 1780-1786, 2002.
25) Iversen PO, Woldbaek PR, Tonnessen T, Christensen G. Decreased hematopoiesis in bone marrow of mice with congestive heart failure. Am J Physiol Regul Integr Comp Physiol 282: R166-172, 2002.
26) Valderabano F, Horl W, Macdougall IC, Rossert J, Rutkowski B, Wauters J-P. PRE-dialysis survey on anemia management. Nephrol Dial Transplant 18: 89-100, 2003.
27) Mancini DM, Katz SD, Lang C, La Manca J, Hudaihed A et al. Effect of erythropoietin on exercise capacity in patients with moderate to severe chronic heart failure. Circulation 107: 294-299, 2003.
28) Fishbane S, Nissenson AR. Anemia management in chronic kidney disease. Kidney Int 78 (Suppl 117): S3-9, 2010.
29) Lundin AP, Delano BG, Quinn-Cefaro R. Perspectives on the improvement of quality of life with epoetin alfa therapy. Pharmacotherapy 10 (2 Part 2): 22S-26S, 1990.
30) Egrie JC, Browne JK. Development and characterization of novel erythropoiesis stimulating protein (NESP). Nephrol Dial Transplant 16 (Suppl 3): 3-13, 2001.
31) Macdougall IC. Novel erythropoiesis-stimulating agents: A new era in anemia management. Clin J Am Soc Nephrol 3: 200-207, 2008.
32) Drueke TB, Locatelli F, Clyne N, Eckardt KU, Macdougall IC et al. Normalization of hemoglobin level in patients with chronic kidney

disease and anemia. N Engl J Med 355: 2071-2084, 2006.
33) Phrommintikul A, Haas SJ, Elsik M, Krum H. Mortality and target haemoglobin concentrations in anaemic patients with chronic kidney disease treated with erythropoietin: a meta-analysis. Lancet 369: 381-388, 2007.
34) Unger EF, Thompson AM, Blank MJ, Temple R. Erythropoiesis-stimulating agents – Time for reevaluation. N Engl J Med 362: 189-192, 2010.

要旨

高齢化とともに慢性腎臓病（chronic kidney disease, CKD）の患者は増え続けており，我が国では腎機能低下を伴ったCKD患者は全国民の18％以上に達すると推定されている．また，CKDは最終的には透析を必要とする末期腎不全に進行するとともに，心血管疾患（cardiovascular disease, CVD）発症の重要な危険因子でもあり，CKDやCVDでよくみられる貧血と合わせ，これら三者は互いに他を増悪しうる悪循環を形成していることから，近年，Cardio-renal anemia（CRA）症候群という疾患概念が提唱されている．CRA症候群では，貧血がCKDやCVDの発症・進展に重要な役割を果たしており，CKDやCVDの適切な治療とともに，貧血の改善が両疾患の進展抑制に欠かせないとされている．1980年代に導入された遺伝子組換えヒトエリスロポエチン製剤をはじめとする、いわゆる赤血球造血刺激薬（erythropoiesis-stimulating agents, ESAs）は，CKDにおける腎性貧血に対して劇的な改善効果をもたらし，現在ではESAsは透析患者だけでなく，透析前の保存期腎不全患者にも広く普及している．一般にESAsによる貧血の改善により，CKD患者やCVD患者ではQOLや死亡率の改善，疾患の進展抑制などがみられるとの報告がこれまでに多数あるが，一方で近年，CKD患者において目標ヘモグロビン値を高く設定すると逆にCVD発症のリスクが増加するとの報告も相次ぎ，過度な貧血の是正には警鐘が鳴らされている．高齢化の進展とともにCKDやCVDの予防・治療はますます重要になるものと思われ，CRA症候群においてどの程度まで貧血を是正すればよいのか，今後更に検討を重ねていく必要がある．

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