Anemia in patients of diabetic kidney disease

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Abstract: Anemia is the major complication resulting from chronic kidney disease (CKD) and also a risk factor for cardiovascular events and a poor quality of life (QoL). Diabetic kidney disease (DKD) is the major cause of CKD. Initially, insulin resistance has been reported to increase erythropoiesis, but it might be a minor issue. DKD-related anemia developed earlier and was more severe than non-DKD-related anemia based on more complicated mechanisms, including greater bleeding tendency associated with antiplatelet effect, less O_2 sensing due to autonomic neuropathy or renin-angiotensin-aldosterone system inhibitor use, inhibitory effect of inflammatory cytokines, urinary loss of erythropoietin (EPO), and poor response to EPO. In DKD patients, prompt correction of anemia allows for a better cardiovascular outcome and QoL, which are similar to the promising effect of anemia correction in CKD patients. However, current evidence recommended that the avoidance of a high or normalized hemoglobin (Hb) level has been suggested in the treatment of anemia in DKD patients. Despite that EPO has a pleotropic effect on renal protection from animal studies, the renal benefit was less evident in CKD and DKD patients. Recently, the antidiabetic agent, sodium glucose cotransporter-2 inhibitors (SGLT2i), has been reported to exhibit the renal benefits due to the tubulo-glomerular feedback in addition to sugar control. It may also be due to less renal ischemic through higher EPO levels, followed by higher Hb levels. More studies are needed to clarify the link between the renal benefit of SGLT2i and EPO production.

Keywords: Anemia; Chronic kidney disease; Diabetic kidney disease; Erythropoietin

1. INTRODUCTION

Anemia is a common and major complication in patients with chronic kidney disease (CKD). The anemia further progresses as the renal function declines. Anemia in CKD is a cause of fatigue, poor quality of life (QoL), congestive heart failure (CHF), and possible further progression of CKD.[1] Anemia itself may further worsen a patient's cardiac condition, which would cause them to become resistant to the standard treatments for CHF. This vicious cycle can only be stopped through proper treatment of anemia. Anemia is defined by the World Health Organization (WHO) as being when serum hemoglobin (Hb) levels ≤12 g/dL in women and ≤13 g/dL in men.[2] This definition is established for the general population and not specific for the CKD population. Renal anemia develops at stage 3 of CKD and increases up to 67% during stage 5 of CKD.[3] Moreover, in a study from Taiwan,[4] the prevalence of renal anemia rose up to 79.2% in stage 4 and 90.2% in stage 5 CKD, respectively. The benefit of the correction of renal anemia relied upon the patient's cardiovascular disease (CVD) and CHF.[5,6] CVD is a major cause of both morbidity and mortality in patients with CKD, during CKD (not yet at dialysis)[7] to end-stage renal disease (ESRD),[8] even after renal transplantation.[9] The correction of renal anemia in CKD has been clearly mentioned in the guidelines of the Kidney Disease Outcomes Quality Initiative (KDOQI).[10,11] Erythropoiesis-stimulating agents in CHF have concluded that anemia treatment improved exercise duration and capacity, ejection fraction, and New York Heart Association class, along with QoL and HF-related hospitalizations according to a systematic review.[12] The treatment goal of Hb in CKD has been recognized as being 10 to 11 g/dl, without more benefit resulting from even higher Hb levels.[11] However, the above observation is for general CKD patients, and is not specific for diabetes mellitus (DM)-related CKD patients.

DM is a leading cause of both CVD and ESRD. DM will cause diabetic kidney disease (DKD). New terminology to describe kidney disease attributable to DM has been introduced in recent guidelines (National Kidney Foundation, 2007) to replace diabetic nephropathy (DN).[13,14] However, in a separate definition,[15] DKD in diabetic patients is due to many causes, including hypertension, progression of acute kidney injury, and DN; which is a specific diagnosis referring to specific pathologic structural and functional changes due to DM.[15] In this review article, we will use the different definitions of DKD and DN in accordance with the later study.[15] DKD and DN will be the cause of >40% of ESRD in all CKD populations. However, no renal anemia guidelines have focused on this population. Moreover, many recent studies have indicated the renal benefits of new diabetic medications, along with their ability to control sugar levels in EMPA-REG,[16] DECLARE-TIMI 58,[17] CANVAS,[18] CREDENCE,[19] and LEADER.[20,21] The renal benefit of sodium glucose cotransporter-2 inhibitor (SGLT2i) can be also linked to the effects of

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erythropoietin (EPO) in DKD patients.[22] Accordingly, we will review renal anemia as it pertains to both DM and DKD.

2. HEMATOLOGIC MANIFESTATION IN DM

It is reasonable to experience renal anemia in DKD. However, prior to its progression to DKD, patients with DM may experience hematologic disorder (increased erythropoiesis). In 1980, Golde et al revealed that growth hormone polypeptides stimulated the proliferation of K562 human erythroleukemia cells.[23] Natural and biosynthetic insulin will also stimulate the growth of human erythroid progenitors in vitro study.[24] This may be due to the stimulatory effects of human insulin on erythroid progenitors (CFU-E and BFU-E) in human CD34+ separated bone marrow cells.[25] It has been noted that polycythaemia found in infants of diabetic mothers may be due to the stimulatory effects on erythroid progenitor growth by the hyperinsulinaemic environment in which they develop in utero.[26] According to Barbieri et al,[27] in-vivo evidence revealed that the relation between hyperinsulinemia/insulin resistance and erythropoiesis involved: red blood cell (RBC) count (r = 0.14; p < 0.001), plasma Hb (r = 0.16; p < 0.001), hematocrit (r = 0.15; p < 0.001), and plasma iron (r = 0.1; p < 0.05) concentrations. An increased RBC count could be considered as a new aspect with regards to insulin resistance syndrome, and that this increased erythropoiesis may be a cause of an increase in CVD. However, not all clinical studies have revealed these associations through the use of direct measurements of insulin resistance. A study of middle-aged and elderly diabetic patients taken by Chen et al[28] measured insulin resistance directly by using a homeostasis model assessment, which is the gold standard when evaluating insulin resistance. The team's results show that an elevated white blood cell count, rather than the RBC count, was significantly associated with insulin resistance and glycemic metabolism.[28] In our opinion, increased erythropoiesis in insulin resistance should not be measured because elderly subjects have an aging kidney and a lower glomerular filtration rate (GFR), which will in turn impair the erythropoiesis. The finding is consistent with results from a population in North East Italy, where obesity (insulin resistance) per se was not associated with high RBC, Hb, and hematocrit.[29] On the contrary, rather than increased RBC counts, 23% of the diabetic patients were diagnosed with anemia in a cross-section study.[30] Insulin resistance-related increased erythropoiesis can only be seen in a few studies taken from basic science.[23–26] These increased RBC counts cannot be detected in many animal studies or cross-sectional human studies[31] because there are many more factors associated with anemia in DM, including factors due to DM-related erythropoietic stress, which were reviewed, where DM will cause earlier and more severe anemia.[32] This may be partially due to the complex interrelationship among all other risk factors in DM-related anemia.[32]

All risk factors for anemia in the general population can also cause anemia in DM or DKD patients, including aging kidneys, source deficiency for RBC production (eg, Fe, folate, and vitamin B12), blood loss (particularly bleeding tendencies in DKD or uremic coagulopathy, or antiplatelet-related coagulopathy,[33] advanced glycation end products [AGE]-related RBC deformability[34]), and chronic inflammation (notably in DM or CKD-related chronic inflammation). In particular, DM was also identified as a risk factor for peptic ulcer bleeding in uremic patients.[33] Impairment of O_2 sensing for EPO production can be due to diabetic autonomic neuropathy,[35] reduced stabilization of hypoxia-inducible factor-1,[36] the adverse effects of medications[37] (eg, angiotensin converting enzyme inhibitors or angiotensin II receptor blocker), and reactive oxidative stress-related EPO insufficiency.[32] Finally, EPO-related factors can be the major components causing anemia, including urinary EPO excretion,[30] inflammatory cytokine (eg, interleukin-1, tumor-necrosis factor, and interferon-γ),[38,39] and AGE-related EPO resistance.[40] Among them, most factors have proved that DM-related anemia is due to DKD-related renal dysfunction, which further leads to EPO deficiency. Most conditions are linked to renal dysfunction.

3. ANEMIA IN DKD VS NON-DKD-RELATED CKD: TMING AND SEVERITY

3.1. Earlier onset

Anemia will begin during stage 3 CKD in all cases regardless of the causes. Notably, nearly all patients with stage 4 CKD will develop anemia. The prevalence of anemia in CKD is reported to be 1% in stage 3 CKD, 9% in stage 4 CKD, and 33% to 67% in stage 5 CKD.[3] In Taiwan, anemia is also a common complication of CKD. Nearly 60% of its prevalence has been reported in stage 4 CKD, while >90% of its prevalence has been reported in stage 5 CKD.[41] In a 2016 consensus stated in India,[42] early identification of anemia for treatment of DKD-related anemia is recommended to improve outcome. The earlier onset of anemia in DKD vs non-DKD-related CKD has previously been mentioned in many studies[32,37,43–45] and its causes have been reviewed in the previous section. Up to 1/3 of patients with DM and normal GFR have anemia as shown in a recent study.[46] DM is considered to be an independent risk factor for anemia (odds ratio = 2.2; p = 0.001).[43] Compared to non-DM patients, 47.8% of all DM patients had anemia (vs 33.2%; p = 0.004).[7] Similarly, in all stages of DM, approximately 30% of DM patients were diagnosed with anemia in an observational study involving one million all-stage CKD patients.[47] This percentage may rise up to 40.5% in all DM patients.[43]

3.2. More severe anemia

In a 2016 consensus stated in India,[42] early treatment of DKD-related anemia can improve outcomes, and is recommended due to there being more severe anemia in DKD. In a recent study,[4] the prevalence of anemia was more severe in both stage 3 and stage 3a CKD when comparing DKD to non-DKD-related CKD: 53.5% vs 33.1% in stage 3, p =0.001 and 60.4% vs 26.4% in stage 3a, p =0.0184. In addition, the distribution was generally toward lower levels in patients with DM (p = 0.024). It was seen that 10.9% of all DM patients experienced <11 g/dl of Hb (compared to 5.4% of all non-DM patients), while 20.7% of all DM patients were between 11 and 12 g/dl of Hb (compared to 12.5% of all non-DM patients). The serum ferritin was higher in diabetic patients than in nondiabetic patients during all stages, which may reflect the role of chronic inflammation in DM.[43] In other studies,[48–50] it was also mentioned that anemia in DM will be more severe than in other cause-related anemia. Earlier onset and more severe anemia in DKD, compared to non-DKD-related CKD, also reflects the higher risk of mortality in DM patients.

4. THE BENEFIT OF TRAETMENT FOR ANEMIA IN DKD

4.1. CV benefit

In all CKD patients, anemia will cause tissue hypoxia, increased sympathetic tone, volume retention, and reduced systemic vascular resistance. This will then further induce a decreased afterload and an increased preload, both of which will increase causing a high cardiac output HF. Therefore, rationale for the correction of anemia was based on a better CV outcome and QoL. However, a very high Hb level may cause hypertension and vascular thrombosis-related cerebrovascular accident,[51] with an increased mortality also being noticed in CHOIR[52] and

CREATE.[53] The optimal Hb level in CKD patients has been suggested to be between 10 and 11 g/dl, to gain peak maximum improvement in QoL, reduced morbidity, and better cardiac health and survival.[54,55] Although it was not a special study performed for DKD, >25% of CKD was DKD related in CHOIR[53] and >46.8% of CKD was DKD related in CREATE.[52] In TREAT in 2009,[56] which was a study regarding DKD-related CKD, the treatment group (those with approximately 13 g/dl of Hb) did not display better composite outcomes surrounding death or a CV event than the placebo group (those with <9 g/dl of Hb). Similarly, in another study (ACORD),[57] which was conducted regarding DKD-related CKD, patients with mild to moderate anemia, along with moderate left ventricular hypertrophy and any correction to an Hb target level of 13 to 15 g/dL, does not decrease the left ventricular mass index. However, normalization of the Hb level could prevent an additional increase in left ventricular hypertrophy, and is considered safe, while improving QoL. Both ACORD and TREAT targeted too high of an Hb level, compared to recent guidelines outlining anemia treatment.[10,11] Therefore, because >40% of CKD was due to DKD, correction of anemia was still suggested, but not too highly, in DKD-related anemia.

4.2. Renal benefit

The correction of anemia in CKD was mostly due to the benefits of CVD, CHF, and QoL. The renal benefit regarding the correction of anemia was less consistent. Hb is an independent risk factor for the progression of nephropathy to ESRD in type 2 DM.[58] In a study of animal models involving CKD,[59] there were pleiotropic actions of EPO, which can ameliorate both ischemic and nephrotoxic acute kidney injury. However, both CREAT[53] and CHOIR[52] cannot have renal benefit after the correction of anemia. Taken from indirect evidence,[60] a poor response to EPO was associated with a higher risk of ESRD (HR = 2.49, 95% CI 1.28-4.84). Recently, in a 2016 animal study of DN models,[61] EPO caused suppression of the inflammatory response, along with oxidative damage. Furthermore, a continuous EPO receptor activator could reduce renal fibrosis in the typical DN mode (db/db mouse), by reducing tubulointerstitial fibrosis.[62] Recently, new DM treatment guidelines have been published and there were renal benefit indicated, in addition to their ability to control sugar levels, including EMPA-REG,[16] DECLARE-TIMI 58,[17] CANVAS,[18] CREDENCE,[19] and LEADER.[20,21] SGLT2i was reported to offer renal benefit due to mainly tubuloglomerular feedback.[63] However, less renal hypoxia and better efficiency of energy usage has also been recently discussed.[63] SGLT2i is associated with a modest increase in hematocrit (2%-4%), relative to a placebo, for all 4 SGLT2is.[22] This cannot be explained by the diuresis effect-related hemoconcentration of SGLTi. The EPO level increased after the initiation of dapagliflozin and reached a plateau in 2 to 4 weeks.[64] SGLT2i may reduce ATP consumption by the Na+/K+ pump, while also reducing metabolic stress in the proximal tubular epithelial cells. Subsequently, reduced hypoxia in the microenvironment around the proximal tubules would cause further reversion of myofibroblasts to EPO-producing fibroblasts. Finally, this would enhance hematopoiesis and bring about a higher Hb. Interestingly, the newest antidiabetic agents offering renal benefit are also linked to EPO.

In conclusion, anemia is a common and major complication in patients with CKD. DKD is the major cause of ESRD. DKD-related anemia occurs earlier, is more severe, and is based on many complicated mechanisms. Early detection and correction will offer CV benefits, better QoL, and possible renal benefit in DKD-related CKD. The treatment goal was based mostly on a "not-only" DKD-related CKD population. The renal benefit of SGLT2i may also be linked to EPO.

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