In the name of GOD

Anemia-Related complication in CKD/ESKD

Dr.R.Abolghasemi
Nephrologist
SBMU
IRAN

Anemia-Related complication in CKD/ESKD

- Anemia is a common complication of CKD.
- It is associated with left **ventricular dysfunction** and **heart failure**, in addition to a **reduction in exercise capacity** and **quality of life**.
- Anemia of chronic renal disease is an independent risk factor for **death**, and it has been shown to promote faster progression of left ventricular hypertrophy**(LVH), increase peripheral oxygen demand**, and **worsen cardiac outcomes**.
- In addition, anemia in renal failure can lead to **depression**, **fatigue**, **stroke**, **reduced exercise tolerance**, and an increased rate of **hospital re-admission**

Anemia-Related complication in CKD/ESKD

- In people with CKD, severe anemia can increase the chance of developing heart problems because the heart is getting less oxygen than normal and is working harder to pump enough red blood cells to organs and tissues.

- People with CKD and anemia may also be at an increased risk for complications due to stroke

Effects of anemia on cardiovascular dysfunction

- Every 1 g/dL reduction in Hb concentration is associated with 6 percent increase in risk of LVH ,particularly when the serum Hb level is < 10 g/dL.
- The risk of morbidity and mortality decrease in CKD cases at Hb level > 11 g/dL
- Studies have shown that anemia correction has no effect on progression from kidney failure to end stage renal disease (ESRD).
- In correcting anemia, if Hb > 13 g/dL happens, then the risk of adverse outcome such as cardiovascular events, stroke and **death** will be increased.

Effects of anemia on cardiovascular dysfunction

- Cardiovascular disease is a major cause of morbidity and mortality in patients with CKD, including those undergoing maintenance dialysis.

- Severe anemia is an important, independent risk factor for the development and progression of (LVH) & (HF) and of adverse cardiovascular outcomes, including mortality.

- anemia among patients with CKD is associated with more HF hospitalizations .

Effects of anemia on cardiovascular dysfunction: LVH

- LVH is a major risk factor for cardiovascular morbidity and mortality in patients with ESKD .

- LVH is common among patients with ESKD or near ESKD, with a reported prevalence of up to 75 percent.

- **Anemia** has been identified as a risk factor for the development of LVH in patients on dialysis and in patients with nondialysis CKD.

Pathophysiology of effects of anemia on cardiovascular dysfunction: LVH

- Potential mechanisms that may explain the relationship between anemia and the development of LVH among CKD patients include:

❑Effects of reduced oxygen delivery to the myocardium, perhaps leading to increased myocyte necrosis and apoptosis.

❑Anemia-related increased COP and reduced SVR.

❑Increased oxidative stress.

❑Activation of the SNS.

Effect of anemia treatment on LVH

- The treatment of severe anemia with ESAs is associated with improvement of left ventricular hypertrophy (LVH).

- Among patients with baseline **severe** anemia ([Hb] levels <10g/dL) ESA treatment to increase Hb levels to ≤12 g/dL was associated with significant reductions in left ventricular mass index.

- The treatment of **moderate** anemia (ie, Hb ≥10 g/dL) to either Hb levels >12 g/dL or ≤12 g/dL was **not** associated with significant changes in the left ventricular mass index.

Effect of treatment of anemia on heart failure

- improvement in the clinical manifestations of HF after prolonged treatment of anemia in CKD patients.
- One study of 126 CKD patients with HF, an increase in the mean Hb level from 10.3 to 13.1 g/dL was associated with a rise in the mean left ventricular EF ,falls in the mean (NYHA) class ,and number of hospitalizations. An index of fatigue and shortness of breath also fell significantly.
- A systematic review of nine randomized trials of ESAs in HF, not all specifically in patients with CKD, concluded that anemia treatment improved exercise duration and capacity, ejection fraction, NYHA class, quality-of-life indicators, and HF-related hospitalizations.

Effect of treatment of anemia on heart failure

- Another meta-analysis of randomized, controlled trials found that ESA treatment improved dyspnea and NYHA class; there was no significant improvement in mortality or hospitalization, but there was increased risk of thromboembolic events.

- Increased morbidity and/or mortality has been associated with attaining normal or near-normal Hb levels with ESAs.

- An increase in thromboembolic events and a nonsignificant increase in strokes .

Coronary heart disease

- Exercise-mediated cardiac ischemia is also ameliorated with partial correction of severe anemia.

Impact of Anemia on Mortality Risk

- Reduced carriage of oxygen to tissues could contribute to mortality risk.
- Observational studies have consistently demonstrated a strong association between lower Hb concentrations in dialysis patients and increased risk for death.
- Hct < 27%, the relative risk for death was 1.33 compared with patients with Hct of 30% to 33%. Several other studies also concluded that lower Hb concentrations in CKD are associated with increased risk for mortality.
- It is important to note that in contrast to these observational studies, interventional trials have failed to find that rHuEPO treatment, generally to near-normal Hb concentrations, improves mortality risk.

Mortality

- Anemia is an important, independent risk for mortality.
- The combination of anemia and LVH may be associated with an even higher risk of adverse cardiovascular outcomes.
- In another study of 415 CKD patients, the combination of anemia and LVH also increased the risk of a cardiovascular event (defined as cardiovascular death, hospitalization for unstable angina or HF, nonfatal myocardial infarction, ventricular arrhythmia, or transient ischemic attack/stroke.
- however, treatment of anemia to normal or near-normal Hb levels with ESAs does not reduce morbidity or mortality among patients with CKD, including dialysis patients.

PROGRESSION OF CHRONIC KIDNEY DISEASE

- Anemia may be a risk factor for progression of CKD, including to end-stage kidney disease (ESKD).

- In study of 415 CKD patients, the combination of anemia and left ventricular hypertrophy (LVH) was also associated with faster renal decline compared with patients with no anemia and no LVH.

PROGRESSION OF CHRONIC KIDNEY DISEASE

- The mechanism for a faster decline in kidney function with more severe anemia is not known with certainty but might

❑involve low-grade kidney ischemia or

❑effects of underlying inflammation causing both anemia and CKD progression.

❑From **animal** models of ischemic and nephrotoxic kidney injury, various mechanisms by which erythropoietin might have **renoprotective** effects have been proposed.

❑These include reduced apoptosis, increased tubular regeneration, decreased caspase activity, and decreased interstitial fibrosis

Does anemia hasten kidney function decline or does anemia simply become more frequent with diminished kidney function?

Effects of Anemia in CKD

- There has been interest in whether anemia might hasten the progression of kidney disease by depriving the kidneys of needed oxygen.
- **RENAAL trial** sought to address the issue.
- In a post hoc analysis, found that among 1,513 participants, initial Hb concentration was a significant predictor of time to dialysis therapy and doubling of serum creatinine concentration.
- For every 1-g/dL decrease Hb concentration, there was 11% greater chance of these dual renal outcomes.

Anemia & CKD

- There is conflicting evidence concerning the effect of correction of anemia on the rate of progression of renal failure.

- Two meta-analyses **(TREAT) &(CHOIR)** trial that included trials comparing higher versus lower hemoglobin targets, or ESA treatment versus control, concluded that there was **no** significant protective effect of higher targets or ESA treatment on CKD progression.

A Trial of Darbepoetin Alfa in Type 2 Diabetes and Chronic Kidney Disease (TREAT TRIAL)

- The use of **darbepoetin alfa** in patients with diabetes, chronic kidney disease, and moderate anemia who were not undergoing dialysis did **not** reduce the risk of either of the two primary composite outcomes (either death or a cardiovascular event or death or a renal event) and was associated with an **increased** risk of stroke.

Correction of Anemia with Epoetin Alfa in Chronic Kidney Disease (CHOIR TRIAL)

- The use of a target hemoglobin level of 13.5 g per deciliter (as compared with 11.3 g per deciliter) was associated with increased risk and no incremental improvement in the quality of life.

SUMMARY AND RECOMMENDATIONS

- **Anemia and adverse cardiovascular outcomes** – Among patients on dialysis, severe anemia is a risk factor for the development and progression of (LVH), (HF), and mortality.
- **Effect of anemia treatment** – The treatment of severe anemia with erythropoiesis-stimulating agents (ESAs) is associated with improvement of LVH and clinical manifestations of HF. However, increased morbidity and/or mortality have been associated with attaining normal or near-normal hemoglobin (Hb) levels with ESAs.
- **Anemia and progression of (CKD)** – Among patient with nondialysis CKD, anemia may be a risk factor for progression of kidney dysfunction to (ESKD). The treatment of moderate anemia with ESAs has not been convincingly demonstrated to decrease progression to ESKD.