

Impact of anaemia management on the quality of life of CKD patients

Chronic kidney disease (CKD) is a global public health problem affecting over 10% of the general population worldwide, amounting to over 800 million individuals. It is associated with increased risks of cardiovascular morbidity and premature mortality, and has an intense impact on a patient's quality of life (QoL). As nephrology is progressing and patients receive more focused care, recognition of the importance of QoL has led to increased interest in this area.

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There is a wide range of instruments that can be used to assess QoL, but the most commonly used in the CKD population are the 36-Item and the 12-Item Short Form Health Surveys (SF-36 and SF-12), and the European QoL 5 Dimensions questionnaire (EQ-5D). SF-36 is a globally established, validated and frequently used questionnaire. The first version was developed in 1988 as a self-report measure of functional health and well-being. It was further modified concerning certain item formulations and possible responses. The questionnaire consists of 36 questions reflecting 8 domains of health: physical functioning, vitality, bodily pain, general health perceptions, role limitations due to physical health, role limitations due to emotional health, social role functioning and mental health. Likert scales and yes/no options are used to score function and well-being. Scales are then standardized to obtain a final score ranging from 0 to 100, with higher scores indicating better health status. The SF-12 was designed as an abbreviated version of the SF-36 and validated based on assessing how well the twelve-item scale scores predicted the 36-item scale scores. Both questionnaires have been validated in the CKD and dialysis populations showing similar prognostic association with death and hospitalization risk.

The EQ-5D is also a widely used instrument which evaluates the generic quality of life with one question for each of the five dimensions - mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The maximum score of 1 indicates the best health state. In addition, there is a visual analogue scale to indicate the general health status with 100 indicating the best health status. Although all these instruments have been extensively used in the CKD population, none of them specifically focused on CKD-related anaemia.



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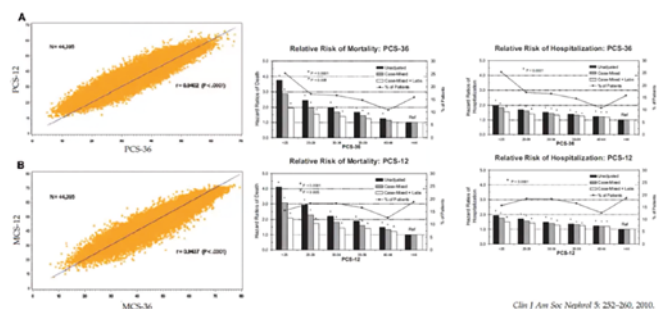


Figure 1.
Correspondence between SF-36 and SF-12 scores in predicting mortality and hospitalization risk

Clin J Am Soc Nephrol 5: 252-260, 2010.

Quality of life and haemoglobin levels

As is well-known, anaemia has a significant adverse impact on the QoL in CKD patients. Therefore, treating CKD-related anaemia notably improves patients' QoL, especially in the domains of fatigue and physical symptoms. These improvements in physical functioning translate into higher work productivity and lower absenteeism. Nevertheless, most data related to the association between haemoglobin levels and QoL rely on observational studies with limited insight into causality. The complexity of this association is further underlined by the conflicting results from different researches. Three large randomized trials investigated the longitudinal impact of anaemia treatment on QoL in over 6,000 non-dialysis-dependent CKD patients. The studies were conducted between 2006 and 2011 with a median follow-up period ranging from 16 months to 3 years. Each study utilized a different erythropoiesis-stimulating agent – epoetin alfa, epoetin beta, or darbepoetin alfa, and QoL was consistently assessed with SF-36 and EQ-5D questionnaires. Epoetin beta treatment to reach target haemoglobin 13-15g/dL compared to target 10.5 – 11.5g/dL resulted in significantly better QoL in domains of general health, mental health, physical function, physical role, social function and vitality after one-year follow-up, and persisted at the end of the two-year follow-up for general health. There was no significant difference in the combined incidence of adverse events between the two groups, although hypertensive episodes and headaches were more prevalent with higher haemoglobin levels. In contrast to these findings, darbepoetin alfa triggered significant improvements only in EQ-5D scores compared to placebo, whereas SF-36 showed only modest and inconsistent improvements in fatigue and physical scores in the treatment group after 97 weeks of follow-up. Finally, epoetin alfa treatment to achieve haemoglobin levels of either 13.5 g/dL or 11.3 g/dL returned matching improvements in the QoL in the two groups, but with an observed increased risk for serious adverse events in the high-haemoglobin group.

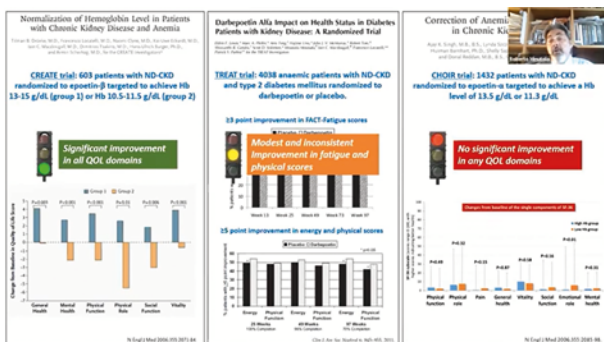


Figure 2.

Effects of achieving different haemoglobin targets on QoL

A subsequently published meta-analysis of 17 randomized controlled trials that evaluated targeting higher versus lower haemoglobin levels with ESAs in over 10,000 CKD patients also showed no significant benefits in QoL, regardless of whether the patients were on renal replacement therapy or not. In fact, as one more recent meta-analysis concluded – reaching haemoglobin above the recommended targets may be associated with small but potentially clinically significant improvement in fatigue, but not in the physical role or physical function. Still, the younger and non-diabetic population might experience larger benefits of higher haemoglobin levels.

Quality of life and iron status

Iron plays a crucial role in erythropoiesis, but it is also essential in many other biological functions, including energy cell metabolism. However, while a decrease in iron availability results in iron deficiency, anaemia, and disturbance of energy metabolism, increased intracellular iron content may result in oxidative injury and cell toxicity. Iron deficiency is a common finding among CKD patients and is associated with worse clinical outcomes in observational studies. A recent multicentric study concluded that low transferrin saturation is associated with the worse physical component of QoL in non-dialysis-dependent CKD patients, regardless of the ferritin levels. Still, iron supplementation does not improve QoL in the long term, even though it does have short-term beneficial effects on exercise capacity and contributes to the reduction of the ESA dose needed to achieve target haemoglobin levels.

The Iron and the Heart Study: RCT in 56 non-anaemic patients (Hb 11-15 g/dL) with CKD 3b-5 and ID (TSAT<20% and/or ferritin <100 ng/mL) comparing 1 g of IV ferric derisomaltose versus placebo in improving exercise capacity. Secondary objectives included QoL (SF-36)

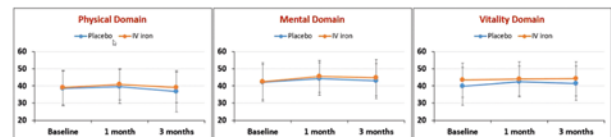


Figure 3.

Effects of intravenous iron supplementation in non-anaemic CKD patients on QoL domains

Quality of life with new anaemia drugs

The approach to anaemia in CKD has seen major progress with the development of several new agents that not only promote erythropoiesis but also modulate iron metabolism and inflammatory activity to support this process. The novel class of hypoxia-inducible factor prolyl-hydroxylase inhibitors (HIF-PHIs) appear to be more physiologic than the currently used ESAs with a favourable safety profile. Their effect on QoL has also been a subject of research in recent years. The ASCEND-NHQ trial assessed the effects of daprodustat compared to placebo on anaemia and QoL in a multicenter, randomized, double-blind, placebo-controlled trial in 614 non-dialysis-dependent CKD patients. According to the recently published results from this investigation, besides substantial anaemia improvement, HIF-PHI was also associated with significantly reduced fatigue after 28 weeks of follow-up. The adverse events rate was similar with HIF-PHI and placebo. Nevertheless, these findings still need to be substantiated in future studies, since several randomized controlled trials comparing HIF-PHI and ESAs did not observe notable differences between these therapeutics related to QoL improvement, likely due to achievement of similar hemoglobin levels.

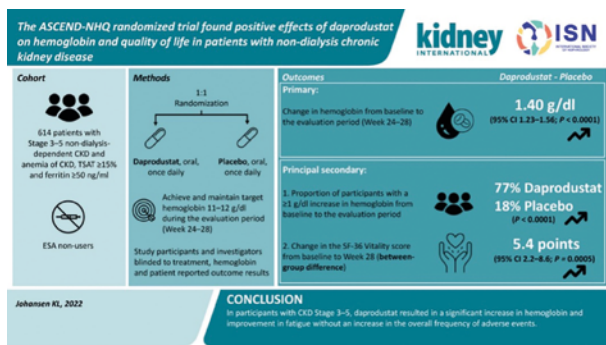


Figure 4.

Effects of achieving different haemoglobin targets on QoL

Limitations of quality of life assessment in dialysis practice and clinical studies

Despite its importance, QoL is still not routinely assessed and followed in the CKD population due to multiple constraints, including a surge in the number of predialysis and dialysis patients, shortages in all care providers in nephrology, erroneous assumption that symptoms are inevitable with CKD, and different perceptions of relevant treatment outcomes among patients and caregivers. While healthcare professionals are primarily focused on quantifiable outcomes such as mortality, adverse events and biological markers, patients tend to prioritize issues that are more relevant to their

daily living and well-being. Therefore, future studies should consider implementing the concepts of minimal detectable change, minimal important change and changes over time in patient's priorities to more accurately interpret patient-related outcome measures, such as symptom burden and QoL.

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All the speakers reviewed and approved the content.

KEY POINTS

- 1 Anaemia is commonly present and significantly associated with lower QoL among CKD patients
- 2 Available randomized studies rendered conflicting results regarding the effects of reaching higher target haemoglobin levels on QoL.
- 3 Iron supplementation does not contribute to long-term improvement in QoL, even though it has short-term beneficial effects on exercise capacity.
- 4 New anaemia drugs, the HIF-PHIs, showed modest results in terms of QoL improvement, mainly in the fatigue domain.
- 5 Future studies should focus more on patient-reported outcomes when assessing the potential benefits of anaemia treatment.

Further readings

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