

ANEMIA OF CHRONIC KIDNEY DISEASE AND END-STAGE RENAL DISEASE: ARE THERE UNIQUE ISSUES IN DISADVANTAGED POPULATIONS?

Several sources of data indicate that there are racial and ethnic disparities in the management of anemia of chronic kidney disease and end-stage renal disease. In this article, I present evidence documenting these disparities and discuss possible factors that may explain the suboptimal anemia management. I also provide recommendations to improve anemia management in disadvantaged populations. (*Ethn Dis.* 2009;19[Suppl 1]:S1-52-S1-55)

Key Words: Anemia, Chronic Kidney Disease, End-stage Renal Disease

ANEMIA MANAGEMENT IN DISADVANTAGED POPULATIONS

In a cross-sectional study of 5222 adult patients with different stages of chronic kidney disease (mostly stages 1–4) who were selected from 237 US physician practices (including family practice, internal medicine, nephrology and endocrinology), the mean hemoglobin levels for Caucasians, African Americans, Hispanics, Asian, Native Americans, and other races were 12.4, 11.7, 11.8, 12.2, 11.5, and 12.4 g/dL, respectively, and the prevalence of anemia, defined as hemoglobin <12 g/dL, was 44%, 59%, 54%, 48%, 60%, and 43%, respectively (Figure 1).¹ In a multivariate analysis that adjusted for age, sex, postmenopausal state, estimated glomerular filtration rate, transferrin saturation, and ferritin, the relative risks (and 95% confidence interval) of having a hemoglobin level <12 g/dL for African Americans, Hispanics, Native Americans, and Asians compared with Caucasians were 1.61 (1.40–1.85), 1.52

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(1.15–2.0), 1.49 (0.52–4.30), and 1.43 (0.95–2.15), respectively. In another study of all patients who began chronic dialysis between 1995 and 1997 in the United States, the percentage of patients with hematocrit <28% for Caucasians, African Americans and other races was 46%, 59%, and 55%, respectively, and the percentage of patients who received predialysis erythropoietin was 23%, 16%, and 21%, respectively.² In a multivariate analysis that adjusted for several factors, the relative risk of having a hematocrit <28% for African Americans and other races compared with Caucasians was 1.40 (1.36–1.44) and 1.33 (1.27–1.39), respectively; likewise, the relative risk for receiving predialysis erythropoietin was .84 (.81–.87) and .94 (.90–1.00), respectively.

Although hematocrit levels and predialysis erythropoietin use among US dialysis patients have improved over time, the racial and ethnic disparities remain. Indeed, among 334,883 incident US dialysis patients from April 1995 through December 1999, the mean hematocrit level at the initiation of dialysis increased from 28.1% to

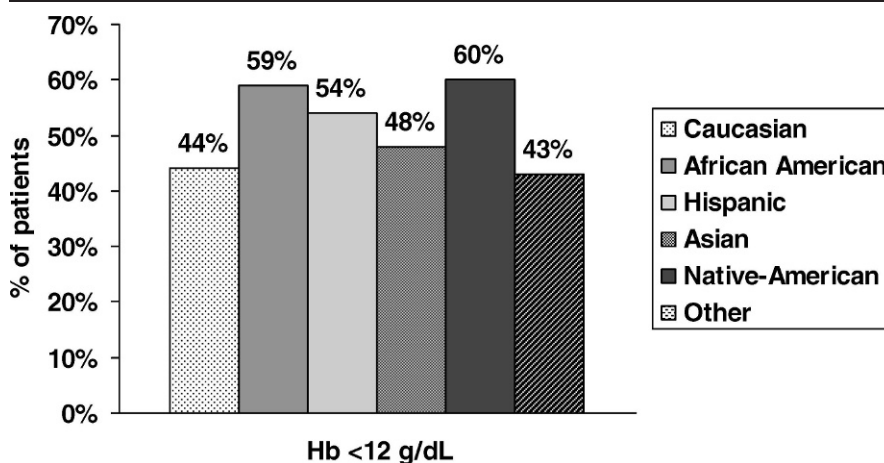


Fig 1. Prevalence of anemia (defined as hemoglobin <12 g/dL) in a cohort of patients with chronic kidney disease

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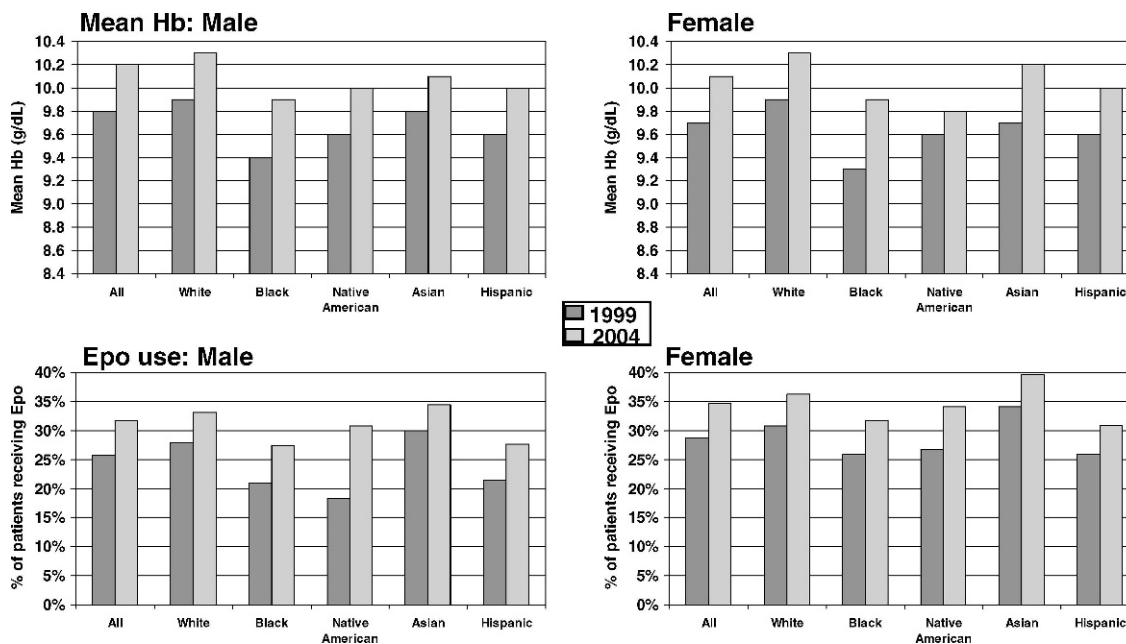


Fig 2. Mean hemoglobin and erythropoietin (Epo) use at initiation of dialysis in incident US dialysis patients (United States Renal Data System Annual Data Report 2006)

29.3%, and the prevalence of predialysis erythropoietin use increased from 21.8% to 28.1% during the study period.³ However, the percentages were significantly lower for African Americans and other races than for Caucasians. More recent data from the US Renal Data Registry (USRDS) also showed a lower mean hemoglobin level at the initiation of dialysis and a lower prevalence of predialysis erythropoietin use between 1999 and 2004 among African Americans and Hispanics than among Caucasians and other races (Figure 2). By contrast, there are no significant racial and ethnic differences in mean hemoglobin level among prevalent hemodialysis patients, suggesting that once patients are on hemodialysis, they receive enough erythropoietin to raise their hemoglobin level to a similar level regardless of race or ethnicity.⁴

Limited data are available regarding anemia management in developing countries. In a retrospective analysis of 84 patients who began chronic hemodialysis between 2002 and 2006 at the National

Institute of Cardiology, a tertiary care center in Mexico City, the mean age of the patients was 29 years, 46% were women, 30% completed primary school, 40% attended high school, and the median monthly income was \$200. The mean hematocrit level at the initiation of dialysis was $22.8\% \pm 6\%$ (range, 9%–37%), 81% of patients had an hematocrit level $<28\%$, and only 4 patients (4.3%) received predialysis erythropoietin. The mean hematocrit among patients who received predialysis erythropoietin was $25.3\% \pm 6\%$ compared with $22.6\% \pm 6\%$ among those who did not (unpublished data). Likewise, at the Civil Hospital of Guadalajara, Mexico, which mostly serves a very poor and uninsured population, the mean hematocrit level of 274 patients who presented with end-stage renal disease in 2003 was $22.8\% \pm 5.7\%$. This level is significantly lower than a mean hematocrit of $27.9\% \pm 5.7\%$ in incident Hispanic USRDS patients who did not have medical insurance and survived at least 90 days after dialysis initiation, regardless of dialysis modality.⁵

In summary, there are racial and ethnic disparities regarding prevalence of anemia of chronic kidney disease and predialysis erythropoietin use in disadvantaged populations. Specifically, African Americans, Hispanics, and Native Americans have a higher prevalence of anemia and a higher adjusted relative risk of anemia and of not having received predialysis erythropoietin compared with Caucasians. Despite overall improvement in trends of predialysis anemia management, the racial and ethnic disparities still remain. Mean hematocrit and predialysis erythropoietin use is quite low in disadvantaged populations of some developing countries.

FACTORS THAT MAY EXPLAIN SUBOPTIMAL ANEMIA MANAGEMENT IN DISADVANTAGED POPULATIONS

We can speculate about factors that may contribute to suboptimal anemia management in disadvantaged popula-

tions. They can be grouped as patient-related, treatment-related, and health-care system-related factors.

Among patient-related factors, race and attitudes toward seeking or accepting medical care appear to be important. African Americans have hemoglobin levels that are .5–.9 g/dL lower than those of Caucasians and Asian populations.^{6–8} Although the reasons for this phenomenon are unknown, unmeasured differences in underlying levels of chronic inflammation or a higher prevalence of certain conditions (ie, hemoglobinopathies) may play a role. The attitudes toward seeking or accepting medical care are influenced by cultural factors, such as level of health education and trust in the medical establishment. In addition, several studies have shown that African Americans are less likely to adhere to medications than Caucasians^{9–11} and that they are more likely to deny the need for a kidney transplant and are less accepting of their situation than are non-African Americans.¹²

Regarding treatment-related factors, lack of access to erythropoietin therapy is a critical issue, particularly in some developing countries where erythropoietin is not available for most patients because of its cost. Differences in erythropoietin and iron dose may also play a role. The USRDS has reported that the mean hemoglobin level of prevalent US hemodialysis patients is similar in all racial and ethnic groups, but African Americans receive significantly higher erythropoietin doses than any other group.⁴ Moreover, the mean hemoglobin level of prevalent peritoneal dialysis patients is lower in African Americans than that of other racial and ethnic groups; however, African Americans receive significantly higher erythropoietin doses compared with the other groups. Although it is unknown why African American dialysis patients require more erythropoietin to achieve the same or lower hemoglobin level, we can speculate that lack of adjustment for body mass index could at least partially explain the

differences. Additional factors may include reimbursement policies for erythropoietin, which may be related to the type of dialysis facility in which African American patients are dialyzed, differences in co-morbidities or inherent response to erythropoietin, and differences in iron use. Regarding the latter factor, a recent study reported no significant difference in the prevalence of intravenous iron use between Caucasian and African American US prevalent dialysis patients.¹³

Regarding healthcare system-related factors, the presence and type of medical insurance can have a profound impact on patient's eligibility for and means to afford erythropoietin. In addition, reimbursement for erythropoietin can vary widely among third-party providers, and may depend in part on the hemoglobin/hematocrit value at the initiation of therapy. In the study previously mentioned of all patients who began chronic dialysis in the US between 1995 and 1997, there was substantial racial and ethnic variation in insurance coverage, with Medicaid and lack of insurance being significantly more common among African Americans and Hispanics than in other racial and ethnic groups.² Not unexpectedly, the prevalence of having a hematocrit <28% at the initiation of dialysis was higher among patients covered by Medicaid or uninsured (59% and 62%, respectively) than that of those covered by private insurance or Medicare (49% and 50%, respectively). Likewise, the prevalence of predialysis erythropoietin use was significantly lower for those covered by Medicaid or uninsured (19.5% and 14.5%, respectively) than that of those covered by private insurance or Medicare (27.5% and 21.5%, respectively). In a multivariate analysis, after adjusting for a variety of factors, such as age, sex, race, employment, diabetes, functional status, dialysis modality, end-stage renal disease network, erythropoietin use (for the hematocrit <28% model) and hematocrit level (for the erythropoietin use model), the type of medical insurance was independently associated with a

hematocrit <28% at the initiation of dialysis and with not having received predialysis erythropoietin. Specifically, compared to private insurance, the adjusted relative risk (and 95% confidence interval) for having a hematocrit <28% at the initiation of dialysis for those covered by Medicaid and the uninsured was 1.22 (1.16–1.27) and 1.34 (1.27–1.41), respectively, and for having received predialysis erythropoietin was .66 (.63–.70) and .49 (.45–.52), respectively. We can conclude from these data that Medicaid and lack of insurance are strong predictors of suboptimal anemia management. However, the contribution of more broad socioeconomic factors unrelated to insurance cannot be excluded.

Other healthcare system-related factors that may contribute to suboptimal anemia management in disadvantaged populations include lack of access to health care and physician referral patterns. Several studies have shown an association between suboptimal anemia management and late referral to the nephrologist. As an example, in a retrospective study of 135 patients who began dialysis at the New England Medical Center, the prevalence of hematocrit <28% at the initiation of dialysis among patients who were referred late (<4 months before initiation of dialysis) was 55% compared to 33% among those who were referred early (≥ 4 months before the initiation of dialysis).¹⁴ Likewise, the prevalence of predialysis erythropoietin use was 17% among those who were referred late compared with 40% among those who were referred early.

RECOMMENDATIONS TO IMPROVE ANEMIA MANAGEMENT IN DISADVANTAGED POPULATIONS

Most clinical practice guidelines recommend starting erythropoiesis-

stimulating agents when the hemoglobin level is <11 g/dL; they also provide recommendations for anemia management.¹⁵⁻¹⁷ A critical factor for improving anemia of chronic kidney disease in disadvantaged populations is to improve access to health care by means of universal coverage, reimbursement for ESAs, and timely referral to the nephrologist. However, since the prevalence of predialysis erythropoietin use remains low even in developed countries where erythropoiesis-stimulating agents are more widely available,⁴ an effort should be made to educate physicians and other healthcare providers on the proper use of these agents as well as iron. In addition, efforts should be made to improve patients' attitudes towards receiving and accepting medical care. Improved access to health care and appropriate use of erythropoiesis-stimulating agents and iron therapy may result in better anemia management in these patients.

REFERENCES

- McClellan W, Aronoff S, Bolton W, et al. The prevalence of anemia in patients with chronic kidney disease. *Curr Med Res Opin.* 2004;20:1501-1510.
- Obrador GT, Ruthazer R, Arora P, Kausz AT, Pereira BJ. Prevalence of and factors associated with suboptimal care before initiation of dialysis in the United States. *J Am Soc Nephrol.* 1999;10:1793-1800.
- Obrador GT, Roberts T, St Peter WL, Frazier E, Pereira BJ, Collins AJ. Trends in anemia at initiation of dialysis in the United States. *Kidney Int.* 2001;60:1875-1884.
- US Renal Data System. *USRDS 2006 Annual Data Report.* Bethesda, Md: National Institutes of Health; 2006.
- Garcia-Garcia G, Briseno-Renteria G, Luquin-Arellan VH, Gao Z, Gill J, Tonelli M. Survival among patients with kidney failure in Jalisco, Mexico. *J Am Soc Nephrol.* 2007;18:1922-1927.
- Meyers L, Habicht J, Johnson C. Components of the difference in hemoglobin concentrations in blood between Black and White women in the United States. *Am J Epidemiol.* 1979;109:539-549.
- Cresanta J, Croft J, Webber L, Nicklas T, Berenson G. Racial differences in hemoglobin concentration of young adults. *Prev Med.* 1987;16:659-669.
- Pan W, Habicht J. The non-iron deficiency related difference in hemoglobin concentration distribution between Blacks and Whites and between men and women. *Am J Epidemiol.* 1991;134:1410-1416.
- Ganz DA, Glynn RJ, Mogun H, Knight EL, Bohn RL, Avorn J. Adherence to guidelines for oral anticoagulation after venous thrombosis and pulmonary embolism. *J Gen Intern Med.* 2000;15:776-781.
- Charles H, Good CB, Hanusa BH, Chang CC, Whittle J. Racial differences in adherence to cardiac medications. *J Natl Med Assoc.* 2003;95:17-27.
- Shenolikar RA, Balkrishnan R, Camacho FT, Whitmire JT, Anderson RT. Race and medication adherence in Medicaid enrollees with type-2 diabetes. *J Natl Med Assoc.* 2006;98:1071-1077.
- Lunsford SL, Simpson KS, Chavin KD, et al. Racial differences in coping with the need for kidney transplantation and willingness to ask for live organ donation. *Am J Kidney Dis.* 2006;47:324-331.
- St Peter WL, Obrador GT, Roberts TL, Collins AJ. Trends in intravenous iron use among dialysis patients in the United States (1994-2002). *Am J Kidney Dis.* 2005;46:650-660.
- Arora P, Obrador GT, Ruthazer R, et al. Prevalence, predictors, and consequences of late nephrology referral at a tertiary care center. *J Am Soc Nephrol.* 1999;10:1281-1286.
- Locatelli F, Aljama P, Barany P, et al. Revised European best practice guidelines for the management of anaemia in patients with chronic renal failure. *Nephrol Dial Transplant.* 2004;19:ii1-47.
- KDOQI clinical practice guidelines and clinical practice recommendations for anemia in chronic kidney disease. *Am J Kidney Dis.* 2006;47:S11-145.
- KDOQI clinical practice guidelines and clinical practice recommendations for anemia in chronic kidney disease. 2007 update of hemoglobin target. *Am J Kidney Dis.* 2007;50:476-530.