therapeutic indications. Aside from undesirable on-target effects, such as increased erythropoietin production and raised red blood cell numbers (also observed by the authors), major issues that will have to be addressed include the need for biomarkers that reliably identify patients who would benefit from treatment with HIF activators, the time point at which treatment would need to be started, the duration of treatment, potential adverse effects associated with long-term treatment, and the efficacy of treatment in patients with advanced disease.

While many questions remain unanswered, the studies by Nordquist and colleagues provide strong rationale for targeting O_2 metabolism and renal hypoxia for the prevention and treatment of hyperglycemic renal injury. Their findings will certainly prompt additional investigations into how the PHD/HIF pathway can be further exploited for therapeutic intervention in DN.

ACKNOWLEDGMENTS

V.H.H. is supported by the Krick-Brooks Chair in Nephrology, by National Institutes of Health grants R01-DK081646 and R01-DK080821, and by a Department of Veterans Affairs Merit Award (1I01BX002348).

DISCLOSURES

None.

REFERENCES

1. Report AD: *Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States. U.S. Renal Data System, USRDS*, Bethesda, MD, National Institute of Diabetes and Digestive and Kidney Diseases, 2013
2. Nordquist L, Friederich-Persson M, Fasching A, Liss P, Shoji K, Nangaku M, Hansell P, Palm F: Activation of hypoxia-inducible factors prevents diabetic nephropathy. *J Am Soc Nephrol* 26: 328–338, 2015
3. Haase VH: Hypoxia-inducible factors in the kidney. *Am J Physiol Renal Physiol* 291: F271–F281, 2006
4. Kaelin WG Jr, Ratcliffe PJ: Oxygen sensing by metazoans: The central role of the HIF hydroxylase pathway. *Mol Cell* 30: 393–402, 2008
5. Loenarz C, Schofield CJ: Expanding chemical biology of 2-oxoglutarate oxygenases. *Nat Chem Biol* 4: 152–156, 2008
6. Yuan Y, Hilliard G, Ferguson T, Millhorn DE: Cobalt inhibits the interaction between hypoxia-inducible factor-alpha and von Hippel-Lindau protein by direct binding to hypoxia-inducible factor-alpha. *J Biol Chem* 278: 15911–15916, 2003
7. Kapitsinou PP, Jaffe J, Michael M, Swan CE, Duffy KJ, Erickson-Miller CL, Haase VH: Preischemic targeting of HIF prolyl hydroxylation inhibits fibrosis associated with acute kidney injury. *Am J Physiol Renal Physiol* 302: F1172–F1179, 2012
8. Kapitsinou PP, Sano H, Michael M, Kobayashi H, Davidoff O, Bian A, Yao B, Zhang MZ, Harris RC, Duffy KJ, Erickson-Miller CL, Sutton TA, Haase VH: Endothelial HIF-2 mediates protection and recovery from ischemic kidney injury. *J Clin Invest* 124: 2396–2409, 2014
9. Haase VH: Pathophysiological consequences of HIF activation: HIF as a modulator of fibrosis. *Ann N Y Acad Sci* 1177: 57–65, 2009
10. Yu X, Fang Y, Liu H, Zhu J, Zou J, Xu X, Jiang S, Ding X: The balance of beneficial and deleterious effects of hypoxia-inducible factor activation by prolyl hydroxylase inhibitor in rat remnant kidney depends on the timing of administration. *Nephrol Dial Transplant* 27: 3110–3119, 2012
11. Vengellur A, Phillips JM, Hogenesch JB, LaPres JJ: Gene expression profiling of hypoxia signaling in human hepatocellular carcinoma cells. *Physiol Genomics* 22: 308–318, 2005
12. Vengellur A, Woods BG, Ryan HE, Johnson RS, LaPres JJ: Gene expression profiling of the hypoxia signaling pathway in hypoxia-inducible factor 1alpha null mouse embryonic fibroblasts. *Gene Expr* 11: 181–197, 2003
13. Hansell P, Welch WJ, Blantz RC, Palm F: Determinants of kidney oxygen consumption and their relationship to tissue oxygen tension in diabetes and hypertension. *Clin Exp Pharmacol Physiol* 40: 123–137, 2013
14. Rosenberger C, Khamaisi M, Abassi Z, Shilo V, Weksler-Zangen S, Goldfarb M, Shina A, Zibertrest F, Eckardt KU, Rosen S, Heyman SN: Adaptation to hypoxia in the diabetic rat kidney. *Kidney Int* 73: 34–42, 2008
15. Catrina SB, Okamoto K, Pereira T, Brismar K, Poellinger L: Hyperglycemia regulates hypoxia-inducible factor-1alpha protein stability and function. *Diabetes* 53: 3226–3232, 2004
16. Botusan IR, Sunkari VG, Savu O, Catrina AI, Grunler J, Lindberg S, Pereira T, Yla-Herttuala S, Poellinger L, Brismar K, Catrina SB: Stabilization of HIF-1 alpha is critical to improve wound healing in diabetic mice. *Proc Natl Acad Sci USA* 105: 19426–19431, 2008
17. Badal SS, Danesh FR: New insights into molecular mechanisms of diabetic kidney disease. *Am J Kidney Dis* 63[Suppl 2]: S63–S83, 2014
18. Fukuda R, Zhang H, Kim JW, Shimoda L, Dang CV, Semenza GL: HIF-1 regulates cytochrome oxidase subunits to optimize efficiency of respiration in hypoxic cells. *Cell* 129: 111–122, 2007
19. Thangarajah H, Yao D, Chang EI, Shi Y, Jazayeri L, Vial IN, Galiano RD, Du XL, Grogan R, Galvez MG, Januszyk M, Brownlee M, Gurtner GC: The molecular basis for impaired hypoxia-induced VEGF expression in diabetic tissues. *Proc Natl Acad Sci U S A* 106: 13505–13510, 2009
20. Cheng K, Ho K, Stokes R, Scott C, Lau SM, Hawthorne WJ, O'Connell PJ, Loudovaris T, Kay TW, Kulkarni RN, Okada T, Wang XL, Yim SH, Shah Y, Grey ST, Biankin AV, Kench JG, Laybutt DR, Gonzalez FJ, Kahn CR, Gunton JE: Hypoxia-inducible factor-1alpha regulates beta cell function in mouse and human islets. *J Clin Invest* 120: 2171–2183, 2010
21. Stokes RA, Cheng K, Deters N, Lau SM, Hawthorne WJ, O'Connell PJ, Stolp J, Grey S, Loudovaris T, Kay TW, Thomas HE, Gonzalez FJ, Gunton JE: Hypoxia-inducible factor-1α (HIF-1α) potentiates β-cell survival after islet transplantation of human and mouse islets. *Cell Transplant* 22: 253–266, 2013

See related article, "Activation of Hypoxia-Inducible Factors Prevents Diabetic Nephropathy," on pages 328–338.

Timing of Arteriovenous Fistula Placement: Keeping It in Perspective

Bradley S. Dixon
Department of Internal Medicine, Carver College of Medicine, University of Iowa, and Veterans Administration Medical Center, Iowa City, Iowa

J Am Soc Nephrol 26: 241–243, 2015.
doi: 10.1681/ASN.2014070709

Timing, they say, is everything. When to swing at the baseball's pitch, when to depart to catch an airplane, when to sell (or

Published online ahead of print. Publication date available at www.jasn.org.

Correspondence: Dr. Bradley S. Dixon, Nephrology Division , University of Iowa School of Medicine, E300D GH, 200 Hawkins Drive, Iowa City, IA 52242-1081. Email: bradley-dixon@uiowa.edu

Copyright © 2015 by the American Society of Nephrology

buy) a stock: act too early or too late and the results may be unsatisfactory. So, it seems, may be the case for placement of an arteriovenous fistula for hemodialysis. Place it too late and it may not be ready to use for hemodialysis, place it too early and it may develop complications or never be needed. However, if the timing is not right (as is so often the case), does it matter whether we are early or late? For baseball and stocks, maybe not, but this distinction is consequential for a plane trip and an arteriovenous fistula.

According to the most recent data from the US Renal Data System, more than 115,000 patients a year in the United States reach ESRD and need RRT.[1] A select few will be fortunate enough to get a pre-emptive kidney transplant, and some will choose peritoneal dialysis, but >90% start hemodialysis and join the slowly expanding population of about 400,000 patients on hemodialysis in the United States. Each of these hemodialysis patients needs a vascular access: an arteriovenous fistula, an arteriovenous graft, or a central venous catheter. A fistula is the preferred hemodialysis access. Once established, it is associated with the longest access survival, lowest cost, and fewest interventions, as well as the best patient survival, of all the choices for hemodialysis access.[2] However, up to 60% of new fistulas may be unsuitable for hemodialysis[3] and require radiologic or surgical interventions to achieve suitability, engendering cost, failed attempts at cannulation, extra clinic visits, and increased reliance on catheters for hemodialysis. These struggles with creating a usable fistula are magnified in the elderly and patients with severe cardiovascular disease, raising questions in the literature on the best choice of access for these patients and about the optimal timing for placement of a fistula to maximize its chances of being ready for use upon initiation of dialysis.

In this issue of *JASN*, Hod *et al.* examine the optimal timing of incident fistula placement in an elderly population.[4] Specifically, they explored the relationship between when a fistula was placed before the start of hemodialysis and its subsequent use at hemodialysis initiation in a retrospective cohort of 17,511 patients from the US Renal Data System dataset. The patients were 67 years of age or older and had their first fistula placed from 2005 to 2008. Overall, 55% of the cohort initiated hemodialysis with a fistula. The success rate was significantly higher for men, whites, and patients with longer predialysis nephrology care; the success rate was poorer for patients with diabetes and congestive heart failure (CHF). After stratification by time of fistula creation before hemodialysis initiation, the odds ratio (OR) for successful fistula use improved steadily for up to 6–9 months, after which the OR remained stable at around 1.0. The cumulative number of access procedures per patient also rose steadily the longer the fistula was placed before hemodialysis initiation and leveled off after 6–9 months. However, in contrast to the fistula success rate, the cumulative number of procedures did continue to increase after 12 months without a corresponding improvement in fistula success. This suggests that these extra procedures were needed to maintain fistula patency before initiation of hemodialysis. Earlier fistula placement, more than a year prior to hemodialysis initiation, was associated with a slight increase in the OR for fistula success for women and blacks as well as patients without diabetes or CHF. In contrast, patients with diabetes or CHF may experience more complications and have a slightly lower OR for fistula usability when the fistula is placed more than a year before hemodialysis initiation.

On the basis of this information, if dialysis initiation were scheduled like an airplane departure, we would want to book our flight 6–9 months in advance. However, it is hard enough to plan a trip 6–9 months in the future, let alone know the timing of hemodialysis initiation in that time frame. Even when the patient is being monitored by a nephrologist, the rate of progression from CKD to ESRD may not be constant, and the need for hemodialysis may be precipitated by random, stochastic unexpected clinical events leading to a sudden drop in renal function. Moreover, the relationship between measures of renal function and the development of clinical symptoms requiring hemodialysis varies between patients.

So if we are liable to be wrong about the exact timing of hemodialysis initiation, should we be early or late? The risks incurred by "early" and "late" fistula placement are not equal. Delaying placement of a fistula risks starting hemodialysis with a catheter and all its substantial complications and costs,[5] while early fistula placement incurs a rather modest increase in cumulative access procedures (or perhaps the patient will never need the fistula at all). In a broader perspective, only 16% of patients in the United States currently start hemodialysis with a fistula, while >80% of patients start with a catheter.[1] The major health imperative in this population is trying to increase fistula use and reduce the number of catheters needed at dialysis initiation. Waiting for the optimal time for fistula placement risks increasing the number of patients who start hemodialysis with a catheter. The article by Hod *et al.*, however, does sharply remind us that our primary focus should be on developing ways to speed and increase fistula maturation so that most fistulas are ready for hemodialysis within 1–2 months after surgical creation rather than having to wait for 6–9 months.

But that is the future, and we have to make plans for today. So should we be early or late? Ideally, we'd like to be able to schedule the flight (fistula placement) at the last minute and still catch the plane, but until that time comes, I prefer to err on the side of being early rather than miss the plane altogether by being late.

DISCLOSURES

B.D. reports receiving consulting fees from Proteon therapeutics, Novita Therapeutics and Shire Regenerative Medicine, stock in Flow Forward LLC and Metactive LLC and grant support from Proteon Therapeutics, Reata Pharmaceuticals and AbbVie Inc.

REFERENCES

1. Collins AJ, Foley RN, Chavers B, Gilbertson D, Herzog C, Ishani A, Johansen K, Kasiske BL, Kutner N, Liu J, St Peter W, Guo H, Hu Y, Kats A, Li S, Li S, Maloney J, Roberts T, Skeans M, Snyder J, Solid C, Thompson B, Weinhandl E, Xiong H, Yusuf A, Zaun D, Arko C, Chen SC, Daniels F, Ebben J, Frazier E, Johnson R, Sheets D, Wang X, Forrest B, Berrini D,

Constantini E, Everson S, Eggers P, Agodoa L: US Renal Data System 2013 Annual Data Report. *Am J Kidney Dis* 63[Suppl]: A7, 2014
2. Ravani P, Palmer SC, Oliver MJ, Quinn RR, MacRae JM, Tai DJ, Pannu NI, Thomas C, Hemmelgarn BR, Craig JC, Manns B, Tonelli M, Strippoli GF, James MT: Associations between hemodialysis access type and clinical outcomes: A systematic review. *J Am Soc Nephrol* 24: 465–473, 2013
3. Dember LM, Beck GJ, Allon M, Delmez JA, Dixon BS, Greenberg A, Himmelfarb J, Vazquez MA, Gassman JJ, Greene T, Radeva MK, Braden GL, Ikizler TA, Rocco MV, Davidson IJ, Kaufman JS, Meyers CM, Kusek JW, Feldman HI; Dialysis Access Consortium Study Group: Effect of clopidogrel on early failure of arteriovenous fistulas for hemodialysis: a randomized controlled trial. *JAMA* 299: 2164–2171, 2008
4. Hod T, Patibandla BK, Vin Y, Brown RS, Goldfarb-Rumyantzev AS: Arteriovenous fistula placement in the elderly: What is the optimal time? *J Am Soc Nephrol* 26: 448–456, 2015
5. Solid CA, Carlin C: Timing of arteriovenous fistula placement and Medicare costs during dialysis initiation. *Am J Nephrol* 35: 498–508, 2012

See related article, "Arteriovenous Fistula Placement in the Elderly: When Is the Optimal Time?," on pages 448–456.

Arteriosclerosis, Bone Biology, and Calciotropic Hormone Signaling: Learning the ABCs of Disease in the Bone-Vascular Axis

Dwight A. Towler
Sanford-Burnham Medical Research Institute Diabetes & Obesity Research Center, Florida Hospital, Translational Research Institute for Metabolism and Diabetes, Division of Endocrinology, Diabetes and Metabolism at University of Florida, Orlando, Florida

J Am Soc Nephrol 26: 243–245, 2015.
doi: 10.1681/ASN.2014080824

Cardiovascular disease and musculoskeletal frailty are prominent in our patients with CKD,[1] synergistically enhanced by concurrent diabetes that drives ESRD in approximately 40% of patients receiving RRT.[2] As London *et al.* first demonstrated,[3] the presence and extent of arterial calcium accrual in patients undergoing dialysis, be it in atherosclerotic intimal disease or medial artery calcification, convey significant morbidity and mortality risk.[3] Importantly, these researchers established that individuals with low-turnover bone disease were at greatest risk for extensive vascular calcium load.[4] Conversely, in community-dwelling older men, the presence of peripheral arterial disease (PAD), routinely defined as an ankle-brachial blood pressure index ratio (ABIx) of <0.9 or >1.3, conveys increased risk of hip fracture.[5] While atherosclerotic calcification lowers ABIx with vessel occlusion, the medial arterial calcification of diabetes and CKD results in elevated ABIx values and equally significant clinical consequences, including limb ischemia *via* vascular stiffening;[6–8] thus, vascular calcium metabolism and musculoskeletal health have emerged as being physiologically linked.[8,9] Consistent with this, women with lower bone mineral density have greater coronary artery calcification scores,[10] and this portends greater probability of future coronary events.[11,12] Guzman applied tibial artery calcification scoring to diabetic and non-diabetic patients with PAD.[13] Intriguingly, the tibial artery calcification score receiver-operating characteristics outperformed the current clinical standard of the ABIx in predicting future progression to critical limb ischemia and lower-extremity amputation.[13] Thus, the appellation CKD–mineral and bone disorder was established[1] to emphasize the endocrinology, integrative physiology, and therapeutic implications of disordered bone-vascular interactions that cause cardiovascular and musculoskeletal disease in CKD. However, a better understanding of these interactions is clearly needed in all clinical contexts.

In the present issue of *JASN*,[14] London and colleagues once again blaze the trail by illuminating the physiologic relationships between osteoblast bone anabolic function, parathyroid hormone (PTH) levels, and clinically relevant PAD. In this cohort of 65 well phenotype patients receiving RRT, approximately one third had elevated ABIx values as consistent with prevalent medial artery calcification, 17% had reduced ABIx values indicating atherosclerotic calcification, and half possessed normal indices.[14] The authors then analyzed the relationship between intact PTH levels and direct measure of osteoblast anabolic function by dynamic bone histomorphometry, comparing individuals with and without PAD. They reasoned that the slope of the regression relationship between PTH—the prototypic bone anabolic hormone—to direct histologic measures of osteoblast anabolic function (dLS/BS) would provide an index of PTH sensitivity.[14] *Via* this enlightened analysis, the authors demonstrated that patients with PAD exhibited a significantly shallower slope in the bone formation–PTH relationship; this indicates a reduced bone anabolic response at prevailing PTH tone in those individuals with PAD (Figure 1). Because PTH exerts important bone anabolic actions in part *via* the inhibition of osteoprogenitor apoptosis,[15] independent assessment of the PTH–osteoblast surface relationship also revealed a distinctly shallower slope in patients with PAD.[14] These relationships persisted after adjustment for C-reactive protein as an index of inflammation. Most important, in stepwise regression dLS/BS—the direct histologic measure of osteoblast anabolic function—continued to significantly contribute, along with inflammation and RRT duration, to the risk for PAD

Published online ahead of print. Publication date available at www.jasn.org.

Correspondence: Dr. Dwight A. Towler, Diabetes and Obesity Research Center, Department Sanford-Burnham Medical Research Institute, 6400 Sanger Road, Orlando, FL 32827. Email: dtowler@sanfordburnham.org

Copyright © 2015 by the American Society of Nephrology