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 O2 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 (I101BX002348).

DISCLOSURES

None.

REFERENCES


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


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. 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. However, up to 60% of new fistulas may be unsuitable for hemodialysis 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. 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 all, 55% of the cohort initiated hemodialysis with a fistula. 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
Heart disease and muscle weakness are common in patients with chronic kidney disease (CKD), 1 whose prevalence is increasing. 2 These symptoms are most likely due to atherosclerotic disease,1 which develops in response to the cardiovascular and arterial stiffening that begins early in the course of CKD.2,3 Indeed, atherosclerosis is a major contributor to cardiovascular disease, which is the leading cause of death in patients with ESRD.4,5 In the United States, cardiovascular disease accounts for 20% to 30% of all deaths in patients undergoing dialysis.6,7

The ESRD network (ESRDNet) was established in 2001 to provide public data on care and outcomes to ESRD patients with a focus on quality improvement.8 It is funded in part by the National Institute of Diabetes and Digestive and Kidney Diseases.9 The ESRDNet has reported a decrease in the mortality rate among patients on RRT over recent years.6,7 Although the causes of this improvement are not fully elucidated, the ESRDNet data may serve as an example of the potential for quality improvement in complex care settings.

Significant morbidity and mortality are associated with both cardiovascular disease and CKD.10,11 The relationship between the two is complex, with diabetes and CKD acting synergistically to increase the risk of cardiovascular disease and death.12,13 In addition, patients with CKD have lower ABIx values and elevated calcium,8,9 which are associated with atherosclerotic disease and lower-extremity amputation.14 Thus, arterial calcium accretion in patients with CKD may contribute to the development of cardiovascular disease, which could be alleviated by reducing calcium accretion in arterial calcification.

In this issue of JASN, Towler and colleagues15 report the results of a randomized trial of arteriovenous fistula (AVF) placement and venous access in older patients with CKD. The authors demonstrated that AVF placement in older patients with CKD was associated with a lower risk of mortality and hospitalization compared with venous catheterization. These results highlight the importance of timely AVF placement in older patients with CKD, and provide evidence that timely AVF placement can improve patient outcomes.

In summary, the arteriovenous fistula is a critical component of patient care in patients with CKD, and timely placement in the elderly is associated with improved patient outcomes. These findings further emphasize the need for timely AVF placement in older patients with CKD, and provide evidence that timely AVF placement can improve patient outcomes.

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

doi: 10.1681/ASN.2014080824

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

Cardiovascular disease and musculoskeletal frailty are prominent in our patients with CKD,1,4 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 (ABx) of <0.9 or >1.3, conveys increased risk of hip fracture.5 While atherosclerotic calcification lowers ABx with vessel occlusion, the medial arterial calcification of diabetes and CKD results in elevated ABx values and equally significant clinical consequences, including limb ischemia via vascular stiffening6–8 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 calci
tification 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–vascular–bone disable was established1 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.