disrupt established collagen IV networks to initiate anti-GBM disease, although they may contribute to impaired basement membrane turnover or repair.

Pathogenic autoreactivity to peroxidasin might also be expected to manifest systemic features outside of the renal and pulmonary systems given the expression of peroxidasin in other basement membranes. Severe loss-of-function mutations in peroxidasin,\(^{11}\) although such mutations have not, dysgenesis in humans, which has been associated with mutations in peroxidasin in Drosophila (the species in which peroxidasin was first identified\(^{9}\)) result in nonviable larvae, with widespread disruption of basement membranes in the midgut visceral muscles.\(^{3}\) In mice, peroxidasin mutations may result in perinatal lethality and developmental ocular defects.\(^{10}\) These defects recapitulate the features of anterior segment dysgenesis in humans, which has been associated with mutations in peroxidasin,\(^{11}\) although such mutations have not, to our knowledge, been identified in association with human renal disease.

The findings reported by McCall et al.\(^{6}\) are, however, highly novel and identify a new autoantibody target to add to the repertoire seen in pulmonary renal syndromes. Peroxidasin is expressed within the GBM, and antiperoxidasin antibodies with inhibitory activity can be identified before the onset of clinical disease, suggesting that they may contribute to disease pathogenesis. In addition, they have clinical implications given that antiperoxidasin reactivity may define a subset of patients with anti-GBM disease who are not truly anti-MPO positive and thus do not require maintenance immunosuppression.\(^{12}\) Further characterization of these antiperoxidasin antibodies and their associations with disease phenotype, particularly in patients found to be “double positive” for ANCA and anti-GBM autoantibodies, are now required to fully understand both their pathogenic and clinical significance.

DISCLOSURES

None.

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The Science of Fistula Maturation

Matthew J. Oliver
Division of Nephrology, Department of Medicine, University of Toronto, Toronto, Ontario


International guidelines strongly recommend that patients with ESRD undergoing maintenance hemodialysis receive an arteriovenous fistula because its use is associated with lower mortality and allows patients to avoid the risk of catheter-related complications.\(^{1–3}\) Fistula use is a frequent target for performance measurement and quality improvement, and it is tied to reimbursement in the United States. These guidelines and policies create strong incentives for providers to aggressively promote fistulas to their patients.

However, the purported benefits of fistulas are not realized unless the vascular access matures. Clinical maturation is a dynamic process in which vascular remodeling is facilitated by.
release of nitrous oxide and breakdown of elastin to permit enlargement of the draining vein. Blood flow through the anastomosing artery increases dramatically and the vein wall thickens to allow regular cannulation. For example, mean blood flow in the radial artery, only 64 ml/min before fistula creation, can increase ten-fold to achieve maturation; mean blood flow in the brachial artery, about 220 ml/min at baseline, often increases to over 1000 ml/min in a mature upper arm fistula. A useful rule of thumb to define clinical maturation proposed by the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative clinical practice guidelines for vascular access is the "rule of sixes," which says that a mature fistula should achieve a blood flow of at least 600 ml/min, a diameter of at least 6 mm, and a depth of 6 mm or less from the surface of the skin.

Studies of fistula outcomes vary in their definitions of the lack of clinical maturation (otherwise known as primary failure), but it is usually defined as some combination of early thrombosis, poor blood flow, inadequate clearance, or unreliable use. A meta-analysis of observational studies by our group estimated the risk of primary failure to be 23%, on the basis of 37 studies. However, two large, randomized clinical trials testing the effect of fish oil or clopidogrel on primary failure found the risk to be much higher, 47% and 62%, respectively. These studies found that neither intervention helped reduce primary failure. Regardless of which estimate is used, the risk of primary failure is likely high in many programs, a frustrating circumstance for both patients and clinicians. It is of paramount importance to better understand clinical maturation and to detect fistulas at risk for failure early to allow for timely intervention.

The Hemodialysis Fistula Maturation study is a large multicenter study that attempted to identify predictors and underlying mechanisms of fistula maturation. The authors measured numerous factors related to vascular anatomy, vascular biology, clinical attributes (demographics, comorbidities, and medications), and processes of care in patients undergoing fistula creation. In this issue of the Journal of the American Society of Nephrology, Robbin et al. describe how postoperative ultrasound measures can predict clinical maturation, defined as fistula use for 75% of treatments over a 4-week period with adequate blood flow and clearance. Clinical maturation occurred in 75% of patients, although 25% required interventions to mature the fistula. Ultrasound imaging took place 1 day and 2 and 6 weeks after fistula creation.

As suggested by the rule of sixes, fistula blood flow, diameter, and depth were significant predictors of maturation. However, the authors describe these relationships in much more detail compared with previous studies. Their primary analysis compared the 15th and 85th percentiles for these three continuous parameters. Compared with the 15th percentile, the increases in fistula blood flow and diameter in the 85th percentile were associated with a four-fold or greater increases in odds of unassisted clinical maturation. The likelihood of clinical maturation also doubled as depth decreased from the 15th percentile to the 85th percentile. The authors also present a number of forest plots, contour plots, and figures showing the likelihood of clinical maturation with different combinations of flow, diameter, and depth. In general, the relationship between flow and maturation was steep between blood flows of 500 ml/min to 1200 ml/min, but it was modified by the depth and diameter. The overall predictive value of these measures was considered moderate. The description of these relationships is novel and greatly increases the precision of predicting maturation.

Measuring flow, diameter, and depth in the postoperative period as part of routine care now seems reasonable to guide clinicians in decision making. Many programs already perform Doppler ultrasound to measure blood flow on newly created fistulas, so adding assessments of diameter and depth would be relatively easy for those not already measuring these parameters. If these three measures become available in most centers, further studies could validate the generalizability of the current findings. It would also be helpful to have a method (e.g., a calculator) to easily generate the predicted chance of maturation at specific time points of postoperative follow-up. Studies could then determine how this new information might improve decision making. On the basis of the predicted likelihood of unassisted maturation, timely intervention to facilitate maturation (e.g., using angioplasty or collateral vein occlusion) or early planning of a second fistula could increase fistula use and reduce exposure to central venous catheters.

A final caveat to this study was the center effect, specifically the differences in maturation probabilities among the participating clinical centers. Despite adjusting for case-mix and the three independent predictors of maturation (flow, diameter, and depth), the center effect was still significant. Unassisted patency across centers ranged from 26% to 68% and assisted patency ranged from 61% to 88%. It is unclear if this center effect is related to surgical experience, volume, or interest in fistulas. Program practices in the preoperative and postoperative periods may also be important. For example, an earlier study this year by Allon et al. from the Hemodialysis Fistula Maturation study found that timing and number of postoperative visits by surgeons, along with presence of vascular access coordinators, influence outcomes. Further studies are required to understand what practices or interventions are driving these differences among centers. In the meantime, careful postoperative measures of flow, diameter, and depth can bring more science to the process of clinical maturation.

DISCLOSURES

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