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Original Investigation

Objectives and Design of the Hemodialysis Fistula Maturation Study

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Background: A large proportion of newly created arteriovenous fistulas cannot be used for dialysis because they fail to mature adequately to support the hemodialysis blood circuit. The Hemodialysis Fistula Maturation (HFM) Study was designed to elucidate clinical and biological factors associated with fistula maturation outcomes.

Study Design: Multicenter prospective cohort study.

Setting & Participants: Approximately 600 patients undergoing creation of a new hemodialysis fistula will be enrolled at 7 centers in the United States and followed up for as long as 4 years.

Predictors: Clinical, anatomical, biological, and process-of-care attributes identified pre-, intra-, or postoperatively.

Outcomes: The primary outcome is unassisted clinical maturation, defined as successful use of the fistula for dialysis for 4 weeks without maturation-enhancing procedures. Secondary outcomes include assisted clinical maturation, ultrasound-based anatomical maturation, fistula procedures, fistula abandonment, and central venous catheter use.

Measurements: Preoperative ultrasound arterial and venous mapping, flow-mediated and nitroglycerin-mediated brachial artery dilation, arterial pulse wave velocity, and venous distensibility; intraoperative vein tissue collection for histopathologic and molecular analyses; postoperative ultrasounds at 1 day, 2 weeks, 6 weeks, and prior to fistula intervention and initial cannulation.

Results: Assuming complete data, no covariate adjustment, and unassisted clinical maturation of 50%, there will be 80% power to detect ORs of 1.83 and 1.61 for dichotomous predictor variables with exposure prevalences of 20% and 50%, respectively.

Limitations: Exclusion of 2-stage transposition fistulas limits generalizability. The requirement for study visits may result in a cohort that is healthier than the overall population of patients undergoing fistula creation.

Conclusions: The HFM Study will be of sufficient size and scope to: (1) evaluate a broad range of mechanistic hypotheses, (2) identify clinical practices associated with maturation outcomes, (3) assess the predictive utility of early indicators of fistula outcome, and (4) establish targets for novel therapeutic interventions to improve fistula maturation.

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Vascular access for maintenance hemodialysis is provided with an autogenous arteriovenous (AV) fistula, synthetic AV graft, or central venous catheter. The fistula is preferred because complication rates and health care expenditures are lower for patients with functioning fistulas than for those with synthetic grafts or central venous catheters.[1] Despite successful efforts to increase the use of fistulas among patients undergoing maintenance hemodialysis, in the United States, only ~60% of patients are dialyzed with a fistula, and ~80% initiate maintenance dialysis treatment with a central venous catheter.[2] An important contributor to the low prevalence of fistulas is the failure of many newly created fistulas to mature adequately for use. Recent studies have documented maturation failure rates ranging from 20%-60%.[3-6]

Fistula maturation is a complex vascular remodeling process that requires vessel dilation, marked increases in blood flow rates in the feeding artery and draining vein, and structural changes in the vessel walls.[7] Our current understanding of these processes and the factors promoting and impeding successful maturation is limited. Major areas requiring research include identification of clinically useful preoperative predictors of fistula outcome, elucidation of the pathophysiology of fistula maturation, identification of early postoperative indicators of fistula outcome, and development of interventions to facilitate maturation.

The Hemodialysis Fistula Maturation (HFM) Study is a multicenter prospective cohort study sponsored by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) designed to identify predictors of fistula maturation failure and elucidate underlying mechanisms. Study participants undergoing fistula creation surgery will be studied pre-, intra-, and postoperatively with collection of comprehensive clinical, anatomical, functional, and pathologic data using standardized procedures. This report describes the objectives and design of the HFM Study, the mechanistic and translational investigations that will be conducted using HFM data and biosamples, and the potential applicability of the study findings to clinical practice and future clinical trials.

STUDY RATIONALE AND METHODS

Need for a Prospective Cohort Study

The development of interventions to improve fistula maturation outcomes has been hampered by a limited understanding of the underlying mechanisms. To date, only a small number of clinical trials of interventions to improve fistula maturation have been conducted. The Dialysis Access Consortium (DAC), also established by the NIDDK, performed a randomized placebo-controlled clinical trial that showed that clopidogrel prevented thrombosis of newly created fistulas, but did not increase the proportion that could be used for dialysis.[4] Based in part on insights from this trial, the NIDDK recognized the need to learn more about processes of fistula maturation through a prospective observational study. Although risk factors for fistula maturation failure have been identified through retrospective analyses of large databases and prospective cohort studies, these efforts have focused in large part on demographic and clinical factors that are not readily modifiable.[6,8] Given the complexity of the maturation process, elucidation of additional clinically useful and, especially, modifiable predictors of maturation failure requires a prospective study with: (1) sample size sufficiently large to allow statistical models that incorporate multiple risk factors and potential confounders, (2) data collection that is broad in scope, and (3) multiple outcome measures, including some that are linked closely to hypothesized biological processes and others chosen for their clinical relevance.

Objectives and Hypotheses of the HFM Study

The HFM Study is designed to identify predictors and underlying mechanisms of fistula maturation success and failure using information from the following 4 domains: (1) vascular anatomy before and after fistula creation; (2) vascular biology characterized by functional, structural, and molecular assessments of vessels and systemic mediators before and shortly after fistula creation; (3) clinical attributes of patients that might independently predict fistula outcomes and potentially modify the associations of vascular anatomical and biological factors with fistula outcomes; and (4) processes of care that might independently predict fistula outcomes and potentially modify the associations of vascular anatomical, biological, and clinical factors with fistula outcomes.

Each of these domains encompasses a set of hypothesized relationships between attributes and fistula outcomes that should be informative from a predictive and/or mechanistic standpoint (Table 1).

Composition of the Multidisciplinary HFM Study Group

The HFM protocol is being implemented by the HFM Study Group (see Acknowledgements), comprising 7 clinical centers; a Data Coordinating Center; core facilities for histopathology, ultrasound, and vascular function testing; a study chair; and NIDDK program scientists. The clinical centers are university-affiliated vascular access referral centers serving diverse patient populations in multiple US geographic regions. Each clinical center has one or more surgical sites and ultrasound facilities, a vascular function testing facility, and multiple affiliated dialysis units. Clinical center principal investigators are nephrologists or vascular surgeons; co-investigators include nephrologists, vascular surgeons,