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Future research directions to improve fistula maturation and reduce access failure

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ABSTRACT

With the increasing prevalence of end-stage renal disease, there is a growing need for hemodialysis. Arteriovenous fistulae (AVF) are the preferred type of vascular access for hemodialysis, but maturation and failure continue to present significant barriers to successful fistula use. AVF maturation integrates outward remodeling with vessel wall thickening in response to drastic hemodynamic changes in the setting of uremia, systemic inflammation, oxidative stress, and pre-existent vascular pathology. AVF can fail due to both failure to mature adequately to support hemodialysis and development of neointimal hyperplasia that narrows the AVF lumen, typically near the fistula anastomosis. Failure due to neointimal hyperplasia involves vascular cell activation and migration and extracellular matrix remodeling with complex interactions of growth factors, adhesion molecules, inflammatory mediators, and chemokines, all of which result in maladaptive remodeling. Different strategies have been proposed to prevent and treat AVF failure based on current understanding of the modes and pathology of access failure; these approaches range from appropriate patient selection and use of alternative surgical strategies for fistula creation, to the use of novel interventional techniques or drugs to treat failing fistulae. Effective treatments to prevent or treat AVF failure require a multidisciplinary approach involving nephrologists, vascular surgeons, and interventional radiologists, careful patient selection, and the use of tailored systemic or localized interventions to improve patient-specific outcomes. This review provides contemporary information on the underlying mechanisms of AVF maturation and failure and discusses the broad spectrum of options that can be tailored for specific therapy.

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1. Introduction

1.1. *The prevalence of end-stage renal disease is increasing*

Chronic kidney disease (CKD) is increasing in incidence worldwide, and with an estimated prevalence of 8%–16%, contributes significantly to the global burden of disease [1,2]. The global prevalence of diabetes in adults is 9.1% (415 million people) according to a report published in 2015 by the International Diabetes Federation, rising beyond 10.4% (642 million people) by 2040 [3], largely due to the global increase in type 2 diabetes and obesity, especially in China, India, and some developing countries in Africa [4–6]. This increase in the number of people developing diabetes has had a major impact on the development of diabetic kidney disease (DKD). DKD and an aging population have become the two challenges in managing end-stage renal disease (ESRD) worldwide. DKD is the leading cause of ESRD, accounting for approximately 50% of cases in the developed world. Although overall incidence rates for ESRD attributable to DKD have recently stabilized in the United States, these rates continue to rise in high-risk groups, such as middle-aged African Americans, Native Americans, and Hispanics. The elderly population constitutes the fastest growing sector of the ESRD population and have unique needs, by virtue of their high prevalence of comorbid conditions, slower progression of renal disease, and reduced survival; in the Medicare population alone, DKD-related expenditure among the elderly was nearly $25 billion in 2011 [7,8]. With the increasing prevalence of ESRD, there is a growing need for renal replacement therapies (RRT).

1.2. *AVF is the preferred form of RRT but is far from optimal*

RRTs are the lifeline for ESRD patients. Modes of RRT include peritoneal dialysis (6.4%), renal transplantation (29.3%), and hemodialysis (HD) (64.2%) [9,10]. In 2010, 64.7% of patients in the United States with ESRD were treated with HD with either arteriovenous fistulae (AVF), arteriovenous grafts (AVG), or tunneled and non-tunneled central venous catheters [11].

The National Kidney Foundation Kidney Disease Outcomes Quality Initiative guidelines and the Fistula First Breakthrough Initiative prefer AVF as the optimal access for HD [12] because they have superior patency rates, fewer complications, and lower health care costs [11,13–15]. Additionally, a recent systematic review and meta-analysis on outcomes of vascular access for hemodialysis remains in support of autogenous access as the best approach when feasible: AVF were associated with the best patency and lowest infection and mortality outcomes, followed by AVG and catheters [16,17]. AVF have also been recommended in the pediatric population [18].

However, AVF are not immediately available for use as an access for HD because they must mature, that is, dilate and thicken. Unfortunately, AVF have a high rate of primary maturation failure, with up to 60% not suitable for HD by 5 months after creation [19–22]. Furthermore, a recent systematic review and meta-analysis reported that the primary patency rates of AVF were 60% at 1 year and 51% at 2 years, with secondary patency rates of 71% at 1 year and 64% at 2 years, clearly suboptimal for a permanent treatment [23]. Although there are conflicting results regarding the influence of sex on AVF failure, most studies found that women have prolonged maturation time and decreased patency rate [17,24,25]; early thrombosis was also associated more frequently with women [26]. Controversially, AVF may not be favored for HD access in older patients [27–29]. Olsha et al [29] found that 88% of their patients who were older than 80 years had vasculature suitable for autogenous access construction, with patency and complications similar to those of their younger counterparts, with adequate preoperative planning and postoperative maintenance. However, elderly patients with ESRD frequently have a high prevalence of comorbidities, short life expectancy, and poor reported quality of life, which is associated with lack of AVF maturation and diminished primary and cumulative AVF patency [28]; in these patients AVG placement might be more beneficial [27,28,30].

1.3. *Lack of well-established clinical criteria to define AVF maturation or failure*

AVF maturation is considered clinically successful if 6 weeks after surgery the fistula supports a flow of 600 mL/min, is located at a maximum of 6 mm from the skin surface, and has a diameter of >6 mm [12], but this definition is difficult for clinical use. The North American Vascular Access Consortium definition may be more useful: a fistula is mature if it can be used successfully for dialysis with two-needle cannulation for two-thirds or more of all dialysis runs for 1 month and if it delivers the prescribed dialysis within the prescribed time frame [31].

Although there are some clinical criteria to define successful AVF maturation, the clinical definition of AVF failure is less clear, with frequent confusion between various types and stages of failure. Based on previous criteria and recent multicenter research [12,26,31], we have defined the three types of AVF failure as: early thrombosis, failure to mature, and late failure (Table 1).

Many variables contribute to successful AVF maturation or AVF failure: patient age, sex, presence of diabetes, obesity, vessel characteristics, surgical technique and surgeon experience, preoperative planning, and mapping [32–34]. Successful access surgeons frequently adhere to the dictum that a successful AVF should be performed in the right patient at the right time in the right circumstances based on a comprehensive understanding of the mechanisms contributing to AVF maturation and AVF failure. The goal of this review was to provide a basic understanding of the adaptive changes of AVF maturation as a framework for understanding the mechanisms of AVF failure, as well as subsequent treatments.