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Could Alpha-Lipoic Acid Improve Arteriovenous Fistula Maturation? A Mechanistic Hypothesis

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To Editor,

Arteriovenous fistula (AVF) maturation failure remains a major challenge in establishing durable vascular access for hemodialysis, affecting nearly half of newly created fistulas despite advances in surgical techniques.[1,2] Although vascular anatomy and operative factors are recognized as major determinants of successful maturation, increasing evidence suggests that vascular biology including arterial stiffness, endothelial dysfunction, oxidative stress, inflammation, and maladaptive vascular remodeling also contributes substantially to AVF outcomes.[1-3]

Successful AVF maturation is a dynamic process initiated by the abrupt increase in blood flow and shear stress following fistula creation. This hemodynamic stimulus promotes endothelial activation, extracellular matrix remodeling, and adaptive outward venous remodeling, ultimately allowing the vein to accommodate repeated cannulation.[2] Conversely, persistent oxidative stress, endothelial injury, and exaggerated inflammatory responses may favor neointimal hyperplasia and venous stenosis, leading to maturation failure.[2,3] Because oxidative pathways participate in both adaptive and maladaptive vascular responses, therapeutic modulation should aim to restore vascular homeostasis rather than indiscriminately suppress physiological redox signaling.[2,3]

Alpha-lipoic acid (ALA) exerts pleiotropic vascular effects beyond its antioxidant activity through modulation of mitochondrial function, endothelial homeostasis, inflammatory signaling, and cellular metabolism.[4-8] Clinical evidence indicates that ALA may improve endothelial function, an effect supported by a recent systematic review and meta-analysis demonstrating significant improvement in flow-mediated dilation following supplementation.[4]

As impaired endothelial responsiveness is considered an important contributor to neointimal hyperplasia and venous stenosis after AVF creation,[2,3] ALA may facilitate the early adaptive phase of vascular remodeling by

improving endothelial function rather than directly preventing structural vascular changes. Although this concept has yet to be explored specifically in AVF models, it provides a biologically plausible rationale for further investigation.

Another potential mechanism involves arterial stiffness. Increased pulse wave velocity (PWV), a validated measure of arterial stiffness, has been associated with unsuccessful AVF maturation.[1] ALA supplementation has been shown to reduce PWV in patients with type 2 diabetes mellitus and cardiac autonomic neuropathy.[5] Although evidence from other vascular settings cannot be directly extrapolated to AVF maturation, these findings suggest that improving arterial compliance may create a more favorable hemodynamic environment during the early remodeling phase following AVF creation.[1,5] In patients with chronic kidney disease, interventions that modulate mineral-bone metabolism have also been linked to improvements in arterial stiffness, highlighting the multifactorial nature of this vascular parameter.[9]

ALA may also influence inflammatory pathways implicated in vascular remodeling. A recent meta-analysis in patients with chronic kidney disease demonstrated improvements in inflammatory and metabolic parameters following ALA supplementation.[6] Likewise, reduced circulating concentrations of IL-8 and TNF-α have been reported in maintenance hemodialysis patients receiving ALA.[7] As these cytokines contribute to venous neointimal hyperplasia, their modulation may facilitate adaptive vascular remodeling. Experimental studies further support the anti-inflammatory and antioxidant effects of ALA.[8] Although circulating biomarkers cannot fully represent local vascular events within the fistula wall, these findings provide additional mechanistic support for investigating ALA in AVF maturation.

Compared with previously investigated antioxidant interventions, which have generally focused on reducing oxidative stress alone, ALA offers a broader pharmacological profile by simultaneously targeting endothelial dysfunction, arterial stiffness, mitochondrial metabolism, and inflammatory signaling.[4-8] Whether this multimodal activity translates into improved AVF maturation remains unknown and warrants further investigation.

Based on the mechanisms discussed above, the proposed hypothesis may be particularly relevant to patients at increased risk of AVF maturation failure, including those with diabetes mellitus, advanced chronic kidney disease, peripheral arterial disease, increased arterial stiffness, or a previous history of vascular access failure.[1,2,5] Whether a similar benefit could be expected in lower-risk patients remains uncertain and requires further investigation.

A pilot randomized, placebo-controlled trial could provide an appropriate first step to evaluate this hypothesis. Oral alpha-lipoic acid at a dose of 600 mg/day, initiated several weeks before AVF creation and continued throughout the early postoperative remodeling period, may provide sufficient time for its endothelial, antioxidant, anti-inflammatory, and Vaso protective effects to develop before the onset of the critical vascular remodeling phase.[4,7] This rationale is supported by clinical studies demonstrating that the beneficial vascular effects of alpha-lipoic acid, particularly improvements in endothelial function, emerge following sustained administration rather than acute dosing.[4,5] However, the optimal timing of treatment initiation before surgery remains unknown and should be established in future clinical trials. In addition to conventional clinical outcomes, future studies should distinguish between different stages of AVF maturation by assessing

ultrasound-defined maturation (vein diameter and access blood flow), successful first cannulation, primary AVF failure, assisted primary patency, and long-term functional patency.[1,2] Measurements of arterial stiffness and circulating inflammatory biomarkers may further help clarify the biological mechanisms underlying any observed clinical effects.[1,5-7]

Although alpha-lipoic acid has generally demonstrated a favorable safety profile and good tolerability in clinical studies, given the limited evidence in patients with advanced CKD and maintenance hemodialysis, future clinical trials should include predefined safety assessments, with particular attention to glycemic status monitoring, thyroid function, concomitant antiplatelet therapy, and perioperative medications.[6,7,10]

Taken together, current evidence suggests that alpha-lipoic acid may influence several biological pathways involved in AVF maturation, particularly endothelial function, arterial stiffness, oxidative stress, and inflammation. Although direct evidence in dialysis vascular access is currently lacking, the convergence of available experimental and clinical findings provides a biologically plausible basis for further mechanistic and clinical investigation. If confirmed in well-designed prospective studies, ALA could emerge as a promising adjunctive strategy to improve AVF maturation in selected high-risk patients.

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Conflicts of Interest

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Data availability

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