Revascularization but Not Supervised Exercise Therapy Prevents Progression of Fibrosis in the Gastrocnemius of Patients With Peripheral Artery Disease While Improving Limb Function

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Introduction: Patients with peripheral artery disease (PAD) develop myofiber degeneration and fibrosis in their ischemic lower extremities, along with limb dysfunction. Walking performance improves with revascularization and exercise therapy, but effects on the myopathy are unknown. We previously showed fibrosis progresses with PAD and positively correlates with expression of vascular transforming growth factor-beta 1 (TGF-β1), a cytokine that stimulates collagen deposition. **Hypothesis:** We hypothesize that revascularization (RVS) and supervised exercise therapy (EXE) improve limb function in association with improved TGF-β1 dependent fibrosis. **Methods:** Gastrocnemius biopsies were collected from PAD patients (Fontaine Stage II; N=56) at baseline and 6 months after RVS (N=20), EXE (N=19), or no intervention (CTL; N=17). TGF-β1 expression was measured as grey scale units (gsu) by quantitative fluorescence microscopy of paraffin-embedded gastrocnemius sections. Collagen abundance was measured as optical density by quantitative multi-spectral bright-field microscopy of Masson Trichrome stained paraffin sections. Six Minute Walking Distance (SMWD), in meters, and Peak Walking Time (PWT), in seconds, were determined at baseline and 6 months. Relationships among TGF-β1, collagen, and limb function were assessed. **Results:** TGF-β1 expression and collagen density increased in CTL and EXE but not RVS patients. SMWD and PWT increased among RVS patients. PWT but not SMWD increased among EXE patients. SMWD and PWT were unchanged among CTL patients. The data are summarized in Table 1.

Table 1. Myofibrosis and Limb Function Before and After Revascularization and Exercise in PAD Patients

	CTL		RVS		EXE	
	Pre	Post	Pre	Post	Pre	Post
TGF-β1 (gsu)	1.26 [0.17]	3.31 [0.49]*	2.53 [0.41]	2.43 [0.55]	1.99 [0.50]	4.29 [0.53]*
Collagen (gsu)	1761 [59]	2201 [83]*	1633 [69]	1677 [70]	1831 [129]	2307 [141]*
SMWD (m)	329 [27]	300 [26]	267 [21]	307 [17]^	333 [12]	353 [30]
PWT (sec)	316 [63]	335 [90]	200 [47]	619 [169]^	240 [38]	571 [90]#

All values are mean [s.e.]
^p < 0.05, #p < 0.01, *p < 0.001 when comparing post *vs.* pre

Conclusions: RVS and EXE improved walking performance of patients with PAD, but only RVS prevented progression of fibrosis in the gastrocnemius of these patients. Over the same 6-month period, fibrosis increased in CTL muscle but was not sufficient to alter walking performance. The data suggest that benefits to the PAD leg may be greater with RVS compared to EXE.