A leading cause of severe disability and limb amputation in the developed world is critical limb ischemia (CLI) from severe peripheral artery disease. Current treatments for CLI, such as surgical revascularization, endovascular intervention, and medical treatment, typically result in less than satisfying results. Furthermore, despite early promise, phase II clinical trials of exogenous proangiogenic growth factors for CLI have not demonstrated efficacy, and the prospects for successful gene and cell therapies for CLI are far from certain.1 In this issue of Arteriosclerosis, Thrombosis, and Vascular Biology, Nagahama et al2 demonstrate an innovative nanoparticle-mediated delivery of pioglitazone for enhancing therapeutic neovascularization in a murine model of hindlimb ischemia.

Although the thiazolidine (TZD) class of peroxisome proliferator–activated receptor-γ agonists such as pioglitazone has been in clinical use as treatment for type-2 diabetes mellitus, recent studies have demonstrated various proangiogenic effects of TZDs. For instance, TZDs have been shown to stimulate endothelial cell and progenitor migration, proliferation, and survival via the expression of angiogenic factors, such as vascular endothelial growth factor and fibroblast growth factor.3−5 Furthermore, pioglitazone has been shown to promote therapeutic angiogenesis in a murine hindlimb ischemia model, although it was unclear whether this reflected a direct effect of pioglitazone on endothelial cells or the secondary effects of improved glycemic control.6 Conversely, there have also been reports of antiangiogenic effects of TZDs in vitro and in vivo models.7,8 The prospects for TZDs as potential proangiogenic therapies were further diminished by the fact that systemic administration of TZDs sometimes resulted in undesirable cardiovascular side effects, such as edema and heart failure.

To clarify the uncertainties of the direct proangiogenic effects of TZDs, Nagahama et al2 used a nanoparticle-mediated drug delivery system for the targeted delivery of pioglitazone to the ischemic vasculature. The authors had previously demonstrated that polylactic-glycolic acid nanoparticles (NPs) accumulated in the capillary and arteriolar endothelium after intramuscular injection in animal models of hindlimb ischemia.9 In the present article, they demonstrate that a single injection of pioglitazone-incorporated NP (Pio-NP) into the ischemic muscles results in a significant augmentation of angiogenesis and arteriogenesis, as well as significant improvements in blood flow to the ischemic limb. Remarkably, the 1-µg/kg dose of Pio-NP used to achieve enhanced blood flow recovery was far lower than the oral pioglitazone dose (1000 µg/kg) necessary for similar improvement. Presumably, such a remarkable enhancement reflects the NP-dependent optimization of drug tissue distribution and release kinetics.

By a number of measures, the therapeutic neovascularization by Pio-NP seems to be mediated by peroxisome proliferator–activated receptor-γ activation. The Pio-NP injection resulted in peroxisome proliferator–activated receptor-γ activation in the ipsilateral limb, and the peroxisome proliferator–activated receptor-γ antagonist GW9662 abrogated the blood flow recovery by Pio-NP. Pio-NP induced multiple proangiogenic genes necessary to form functional collateral vessels. Furthermore, the therapeutic effects of Pio-NP required endothelial NO synthase activation, as these were not observed in endothelial NO synthase−deficient mice. Importantly, therapeutic neovascularization by Pio-NP injection was independent of systemic insulin sensitivity.

The nanoparticle-mediated delivery of pioglitazone offers an exciting new therapeutic modality with numerous opportunities for follow-up studies. An interesting finding was the persistence of therapeutic effects 21 days after a single intramuscular injection. One wonders whether such a sustained effect is a result of the fact that pioglitazone acts upstream of vascular growth factors and endothelial NO synthase, thereby stimulating a cascade of multiple proangiogenic programs. Thus, although pioglitazone itself might disappear from tissues only after several days, the downstream mediators remain activated for much longer. It also seems plausible that the Pio-NP delivery system may be useful for promoting therapeutic angiogenesis in other contexts, such as cerebral or myocardial ischemia. Finally, pioglitazone is already Food and Drug Administration approved, which should facilitate the translation into clinical testing. Prior studies indicate that the synthetic polylactic-glycolic acid NPs gradually undergo hydrolysis over 21 days9 and are generally nontoxic10; however, future studies will need to rigorously address their clearance and safety in preclinical models and eventually in humans. With luck,
the neovascularization strategies involving the nanoparticle-mediated delivery of pioglitazone and other proangiogenic compounds may prove efficacious in patients with severe peripheral artery disease and CLI.

**Disclosures**

None.

**References**


Mixing of the Old With the New: Nanoparticle-Mediated Pioglitazone Delivery to Enhance Therapeutic Neovascularization
Calvin C. Sheng and Charles C. Hong

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