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TARGETED MUSCLE REINNERVATION FOR AMPUTEES: MECHANISM, OUTCOMES, AND FUTURE APPLICATIONS

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ABSTRACT
Amputation has a significant negative effect on patients' quality of life, and often results in complications including painful neuromas, residual limb pain, and phantom limb pain in up to 75% of patients. At the same time, intuitive control of myoelectric prostheses presents a significant rehabilitation challenge. Targeted muscle reinnervation is an innovative microsurgical procedure that solves both problems. Targeted muscle reinnervation was initially conceived to enhance electromyographic signals for targeted upper-extremity bioprosthetics, and entails the transfer of severed peripheral nerves to redundant motor branches of functionally expendable muscle. This allows for a vascularized scaffold and a target for transected nerves, thus eliminating the formation of disorganized axonal sprouts that may form the basis of a neuroma. In this review, comparative and quantitative data from recent clinical trials, prospective cohorts, and meta-analyses are reviewed to assess the two-fold efficacy of targeted muscle reinnervation. Acute and delayed targeted muscle reinnervation is shown to reduce pain scores, opioid use, and symptomatic neuroma recurrence when compared to traction neurectomy. Moreover, targeted muscle reinnervation dramatically increases walking ability (in lower-extremity amputees) and has high success rates in intuitive myoelectric control (in upper-extremity amputees). This review, which combines quantitative results from several studies, supports consideration of targeted muscle reinnervation as standard-of-care surgery to prevent neuropathic pain and to enhance the performance of prostheses.

KEYWORD: TMR, Amputation, Neuroma, Myoelectric prosthesis, Nerve transfer.

INTRODUCTION
Amputation is a devastating physical and psychological event, often complicated by persistent post-amputation pain and the formidable learning process of using artificial limbs. When a major limb is amputated, the transected peripheral nerves will begin to regrow.[1] The lack of an appropriate target for axonal regeneration causes disorganized axonal sprouting, forming a painful neuroma. Neuromas are a major cause of residual limb pain (RLP) and are highly correlated with the development of phantom limb pain (PLP), problems which affect most amputees and severely limit their comfort wearing prosthetics.[2]

Traditionally, these transected nerves have been treated with standard traction neurectomy, nerve entrapment (in muscle and bone), or a variety of caps.[3] However, these techniques have variable success. This has all changed with Targeted Muscle Reinnervation (TMR). Originally designed by Dr. Todd Kuiken and Dr. Gregory Dumanian to enhance control of myoelectric prostheses, TMR is based on the simple idea of "giving a nerve somewhere to go and something to do".[4]

TMR achieves this by redirecting amputated nerves to motor nerve branches of adjacent, expendable muscles, allowing for new neuromuscular junctions to form. This not only increases myoelectric signals for bionic control, but also prevents painful neuroma formation, making TMR a therapeutic and reconstructive procedure.[5]

CORE PRINCIPLES AND CLINICAL OUTCOMES OF TARGETED MUSCLE REINNERVATION

1. Pathophysiology and mechanism of TMR

After peripheral nerve transection, the proximal stump continues to grow and release neurotrophic factors and growth cones. This occurs in an empty space in conventional amputations, resulting in a tangled mass of axons and scar tissue or a neuroma.[1] TMR prevents this process. It involves anastomosis of the transected mixed or sensory nerves to the motor endplates of adjacent muscles.[6] Through the use of a biological amplifier and a direct path for reinnervation, TMR neurophysiologically reprograms the sensory nerves to prevent both the pain response and axonal disorganization.[7]

This functional nerve transfer guarantees that the new neuromuscular junctions receive physiologically meaningful signals from the brain, resulting in distinct electromyographic (EMG) signals on the surface of the residual limb.[4] These unique muscle contractions can be detected by surface electrodes to drive multi-articulated myoelectric limbs.[4,5]

2. TMR prevents and treats pain

The effectiveness of TMR in pain prevention and treatment has been extensively tested in quantitative studies. The first randomized clinical trial (RCT) of TMR versus standard neurectomy was conducted in 28 amputees with pain.[8] An intention-to-treat analysis showed that at 1 year, TMR was associated with a significantly greater decrease in PLP scores (mean difference of 3.4 points on the numerical rating scale, $p = 0.03$) than standard care.[8]

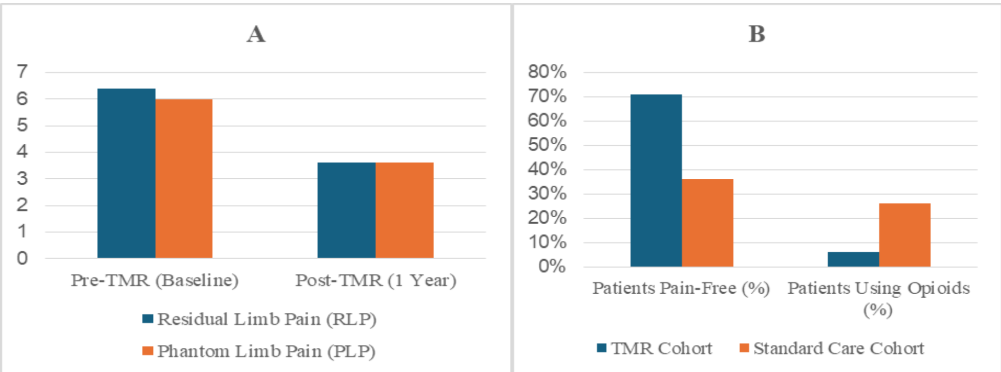
These results were supported by prospective studies. In a study of 33 major limb amputees, residual limb pain went from a Numerical Rating Scale (NRS) of 6.4 to 3.6 ($p < 0.001$) and phantom limb pain from 6.0 to 3.6 ($p < 0.001$) 1 year after TMR (see Figure 1A).[9]

Not only does the numerical pain scale improve, the Patient-Reported Outcome Measurement Information System (PROMIS) pain intensity and interference scores show a large improvement, which is a measure of a systemic effect on the quality of life for the patient. These improvements in pain management also lead to a very different clinical picture compared to conventional therapy. For instance, in a large retrospective cohort of 200 below-knee amputees, 71% of TMR patients were completely free of pain in contrast to 36% in the standard group. This dramatic reduction in pain also translates into markedly reduced use of narcotics to manage pain (only 6% of the TMR group used opioids, compared to 26% in the standard group - see Figure B).[3]

Timing of TMR - acute (at the time of primary amputation) versus delayed (after neuroma formation) - is also important.[10] Acute, preventive TMR is more effective in preventing neuropathic pain prior to central sensitization. In a study of 103 patients, symptomatic neuromas recurred in 19% of delayed TMR limbs compared to 1% of acute TMR limbs ($p < 0.05$), highlighting the importance of acute nerve transfer for long-term prevention (see Figure 1C).[11] The relative pain outcomes are summarised in the following table.

Table 1: Comparative pain outcomes in major TMR studies.

Study (Year)	Design	Cohort (N)	Primary Pain Outcomes (TMR vs Standard/Baseline)
Dumanian et al. (2019) [8]	Randomized Clinical Trial	28 amputees	Greater drop in PLP for TMR (mean diff = 3.5, p=0.03) vs standard neurectomy.
Mioton et al. (2020) [9]	Prospective Study	33 amputees	NRS for RLP dropped 6.4 to 3.6 (p<0.001); PLP dropped 6.0 to 3.6 (p<0.001).
Chang et al. (2021) [3]	Retrospective Cohort	200 below-knee amputees	71% TMR pain-free vs 36% standard (p<0.01); Opioid use 6% vs 26% (p<0.01).
Goodyear et al. (2023) [11]	Cross-Sectional	103 patients	Neuroma recurrence: 1% in acute TMR vs 19% in delayed TMR (p<0.05).



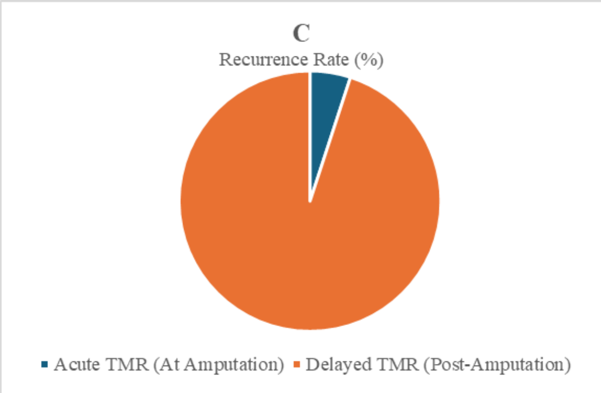


Figure 1: Pain and symptom management outcomes. (A) Pain score reductions (RLP vs. PLP). (B) Clinical pain outcomes & opioid Use. (C) Symptomatic neuroma recurrence rates.

3. Advancing myoelectric prosthesis control

While the pain-relieving effect of TMR has widened the use of TMR, the ultimate goal of TMR is still to enhance the human-machine interface. Many myoelectric prostheses use two-site control (e.g., residual biceps to close the hand and residual triceps to open the hand), which is cumbersome, non-intuitive, and allows only single-joint control at a time.[4]

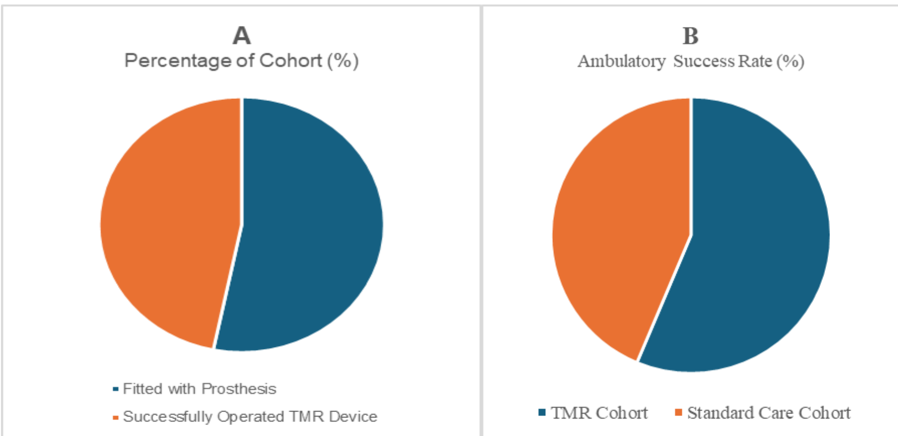
TMR enables multiple, independent myoelectric sites by redistributing multiple transected nerves to different muscle segments. This enables upper-extremity amputees to simultaneously control multiple functions. In a landmark study of 26 amputees (16 transhumeral, 10 shoulder disarticulations), 100% of patients were able to be fitted with a prosthesis, and 88% (23 of 26) were able to successfully use a TMR-based, sophisticated myoelectric prosthesis (see Figure 2A).[12]

This improved neural integration leads to significant improvement in patient's function. Mioton et al.[9] report that TMR patients have greatly improved scores on standardized quality-of-life indicators, including both upper and lower extremity amputations, with OPUS Rasch scores and Neuro-QOL scores consistently improving from baseline (see Figure 2C).

In addition, the use of TMR has a profound effect on mobility and independence in patients with lower-limb amputations. A study that compared 100 patients who received TMR during below-knee amputations to 100 patients who received conventional care found 90.9% of patients in the TMR group regained their ambulatory status, whereas only 70.5% of the patients in the control group regained ambulation ($p < 0.01$) (see Figure 2B).[3] The dramatic relief of pain and improved muscular control allow quicker and more prolonged physical therapy and prosthesis use. These functional gains are outlined in Table 2.

Table 2: Prosthetic use and function.

Study (Year)	Target Population	Key Functional Metric	Quantitative Results
Souza et al. (2014)[12]	Transhumeral & Shoulder Disarticulation (n=26)	Prosthetic Fit & Operation	100% fitted with prosthetics; 88% successfully operated TMR-controlled devices.
Mioton et al. (2020)[9]	Major Limb Amputees (n=33)	OPUS Rasch (Upper) / Neuro-QOL (Lower)	Upper limb scores improved 53.7 to 56.4 (p<0.001); Lower limb improved 32.9 to 35.2.
Chang et al. (2021)[3]	Below-Knee Amputees (n=200)	Postoperative Ambulation	90.9% ambulation in TMR vs 70.5% in standard care cohort (p<0.01).



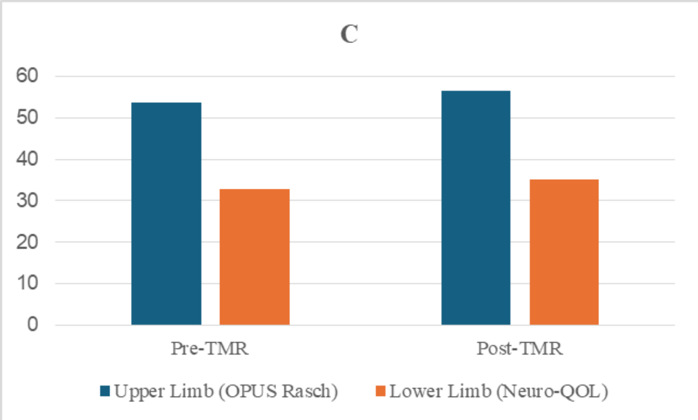


Figure 2: Functional and prosthetic integration outcomes. (A) Prosthetic integration success (fitted vs. operated). (B) Postoperative ambulation rates. (C) Functional and quality of life scores (OPUS Rasch/Neuro-QOL).

4. Broader applications and new applications

The impressive physiological outcomes of TMR have sparked its application beyond limb amputation. Recent scoping reviews have reported successful use of TMR to treat limb non-amputees who suffer from pain in a peripheral nerve, such as a sural nerve neuroma or hand neuroma, with excellent psychosocial effects and a very low risk of complications.[13]

The future of bionic reconstruction is combining TMR with implantable electromyographic interfaces and osseointegration.[5] This allows for implanted sensors that bypass the skin envelope, resulting in a dramatic increase in the signal-to-noise ratio of the reinnervated muscles and the possibility for bidirectional feedback for the development of fully functional robotic prostheses. To put into perspective the continued success of these new and old indications, Table 3 illustrates the overall safety and prevention profiles.

Table 3: Safety and prevention of neuroma.

Study (Year)	Target Population	Key Functional Metric	Quantitative Results
Souza et al. (2014)[12]	Transhumeral & Shoulder Disarticulation (n=26)	Prosthetic Fit & Operation	100% fitted with prosthetics; 88% successfully operated TMR-controlled devices.
Mioton et al. (2020)[9]	Major Limb Amputees (n=33)	OPUS Rasch (Upper) / Neuro-QOL (Lower)	Upper limb scores improved 53.7 to 56.4 ($p<0.001$); Lower limb improved 32.9 to 35.2.
Chang et al. (2021)[3]	Below-Knee Amputees (n=200)	Postoperative Ambulation	90.9% ambulation in TMR vs 70.5% in standard care cohort ($p<0.01$).

CONCLUSION

Targeted Muscle Reinnervation is a successful, intuitive, biologically based approach to address the problems of post-amputation neuropathic pain and prosthetic control. TMR eliminates painful neuromas by offering transected peripheral nerves an alternative, functional target. The clinical evidence strongly supports TMR over traditional neurectomy, as TMR dramatically reduces phantom and residual limb pain, markedly reduces opioid use and dramatically improves ambulatory and functional outcomes. As surgical experience with TMR accumulates, especially in the acute setting (at the time of amputation), it should be routinely adopted as the gold standard care to improve patient outcomes and bionic integration.

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