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THE POTENTIAL ROLES FOR ADIPOSE TISSUE IN PERIPHERAL NERVE REGENERATION

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Abstract

Introduction—This review summarizes current understanding about the role of adipose-derived tissues in peripheral nerve regeneration and discusses potential advances that would translate this approach into the clinic.

Methods—We searched PubMed for *in vivo*, experimental studies on the regenerative effects of adipose-derived tissues on peripheral nerve injuries. We summarized the methods and results for the 42 experiments.

Results—Adipose-derived tissues enhanced peripheral nerve regeneration in 86% of the experiments. Ninety-five percent evaluated purified, cultured, or differentiated adipose tissue. These approaches have regulatory and scaling burdens, restricting clinical usage. Only one experiment tested the ability of adipose tissue to enhance nerve regeneration in conjunction with nerve autografts, the clinical gold standard.

Conclusion—Scientific studies illustrate that adipose-derived tissues enhance regeneration of peripheral nerves. Before this approach achieves clinical acceptance, fat processing must become automated and regulatory approval achieved. Animal studies using whole fat grafts are greatly needed for clinical translation.

Peripheral nerve injuries affect 2.8% of trauma patients, often leading to chronic disability.[1] Annually, over 360,000 Americans suffer from upper extremity paralytic syndromes alone.[2] Peripheral nerve injuries also cause over 8.6 million restricted activity days (calendar days in which an employee can no longer perform one or more of their routine job functions) and over 4.9 million bed/disability days annually, creating a major economic burden on society.[2] It is possible for peripheral nerve fibers to spontaneously regenerate when continuity of the nerve is maintained during injury. However, completely severed nerves will not regenerate without surgical intervention to reestablish continuity. Nerve autografts are the gold standard for reconstruction of nerve gaps,[3,4] but there are incomplete recovery of motor and sensory functions following these repairs, even under ideal circumstances.[5–7] In addition, nerve autografting has several intrinsic disadvantages: long operative time, high facility cost, lack

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of sufficient graft material to reconstruct long nerve gaps or multiple nerve gaps, and donor site morbidity (painful neuroma, scarring, and sensory loss).[8]

Due to these disadvantages with nerve autografting, a majority of research efforts have focused on developing nerve conduits, which can be used “off the shelf” to reconstruct nerve gaps.[9–11] However, nerve conduits have decreased ability to concentrate essential growth factors as the length and diameter of the nerve conduit increases; they also lack cellular elements, appropriate neurotrophic support, and appropriate extracellularmatrix (ECM) and structural adhesion molecules to support regeneration across large nerve gaps.[9,12–14] Numerous studies have investigated supplementing nerve conduits with growth factors to enhance nerve regeneration across longer gaps,[15–24] but there have not been consistent reports on a single construct for successful regeneration of longer nerve gaps.[13]

Cellular-based therapy is an area of focus that has shown a positive effect on nerve regeneration, but continued research is needed to bring these techniques into the clinical setting. Addition of autologous Schwann cells (SCs), bone marrow mesenchymal stem cells (BMSCs), and adipose-derived stem cells (ASCs) have all shown positive effects on nerve regeneration during in vivo studies.[8,9,25–30] Of these cellular approaches, ASCs have the greatest clinically translatable therapeutic potential because of their trophic factor secretion, differentiation potential, and ease of harvest.[31–37]

There are five major forms of adipose-derived tissues that are experimentally reinjected into nerve injury sites to promote nerve repair: (1) autogenous fat grafts (adipocytes), (2) uncultured undifferentiated ASCs (uuASCs), (3) cultured undifferentiated ASCs (cuASCs), (4) cultured differentiated ASCs (cdASCs), and (5) dedifferentiated mature adipocytes (DFAT).

Autogenous fat grafts consist of unpurified whole adipose tissue that is simply harvested and reinjected as a lipoaspirate into nerve injury sites without isolating ASCs. To obtain uuASCs, researchers purify whole fat through collagenase digestion, filtration, neutralization, centrifugation, and resuspension.[26] To obtain cuASCs, uuASCs are cultured in various mediums until passage 2–12 to increase their quantity.[31,32,38] To obtain cdASCs, some studies induce SC-lineage differentiation of cuASCs to increase their secretion of neurotrophic factors and more closely mimic SCs involved in the innate mechanism of nerve regeneration.[25,39] On the other hand, to obtain DFAT, purified mature adipocytes are dedifferentiated in culture. DFAT has re-established proliferative capacity, increased homogeneity, decreased risk of spontaneous redifferentiation, and decreased risk of contamination than ASCs.[40] uuASCs, cuASCs, cdASCs, and DFAT have all demonstrated regenerative effects on peripheral nerve injuries in vivo. These studies have greatly advanced our understanding of peripheral nerve injuries and adipose biology, but their lack of clinical translatability has largely prevented them from changing the clinical treatment of peripheral nerve injuries from what it was five decades ago.

This review explores the potential role of adipose tissue and its derivatives in peripheral nerve regeneration, summarizes the relevant published articles, and discusses what studies are needed to move this regenerative medicine approach into the clinical arena.

MATERIALS AND METHODS

We searched PubMed (June, 2015) for all articles with the following words in the title or abstract: adipo* and nerve and (repair or regeneration). This search yielded 177 articles. Only original in vivo experimental animal studies on peripheral nerve injuries that directly compared the regenerative effects of adipose tissue to a similarly treated control group without adipose tissue were included. Thirty-eight articles matched our search criteria; four of the articles had two separate adipose tissue experimental groups, so we included 42 experiments in total. For each experiment, we determined the fat processing method, nerve injured, nerve gap size, nerve repair method, control group repair method, final evaluation time, outcome measures, and results.

The following outcome measures were considered functional: walking track and motor analysis (WTM), nerve conduction studies (NCS), erectile function (EF), and sensory function (SF). Walking track and motor analyses were used to calculate the sciatic functional index (SFI),[41] peroneal functional index (PFI),[31] and static sciatic index (SSI).[42] This walking track and motor analysis category includes tests to record foot placement and crossing time on ladder, terminal stance phase angle for functional gait cycle, muscle tension ratio, toe spread, grasping, and muscle force measurements. Nerve conduction studies assessed nerve conduction velocity (NCV) and compound muscle action potential (CMAP) amplitude and latency. Erectile function testing identified the intercavernous pressure to mean arterial pressure ratio. Sensory function studies included pinch test, vibrissae movements, and von Frey hair sensitivity (withdrawal threshold to pain).

Non-functional outcome measures included target muscle weight and histology. Histology was used to assess myelin thickness, number of myelinated axons, nerve fiber diameter, axon diameter, axonal regeneration distance, number of regenerated neurons, nerve cross-sectional area, neurite length, neurites per neuron, smooth muscle to collagen ratio, vascular density, number of neuromas, and expression of various cellular markers. We then summarized our findings and determined what essential information is missing from the literature, and thus, should be obtained before adipose tissue can make its way into common clinical treatment of peripheral nerve injuries.

RESULTS

All 38 articles that matched our search criteria were published between 2009 and 2015. The four articles that examined both cuASCs and cdASCs were each counted as one experiment on cuASCs and one experiment on cdASCs. The design and results of the 42 experiments are summarized in Table 1. Thirty-six experiments (86%) demonstrated significant regenerative effects of fat on peripheral nerve injuries according to their main outcome measures. Ten of the experiments injected human fat into athymic rodents, and eight saw a positive effect on regeneration, suggesting that human adipose tissue also has regenerative effects on peripheral nerves. Outcomes of the available research in each of the fat graft categories are discussed in the following sections.

Autogenous Fat Grafts

Two experiments on autogenous fat grafts matched our search criteria; one reported a negative effect on regeneration at six weeks,[43] and the other reported a positive effect on nerve regeneration at 4 weeks.[44] In the first experiment,[43] Papilla and colleagues injected uncentrifuged autogenous fat grafts into a nerve conduit to reconstruct a 10-mm median nerve gap in rats. The experimental group supplemented with autogenous fat illustrated a significantly lower recovery of motor function (grasp test) than the control group. In addition, the experimental group had a significantly lower total number of myelinated axons, mean fiber diameter, and myelin thickness compared with controls. The authors attributed the negative results to a physical obstruction to axonal regeneration by the fat in the nerve conduit. In the experiment by Kilic and colleagues,[44] crush injury was performed, and inguinal adipose tissue with its vascular pedicle was mobilized and wrapped around the nerve lesion. Maximum isometric tetanic force recovery was significantly greater in the autogenous fat graft group compared with the control (untreated nerve crush). In addition, myelin thickness, total axon count, and nerve fiber density were significantly increased compared to the control group. No changes were noted in muscle mass. While pedicled flaps allow for fat grafting without tissue processing, avascular fat grafting still provides the most simple, minimally invasive approach to enhancing peripheral nerve regeneration. Furthermore, freely transferred fat grafts serve as a good protective barrier in peripheral nerve surgery, reducing fibrosis and adhesions.[74] Although autogenous fat grafting is relatively simple to perform clinically, more studies must be performed to demonstrate the effectiveness of whole avascular autogenous fat grafts on peripheral nerve regeneration.

Uncultured Undifferentiated ASCs

All three experiments on uncultured undifferentiated ASCs (uuASCs) demonstrated a significant regenerative effect according to all recorded outcome measures.[42,45,46] Suganuma and colleagues found that the uuASC group had significantly more axonal regeneration compared with controls (saline-filled conduit).[45] Mohammadi and colleagues found that the uuASC group had significantly improved SFI and SSI and increased nerve fiber number and axon diameter compared to controls (empty conduit).[42] Song and colleagues found that the uuASC group had significantly improved erectile response to cavernous nerve stimulation and increased endogenous eNOS (phospho-endothelial nitric oxide synthase) phosphorylation and angiogenic factors compared with controls (nerve crush + phosphate buffered saline).[46]

Based on these experiments, uuASCs improved regenerative potential, but regulatory and scaling burdens currently associated with ASC purification still may create a barrier to widespread clinical use. uuASC purification entails routine chemical processing, which could be incorporated into the surgical protocol without adding unreasonable time and expenses; however, as soon as adipose tissue undergoes any chemical processing, the Food & Drug Association (FDA) considers it a regulated drug, restricting its use clinically.[75] However, technological advancements and enhanced scientific understanding of ASC biology may eventually resolve these burdens.

Cultured Undifferentiated ASCs (cuASCs)

Nineteen of the 23 experiments (83%) on cultured undifferentiated ASCs (cuASCs) demonstrated a significant beneficial effect on nerve regeneration according to their primary outcome measures.[11,32,38,47–66]

Six experiments examined the effects of cuASCs on nerve regeneration following injury to the cavernous nerve in rats.[38,49,50,53–55] All six of these experiments reported significantly improved values for erectile function compared with controls (nerve crush). In addition, five of the six experiments (83%) reported significantly improved histological parameters, including nNOS (neuronal nitric oxide synthase) expression, eNOS expression, smooth muscle to collagen ratio, and myelinated axons.

Fourteen experiments examined the effects of cuASCs on nerve regeneration following injury to the sciatic nerve.[11,32,48,51,52,56–61,63,65,66] Of the ten experiments that examined walking track and motor analysis, seven illustrated significant improvement compared with the controls. Four of the experiments examined nerve conduction, and three showed significant increases compared with controls. One experiment used the pinch test to determine sensory function and demonstrated significantly improved recovery compared to controls.[11] Three of the five experiments that evaluated target muscle weight found a significant increase compared with controls. Thirteen of the 14 experiments (93%) demonstrated significant improvements in histologic outcomes compared to controls. One of these 14 experiments evaluated the effects of cuASCs on enhancing regeneration of nerve gaps treated with autografts and demonstrated positive histological results, but lacked functional outcome measures.[52]

Three experiments examined the effects of cuASCs on nerve regeneration following injury to the facial nerve.[47,62,64] Two of the experiments examined nerve conduction,[47,64] and one showed a significant increase compared with controls. Two of the experiments also used vibrissae movements to examine sensory function,[62,64] and both showed significant increases compared with controls. All three experiments examined histological outcomes, and only one demonstrated significant improvements in histologic outcomes compared with controls.

Thus, cuASCs hold great promise for the enhancement of nerve regeneration, but they have the same regulatory and scaling burdens as uuASCs with an added burden and time delay involved with culturing the cells.

Cultured Differentiated ASCs

Twelve of the 13 experiments (92%) on cultured differentiated ASCs (cdASCs) demonstrated a significant beneficial effect on nerve regeneration according to their primary outcome measures.[26,31,63–73] One experiment on the effects of cdASCs on nerve regeneration following injury to the facial nerve demonstrated significant improvements in nerve conduction, vibrissae movements, and histological outcomes compared with controls.[64]

Of the 12 other experiments on cdASCs, seven examined walking track and motor analysis, and six (86%) illustrated significant improvement compared to the controls. Four of the experiments examined nerve conduction, and three showed significant increases compared with controls. Two experiments used the von Frey hair sensitivity test, and one demonstrated significantly improved sensitivity to applied stimulus compared with controls. All six experiments that evaluated target muscle weight found a significant increase group compared with controls. All 12 demonstrated significant improvements in histologic outcomes compared with controls.

Four experiments compared cdASCs to cuASCs.[63–66] Two of these experiments evaluated walking track and motor analysis, and one found a significant improvement in the cdASC group compared with the cuASC group. Two of the experiments evaluated nerve conduction, and one found a significant improvement in the cdASC group compared to the cuASC group. One experiment evaluated vibrissae movement and observed no difference between cdASC and cuASC group. One experiment evaluated target muscle weight and demonstrated a significant increase in the cdASC group compared with the cuASC group. Three of the four experiments observed improved histological outcomes in the cdASC group compared to the cuASC group. The effects of differentiation of ASCs regenerative effects remain unclear; moreover, in addition to the regulatory and scaling burdens associated with cuASCs, cdASCs have an added burden of inducing *in vitro* differentiation clinically. Additionally, the length of viability and exact contribution of cdASCs remains an area of needed investigation.

Dedifferentiated Mature Adipocytes

One experiment on dedifferentiated mature adipocytes (DFAT) matched our search criteria and reported a positive effect on regeneration at 13 weeks.[40] In this experiment, Matsumine and colleagues injected DFAT into a nerve conduit to reconstruct a 7-mm facial nerve gap in rats. The experimental group supplemented with DFAT illustrated a significantly higher CMAP amplitude than controls (empty conduit). In addition, the DFAT group had a significantly higher nerve fiber diameter, axon diameter, and myelin thickness compared with controls. Although DFAT has therapeutic potential, it does not avoid any of the regulatory or scaling burdens associated with cdASCs.

DISCUSSION

Peripheral nerve injuries remain a common problem with suboptimal treatment options; our literature review suggests that adipose-derived tissues have significant regenerative effects on peripheral nerve injuries *in vivo* and could theoretically provide a beneficial adjunct to current treatments. Adipose-derived tissues are believed to exert their effects through secretion of high quantities of angiogenic, neurotrophic, and anti-apoptotic factors known to enhance peripheral nerve regeneration. In their recent review on peripheral nerve regeneration, Widegrow and colleagues suggest that this ASC “secretome” should be maximized by *in vitro* priming prior to implantation.[76] However, as pointed out in the current review, to make this approach clinically relevant, adipose-derived tissues must require minimal modifications to avoid regulatory and scaling burdens.

The FDA classifies all cells purified from adipose tissue as manufactured drugs subject to regulation.[75] Furthermore, adipose cells that have undergone additional culturing, differentiation, or dedifferentiation are subject to even greater regulation. Technological advancements may minimize the scaling burdens associated with adipose tissue processing, and advancements in scientific understanding of stem cell biology may alter the regulatory burdens; however, minimally processed adipose tissue has the greatest potential to supplement clinical treatment of peripheral nerve injuries in the near future.

In this review, 95% of the experiments identified used adipose tissue that was modified by purification, culturing, differentiation, or dedifferentiation. In addition to the regulatory burdens, adipose tissue modification creates scaling burdens that would make this approach difficult for most clinicians to adopt due to the lack of equipment and expertise to isolate, purify, amplify, and differentiate adipose tissue. Use of unpurified autogenous fat grafts would be an ideal way to avoid potential regulatory and scaling issues. Minimally processed adipose tissue already has vast clinical utility;[77] its regenerative potential has been beneficial in the treatment of radiotherapy breast tissue damage[78,79] and other restrictive scar formations.[80] However, additional studies are needed to further define the regenerative effects of whole autogenous fat on peripheral nerve injuries.

In addition to the regulatory and scaling burdens, the experiments that matched our search criteria had several design limitations that limit their clinical translatability. Of the 40 experiments on rodents, all examined nerve gaps of 15 mm or less. Rodents have an intrinsic ability to effectively regenerate nerves across short gaps;[4,9] therefore, these experiments do not isolate the benefits of adding adipose tissue from the intrinsic ability of the nerve to regenerate itself. Furthermore, the clinical gold standard for repair of critical peripheral nerve gaps remains nerve autografts, and only one of the experiments evaluated the effectiveness of adipose tissue in supplementing nerve autografts.[52] While this study demonstrated positive histological results, it lacked functional outcome measures. To have a translatable clinical impact, adipose tissue would have to demonstrate improved functional outcomes when used as an adjunct to nerve autografts for the treatment of critical nerve gaps (20 mm or more).

Although 35 of the included experiments (83%) have at least one functional outcome measure, none evaluated performance of the nerve under conditions of prolonged nerve signaling (fatigue testing). Repeatedly signaling the nerve for an extended time gives a more accurate depiction of the natural variation of muscle actions and endurance necessary for true functionality. In addition, there exists a tight correlation between CMAP and contractile force.[81] Thus, measuring muscle forces during periods of repeated signaling allows researchers to more comprehensively evaluate the degree of nerve regeneration.[82] Future experiments would be enhanced by the inclusion of muscle fatigue testing.

Despite the exciting trend of the use of adipose-derived tissues in regenerative medicine, a paucity of literature exists demonstrating the prolonged viability of these tissues once transplanted to a non-native location. Grafted avascular adipose tissue has a dynamic regenerative process[83] and can only survive under specific conditions.[84] How long the adipose-derived cells survive in a nerve gap and how long the growth factors are released has

also not been thoroughly investigated. This information could potentially make for improved clinical regimens where additional adipose-derived tissues or growth factors are reinjected at multiple time points.

CONCLUSIONS

Adipose tissue is easy to obtain and has the theoretical capability to enhance peripheral nerve regeneration. Adipose tissue processing must be minimized or regulatory burdens must be overcome. Future animal experiments must use more rigorous functional outcome measures to analyze the effects of supplementing nerve autografts with autogenous fat grafts for the treatment of critical nerve gaps. This strategy would provide us with an opportunity to enhance functional outcomes following reconstruction with nerve grafts.

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Table 1

Summary of Experimental Design and Results Contained in 38 Articles that Matched Study Criteria for Regenerative Effects of Adipose Tissue on Peripheral Nerve Injuries

1st Author, Year[Citation]	Fat processing method (animal)	Nerve (animal)	Nerve gap + repair method	Control group repair method	Time	Functional outcomes					
						WTM	NCS	EF	SF	MW	H/I
Papalia, 2013[43]	Whole fat graft (rat)	Median (rat)	10-mm + conduit	Muscle-vein graft	6 months	†					†
Kilic, 2013[44]	Whole fat graft (rat)	Sciatic (rat)	Crush + none	None	4 weeks	*				NS	*
Suganuma, 2013[45]	uuASC (rat)	Sciatic (rat)	10-mm + conduit	Empty conduit	2 weeks						*
Mohammadi, 2014[42]	uuASC (rat)	Sciatic (rat)	10-mm + conduit	Empty conduit	12 weeks	*	*			*	*
Song, 2014[46]	uuASC (mouse)	cavernous (mouse)	Crush + none	PBS	2 weeks			*			*
Ghoreishian, 2013[47]	cuASC (dog)	Facial (dog)	7-mm + conduit	Empty conduit	12 weeks		*				NS
Luo, 2012[48]	cuASC (dog)	Sciatic (dog)	50-mm + conduit	Empty conduit	24 weeks						*
Jeong, 2013[49]	cuASC (human)	Cavernous (rat)	Crush + none	None	4 weeks			*			*
Piao, 2012[38]	cuASC (human)	Cavernous (rat)	Crush + none	None	4 weeks			*			*
You, 2013[50]	cuASC (human)	Cavernous (rat)	Dissection + none	PBS	4 weeks			*			NS
Marconi, 2012[32]	cuASC (human)	Sciatic (mouse)	Crush + none	PBS	3 weeks	*					*
Santiago, 2009[51]	cuASC (human)	Sciatic (rat)	6-mm + conduit	Empty conduit	12 weeks	NS				NS	*
Masgutov, 2015[52]	cuASC (human)	Sciatic (rat)	10-mm + autograft	Autograft + NaCl	65 days						*
Fandel, 2012[53]	cuASC (rat)	Cavernous (rat)	Crush + none	PBS	4 weeks			*			*
Qiu, 2012[54]	cuASC (rat)	Cavernous (rat)	Crush + none	Saline	12 weeks			*			*
Ying, 2013[55]	cuASC (rat)	Cavernous (rat)	Crush + none	PBS	3 months			*			*
Liu, 2011[56]	cuASC (rat)	Sciatic (rat)	15-mm + end-to-end	Empty allograft	12 weeks	*				*	*
Dai, 2013[57]	cuASC (rat)	Sciatic (rat)	15-mm + conduit	Empty conduit	8 weeks	NS	NS				*
Erba, 2010[58]	cuASC (rat)	Sciatic (rat)	10-mm + conduit	Empty conduit	2 weeks						*
Carriel, 2013[11]	cuASC (rat)	Sciatic (rat)	10-mm + conduit	Empty conduit	12 weeks	*	*		*		*
Mohammadi, 2013[59]	cuASC (rat)	Sciatic (rat)	10-mm + conduit	Empty conduit	12 weeks	*				*	*
Shen, 2012[60]	cuASC (rat)	Sciatic (rat)	10-mm + conduit	Empty conduit	8 weeks	*	*				*
Wei, 2011[61]	cuASC (rat)	Sciatic (rat)	10-mm + conduit	Empty conduit	24 weeks	*				*	*
Sun, 2011(A)[62]	cuASC (rat)	Facial (Rat)	8-mm + conduit	Empty conduit	8 weeks				*		*

1st Author, Year[Citation]	Fat processing method (animal)	Nerve (animal)	Nerve gap + repair method	Control group repair method	Time	Functional outcomes					
						WTM	NCS	EF	SF	MW	H/I
Kim, 2014[63]	cuASC/cdASC (human)	Sciatic (rat)	15-MM + CONDUIT	Empty conduit	6 weeks		*/*				*/*
Sun, 2011(B)[64]	cuASC/cdASC (rat)	Facial (rat)	8-mm + conduit	Empty conduit	8 weeks		NS/*		*/*		NS/*
Schaakxs, 2013[65]	cuASC/cdASC (rat)	Sciatic (rat)	Bisect + end-to-end	Growth medium	1 month	NS/*				NS/*	NS/*
Orbay, 2012[66]	cuASCs/cdASCs (rat)	Sciatic (rat)	10-mm + conduit	Empty conduit	6 months	*/*					*/*
Lopatina, 2011[31]	cdASC (human)	Peroneal (mouse)	Crush + none	Growth medium	11 days						*
Hsueh, 2014[67]	cdASC (human)	Sciatic (rat)	10-mm + conduit	Empty conduit	6 weeks	NS				*	*
Li, 2013[68]	cdASC (mouse)	Sciatic (mouse)	10-mm + conduit	Empty conduit	4 weeks						*
Zhao, 2010[69]	cdASC (mouse)	Sciatic (mouse)	14-mm + conduit	Empty conduit	12 weeks	*			NS		*
Tomita, 2012[70]	cdASC (rat)	Peroneal (rat)	3-mm + conduit	Empty conduit	10 weeks	*	*			*	*
di Summa, 2010[26]	cdASC (rat)	Sciatic (rat)	10-mm + conduit	Empty conduit	2 weeks						*
di Summa, 2011[71]	cdASC (rat)	Sciatic (rat)	10-mm + conduit	Empty conduit	15 weeks		*			*	*
Schaakxs, 2015[72]	cdASC (rat)	Sciatic (rat)	10-mm + fibrin strips	Fibrin strips	12 weeks	*	NS			*	*
Wang, 2012[73]	cdASC (rat)	Sciatic (rat)	15-mm + conduit	Empty conduit	12 weeks	*			*	*	*
Matsumine, 2014[40]	DFAT (rat)	Facial (rat)	7-mm + conduit	Empty conduit	13 weeks		*				*

Abbreviations: MW, Muscle Weight; H/I, Histology/Imaging; WTM, Walking Track and Motor Analysis; NCS, Nerve Conduction Studies; EF, Erectile Function; SF, Sensory Function; uuASCs, uncultured undifferentiated adipose-derived stem cells; cuASCs, cultured undifferentiated adipose-derived stem cells; cdASCs, cultured differentiated adipose-derived stem cells; DFAT, dedifferentiated mature adipocytes; PBS, Phosphate buffered saline; NaCl, Sodium chloride. Decellularized nerve grafts and vein grafts were labeled as nerve conduits. “Empty” refers to no adipose cells added.

Control groups all had the same nerve injuries as the listed experimental groups.

Significance was determined by referring to the corresponding control group in each major category tested: *P < 0.05 (statistically significant improvement),

†P < 0.05 (statistically significant decline),

NS (not significant, P > 0.05).