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FIBROMYALGIA , CHRONIC MIGRAINE, AND MYOFASCIAL PAIN

ALSO INSIDE

Autologous Stem Cell Therapy

A NATUROPATHIC APPROACH FOR THE TREATMENT OF CHRONIC MUSCULOSKELETAL PAIN CONDITIONS—Part I of II

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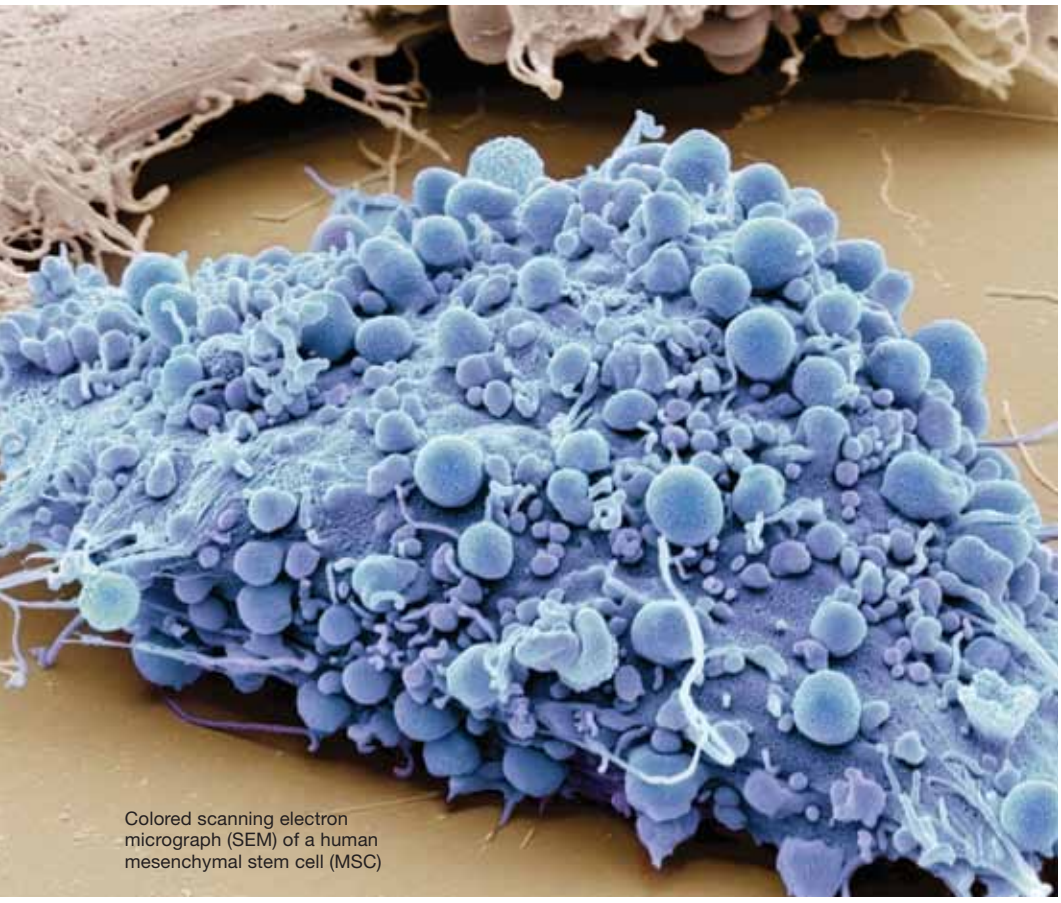
An emerging approach to the treatment of chronic musculoskeletal pain is the harvest and concentration/isolation of autologous mesenchymal stem cells (MSCs) for reinjection into damaged or degenerated joints, ligaments, tendons, and muscles. MSCs have been dubbed "patient-specific drug stores for injured tissues" because of their ability to secrete bioactive factors and signals at variable concentrations in response to local microenvironmental cues (1). MSCs are found throughout the body in many tissue types, but they are particularly abundant and easily harvested from the medullary cavity of flat bones and from adipose tissue (2,3). MSCs can be easily concentrated from bone marrow with simple centrifugation. With a little more effort, MSCs can be isolated from adipose tissue through a multistep process of incubation/enzymatic digestion with collagenase followed by centrifugation and filtration. When injected into the site of damage or degeneration, MSCs release a spectrum of antiinflammatory, immunomodulatory, and trophic factors that trigger the regeneration and healing of connective tissues through activation of stem cells endogenous to the site.

As the pool of data continues to grow, the site-specific injection of autologous stem cells has shown promise in musculoskeletal pain conditions such as osteoarthritis (4), sports/traumatic injury (5), low back and discogenic pain (6), neck pain with or without cervicogenic headaches (7), and osteonecrosis (8). Of note, concurrent bodies of data continue to grow that appear to refute the validity of arthroscopic surgery for knee pain (9) and cast doubt upon the validity of steroid epidurals for low back pain (10,11).



Colored scanning electron micrograph (SEM) of a human mesenchymal stem cell (MSC)

STEVE GSCHMEISSNER / SCIENCE SOURCE

Naturopathic physicians in the U.S. and Canada have a rich history of performing prolotherapy, introduced to the profession first and foremost by the deceased Rick Marinelli, ND, past president of The American Academy of Pain Management. The injection of autologous stem cells for the treatment of chronic musculoskeletal pain can be viewed as the natural evolution of prolotherapy, and its proposed mechanism of action, namely the regeneration of damaged or degenerated tissues through triggering the body's own healing response, is perfectly aligned with the guiding principles of naturopathic medicine (see Table 1).

This article is part I of a two-part series on the naturopathic approach to the use of autologous stem cells for the treatment of chronic musculoskeletal pain conditions. Part I examines the laying

TABLE 1
The Guiding Principles of Naturopathic Medicine (12)

• **The healing power of nature** (*vis medicatrix naturae*): Naturopathic medicine recognizes an inherent self-healing process in people that is ordered and intelligent. Naturopathic physicians act to identify and remove obstacles to healing and recovery, and to facilitate and augment this inherent self-healing process.
• **Identify and treat the causes** (*tolle causam)*: The naturopathic physician seeks to identify and remove the underlying causes of illness rather than to merely eliminate or suppress symptoms.
• **First do no harm** (*primum non nocere*): Naturopathic physicians follow three guidelines to avoid harming the patient: —Use methods and medicinal substances that minimize the risk of harmful side effects, using the least force necessary to diagnose and treat —Avoid when possible the harmful suppression of symptoms —Acknowledge, respect, and work with individuals' self-healing process
• **Doctor as teacher** (*docere*): Naturopathic physicians educate their patients and encourage self-responsibility for health. They also recognize and employ the therapeutic potential of the doctor-patient relationship.
• **Treat the whole person** (*tolle totum*): Naturopathic physicians treat each patient by taking into account individual physical, mental, emotional, genetic, environmental, social, and other factors. Since total health also includes spiritual health, naturopathic physicians encourage individuals to pursue their personal spiritual development.
• **Prevention** (*praevenire*): Naturopathic physicians emphasize the prevention of disease by assessing risk factors, heredity, and susceptibility to disease, and by making appropriate interventions in partnership with their patients to prevent illness.

of a foundation of optimal cellular metabolism, connective tissue health, and overall function of the human organism through non-invasive and natural modalities that are not exclusive to naturopathic medicine: diet, exercise, hormone optimization, nutritional/botanical supplements, and intravenous micronutrient therapy.

Nutrition

According to naturopathic doctrine, a diet consisting of a variety of whole foods, adequate protein, healthy fats, and nutrient-dense vegetables and leafy greens, in conjunction with stem cell therapy, can only serve to improve outcomes (13,14). Protein is essential for proper bone development and remodeling as well as collagen deposition. Vitamin C from food sources is critical in collagen synthesis.

Glucose intolerance hinders tissue healing after injury (15). Our clinical experience suggests that diabetic patients tend not to respond as well to regenerative injection therapies as do non-diabetic patients (7,16). As the incidence of obesity and diabetes continues to explode worldwide, dietary intervention is a critical component of naturopathic medicine to improve outcomes with regenerative and stem cell therapies as well as to contribute to the health and wellbeing of society as a whole.

Exercise

Naturopathic physicians subscribe to the belief that exercise may be the single most powerful tool for health and longevity (17) and exercise should always be the first prescription (18). From increasing mitochondrial output as well as synthesis of new mitochondria, to improving blood sugar regulation and insulin sensitivity, regular exercise provides broad-reaching benefits to cellular metabolism (19).

Exercise triggers an increase in mitochondrial biogenesis through the stimulation of AMP-activated protein kinase (AMPK) (20). Moreover, exercise has been shown to reverse the inhibition of neural stem cells caused by alcohol consumption (21). The effects of strength training on increasing human growth hormone and testosterone levels are well known. In addition, movement and exercise are thought to be beneficial after stem cell therapy as they promote and improve collagen synthesis during the remodeling phase (22).

Hormone Optimization

Hormones affect nearly every cellular process in the human organism and bio-identical hormone optimization is a major cornerstone of naturopathic training and practice. As such, naturopathic physicians consider the impact hormonal imbalances may have on clinical outcomes with every patient and, certainly when providing stem cell therapies the optimization of the anabolic hormone, testosterone, and the metabolic hormone, thyroid, is important.

Testosterone is anabolic and as such promotes tissue deposition and growth. Testosterone has been used as a site-specific percutaneous injection to stimulate target tissues in prolotherapy treatments for ligamentous laxity (23). Testosterone's beneficial androgenic effects on wound healing, immune status, and inflammatory responses during acute wound healing have all been well documented. Testosterone production decreases with age in men and

women and supplementation to physiologic levels appears to be safe (24).

Thyroid hormone stimulates metabolic rate. A hypothyroid state can lead to decreased wound healing and slowed stem cell proliferation (25). Thyroid production decreases with age and supplementation to physiologic levels appears to be safe (26).

Nutritional/Botanical Supplements

Vitamins, Minerals, and Amino Acids

The roles that essential vitamins and minerals play in stem cell metabolism and function are well described in the basic science literature. The concept that a well-balanced micronutrient milieu is required for proper stem cell function is reasonable and based in the available data. The fat-soluble nutrients, vitamins A, D, E, and K, the water-soluble ascorbate, as well as every B-vitamin and associated nutrient (such as biotin and PABA) are critical for proper stem cell function. The minerals copper, magnesium, iron, selenium, and zinc have been shown to be vital to stem cell function. Many amino acid structures, specifically acetyl-l-carnitine (ALCAR), tyrosine, tryptophan, lysine, glycine, glutamate, cysteine, and the tripeptide glutathione have been well studied in relation to stem cell metabolism and function.

An oral supplement regimen for patients undergoing stem cell therapy includes essential vitamins and minerals, essential fatty acid, dietary algae, and ALA.

Other Supplements

Fatty acids, such as fish oils and the omega 3 fatty acids are necessary for stem cell propagation. Basic antioxidants, in addition to those mentioned above, including anthocyanidins (blueberry and beet root), spirulina, green tea polyphenols, and fucoxanthin play a role in stem cell metabolism and function. Other cofactors such as alpha-lipoic acid (ALA) and ubiquinone (coenzyme Q10; CoQ10), as well as the trophic nutrients glycerophosphocholine (GPC) and phosphatidylserine (PS), appear to be required for proper stem cell function. Blueberry and fucoidan (a polysaccharide derived from brown seaweed) have been shown to promote stem cell release and function.

Based on these data, a reasonable oral supplement regimen for patients undergoing stem cell therapy would include essential vitamins and minerals, ideally in a multiproduct formula, an essential fatty acid product, some form of dietary algae, and alpha-lipoic acid.

Intravenous Micronutrient Therapy

The administration of relatively large doses of micronutrients via the intravenous route (IVMT) is a novel method to replete a person before and during stem cell therapy. The premise of IVMT is that the serum concentrations of micronutrients taken orally are limited by GI absorption, whereas administering micronutrients intravenously achieves serum concentrations far beyond what GI absorption will allow, thereby better replenishing depleted cells (27). The basic nutrients such as the water-soluble vitamins and minerals can all be safely administered as IVMT. Likewise amino acids (as mixtures or separate additions), glutathione, and other support nutrients are also used in the IV form. A few specific nutrients for IV use are listed here:

Alpha Lipoic Acid (ALA)

ALA is a thiol and as such is known in basic science to support levels of glutathione in the liver and other tissues. In experimental models, ALA has been shown to be helpful in pushing the redox balance in a positive direction via modulation of inflammatory cytokines such as tumor necrosis factor and NF-kappa-b.

Lipoic Acid Mineral Complex (LAMC)

Known as the proprietary formula Poly MVA® in North America, LAMC has shown to be helpful in cellular repair, mitochondrial repair, and radioprotection. We have found that low IV doses (5-15 mL) combined with low oral doses (5-10 mL BID) improve energy via mitochondrial support (28).

Taurine and Carnitine

Carnitine (either in the "l" form or the more bioavailable "acetyl-l" form) is useful in varied targets including decreasing neurotoxicity (29), decreasing lactic acid build up (30) as well as its more commonly known biochemical function of transporting fatty acids into the mitochondria for beta oxidation based energy production. We administer the l-carnitine form most frequently in IV doses of 500-4000 mg and the acetyl-l-carnitine form in doses of 100-1000 mg.

Taurine is the master osmolyte in the human body and as such regulates distribution of the excitable ions (Na, K, Ca, Mg, and Cl) to their appropriate sides of the cell membrane (31). In this role, we have observed adding 200-1000 mg taurine to IV formulas containing magnesium and other excitable tissue-acting minerals results in a greater benefit as reported by patients. Taurine is used constantly at the cell membrane and thus depleted both in low dietary intake as well as by oxidative stressors.

Glutathione

Commonly used by doctors performing IVMT, glutathione appears to have positive effects in the treatment of a wide range of illnesses (32). General doses are between one and three grams but far greater doses have been documented. As some patients will have sulfation SNP defects and other reasons not to tolerate glutathione, we typically use a lower test dose on the first IV infusion of glutathione, ranging from 100-500 mg.

Conclusion

Part I of this series has been intended to be an overview of the most basic and fundamental methods employed by the naturopathic physician for laying a foundation of optimal cellular metabolism, connective tissue health, and overall function of the human organism in order to optimize stem cell therapy. Part II of this series will detail the methods for harvest and concentration/isolation of bone marrow aspirate concentrate (BMAC) and adipose-derived stromal vascular fraction (SVF) and present original research comparing three methods for treating low back pain and osteoarthritis of the knee: 1) the use of bone marrow aspirate concentrate (BMAC); 2) the use of adipose-derived stromal vascular fraction suspended in platelet rich plasma (SVF/PRP); and 3) the use of SVF suspended in BMAC (SVF/BMAC).

References

1. Murphy MB, Moncivais K, Caplan A. Mesenchymal stem cells: environmentally responsive therapeutics for regenerative medicine. *Exp Mol Med*. 2013; 45:e54. doi:10.1038/emm.2013.94.
2. Hendrich C, Engelmaier F, Waertel G, Krebs R, Jager M.. Safety of autologous bone marrow aspiration concentrate transplantation: initial experiences in 101 patients. *Orthop Rev (Pavia)*. 2009 Oct 10; 1(2):e32.
3. Michalek J, Moster R, Lukac L, et al. Autologous adipose tissue-derived stromal vascular fraction cells application in patients with osteoarthritis. *Cell Transplant*. 2015 Jan 20.
4. Goldberg, Victor M. Stem cells in osteoarthritis. *HSS J*. 2012 Feb;8(1):59-61.
5. Quintero AJ, Wright VJ, Fu FH, Huard J. Stem cells for the treatment of skeletal muscle injury. *Clin Sports Med*. 2009;28(1):1-11.
6. Orozco L, Soler R, Morera C, et al. Intervertebral disc repair by autologous mesenchymal bone marrow cells: a pilot study. *Transplantation*. 2011 Oct 15;92(7):822-8.
7. Adelson H. Bone marrow and adipose derived autologous stem cells for the treatment of chronic musculoskeletal pain. Paper presented at Annual Meeting of the American Academy of Pain Management; September 2014; Phoenix, Arizona.
8. Pak J. Regeneration of human bones in hip osteonecrosis and human cartilage in knee osteoarthritis with autologous adipose-tissue-derived stem cells: a case series. *J Med Case Rep*. 2011 Jul 7;5:296.
9. Thorlund JB, Juhl CB, Roos EM, Lohmander LS. Arthroscopic surgery for degenerative knee: systematic review and meta-analysis of benefits and harms. *BMJ*. 2015 Jun 16;350:h2747.
10. Radcliff K, Kepler C, Hilibrand A, et al. Epidural steroid injections are associated with less improvement in the treatment of lumbar spinal stenosis: a subgroup analysis of the Spine Patients Outcomes Research Trial. *Spine* (Phila Pa 1976). 2013 Feb 15;38(4):279-91.
11. Pinto RZ, Maher CG, Ferreira ML, et al. Epidural corticosteroid injections in the management of sciatica: a systematic review and meta-analysis. *Ann Intern Med*. 2012 Dec 18;157(12):865-77.
12. American Association of Naturopathic Physicians. House of Delegates Position Paper. Definition of Naturopathic Medicine. http://www.naturopathic.org/files/Committees/HOD/Position%20Paper%20Docs/Definition%20Naturopathic%20Medicine.pdf. Accessed August 3, 2015.
13. Hankenson KD, Watkins BA, Schoenlein IA, Allen KG, Turek JJ. Omega-3 fatty acids enhance ligament fibroblast collagen formation in association with changes in interleukin-6 production. *Proc Soc Exp Biol Med*. 2000 Jan;223(1):88-95.
14. Mihaylova MM, Sabatini DM, Yilmaz ÖH. Dietary and metabolic control of stem cell function in physiology and cancer. *Cell Stem Cell.* 2014 Mar 6;14(3):292-305.
15. Fadini GP, Pucci L, Vanacore R, et al. Glucose tolerance is negatively associated with circulating progenitor cell levels. *Diabetologia*. 2007 Oct;50(10):2156-2163.
16. Gallagher M, Moore T. Masqueraders of orthopedic pain: the gut-brain connection to chronic pain and the protocols to fix it. Presented at: 32nd Annual Conference and Seminar of the American Association of Orthopedic Medicine; April 2015; New Orleans, Louisiana.
17. Lee IM, Shiroma EJ, Lobelo F, et al. Effect of physical inactivity on major non-communicable diseases worldwide: an analysis of burden of disease and life expectancy. *Lancet*. 2012 Jul 21;380(9838):219-229.
18. Pizzorno JE, Murray MT. 4th Ed. Textbook of Natural Medicine. St. Louis, Missouri: Elsevier Health Sciences; 2012.
19. Petersen AM Pedersen BK. The anti-inflammatory effect of exercise. *J Applied Physiol*. 2005;98(4):1154-1162.
20. Hawke TJ. Muscle stem cells and exercise training. *Exerc Sport Sci Rev*. 2005;33 (2):63-68.
21. Crews FT, Nixon K, Wilkie ME. Exercise reverses ethanol inhibition of neural stem cell proliferation. *Alcohol*. 2004;33(1):63-71.
22. Kjaer M, Magnusson P, Krogsgaard M, et al. Extracellular matrix adaptation of tendon and skeletal muscle to exercise. *J Anat*. 2006 Apr;208(4): 445-450.
23. Ravin T. The use of testosterone and growth hormone for prolotherapy. *J Prolotherapy.* 2010; 2(4):495-503.
24. Gruenewald DA, Matsumoto AM. Testosterone supplementation therapy for older men: potential benefits and risks. *J Am Geriatr Soc*. 2003;51:101-115.
25. Lemkine GF, Raj A, Alfama G, et al. Adult neural stem cell cycling in vivo requires thyroid hormone and its alpha receptor. *FASEB J*. 2005;19(7):863-865.
26. Fatourechi V. Subclinical hypothyroidism: an update for primary care physicians. *Mayo Clin Proc.* 2009;84(1):65-71.
27. Ali A, Njike VY, Northrup V, et al. Intravenous micronutrient therapy (Myers' Cocktail) for fibromyalgia: a placebo-controlled pilot study. *J Altern Complement Med*. 2009;15(3): 247-257.
28. Anderson P. IV nutrient therapy. Presented at: The Orthobiologic Institute 5th Annual PRP and Regenerative Medicine Symposium; June 2014; Las Vegas, Nevada.
29. Virmani A, Gaetani F, Binienda Z. Effects of metabolic modifiers such as carnitines, coenzyme Q10, and PUFAs against different forms of neurotoxic insults: metabolic inhibitors, MPTP, and methamphetamine. *Ann N Y Acad Sci*. 2005 Aug;1053:183-91.
30. Claessens YE, Cariou A, Chiche JD, Dauriat G, Dhainaut JF. L-Carnitine as a treatment of life-threatening lactic acidosis induced by nucleoside analogues. *AIDS*. 2000 Mar 10;14(4):472-3.
31. Lambert IH. Regulation of the cellular content of the organic osmolyte taurine in mammalian cells. *Neurochem Res*. 2004 Jan;29(1):27-63.
32. Ashtiani HR, Bakhshandi AK, Rahbar M, et al. Glutathione, cell proliferation and differentiation. *Afr J Biotechnol.* 2011;10(34):6348-6363.



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