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Adjunctive Treatment Considerations for the Addressment of Inflammation in Neuromuscular Disorders

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Abstract

Objective: To explore the use of IGF-1 platelet rich plasma/adipocyte mesenchymal stem cells to address inflammation in its role seen in neuromuscular disorders.

Methods: IGF-1 applications in the clinical setting. Platelet rich plasma/adipocyte mesenchymal stem cell harvesting techniques.

Main outcome measurements: Functional improvement with basic and advanced activities of daily living and improved management of Pain.

Conclusion: IGF-1/adipocyte mesenchymal stem cell/PRP as possible adjunctive treatment options exist in the addressment of inflammation seen in neuromuscular disorders.

Keywords: Adipocyte; Stem cell; Cardiovascular; Pro inflammatory cells

Introduction to Inflammation

At the root of many of society's major health concerns plaguing millions of Americans each year is the concept of inflammation. Encompassing cardiovascular, oncologic, dermatologic, pain management, and neurologic diseases, the peripheral and systemic manifestations of inflammation has been increasingly shown to be a major culprit in disease spread.

Broad examples of this can be seen in various neurologic disease states.

Demyelinating diseases such as Multiple Sclerosis and degenerative changes associated with dementia have many factors with inflammation being one of those. The inflammatory cascade with its incorporation of pro inflammatory cytokines and transcriptional factors has been shown to be suggestive in the pathophysiology of these diseases [1]. Similarly, glial cells, acting as neural supports, have been shown to play a role in the production of these same pro inflammatory cells (IL-1B, IL-6, IL-8, TNF-alpha). The overproduction of these mediators is suggestive of neurodegenerative progression in both acute (ischemic injury) and chronic degenerative neural disorders [2]. Acknowledgement and addressment of the inflammatory cascade has led to novel treatment strategies such as the use of sirtuins. Sirtuins (SIRTs) are a family of regulatory proteins of genetic code involved in a myriad of physiologic functions including aging and metabolism. Indeed, SIRT1 has been shown to play an important role in the prevention and progression of neurodegenerative diseases [3]. Moreover, the inbred link between inflammation and the immune system has been concurrently studied in a variety of fields. Indeed, inflammatory-immune implications ranging from neuromuscular (Parkinson's) to rheumatologic diseases with organic manifestation (Crohn's) has been found [4,5]. Weidenbusch has commented on the role of "innate immunity" and inflammation seen in the diagnosis of SLE, additionally. An extrapolation, certainly potential treatment implications in combination with or as an adjuvant are implied utilizing the "Inflammatory-Immune" model in a myriad of disease processes as aforementioned inclusive of solid tumors [6-10].

With chronic inflammation seen at the heart of a myriad of disease states as prior outlined, concomitant oxidative stress with PI3K/mTor/aKt inflammatory pathway activation producing reactive oxide and nitrate species and uncoupling nitric oxide synthase are potential outcomes contributing to mitochondrial dysfunction. Sirtl1 and CTRP9, both free-radical scavengers are, thus, potential treatments in keeping with this proposed model.

Similarly, the naturally occurring phenol, resveratrol, has been shown as a sirtuin activator and having implied anticarcinogenic and anti-inflammatory effects [9]. The activation of the inflammatory cascade with resultant affect and effect on the body's immunomodulators and hastening of cell apoptosis or cell death is increasingly at the heart of diagnostic and therapeutic regimens.

Through regulation of inflammation, aging, and cellular senescence, then, the inclusion of sirtuins offer a novel glimpse of future treatment considerations.

In the field of Oncology, the focus of inflammation has been at the forefront of attention as well For example, nitric oxide has been closely correlated with inflammation seen in hepatocellular carcinoma. Similarly, Pim proteins represent serine/threonine kinases which have been found to be overproduced in prostate cancer. The ensuing inflammation related to their overproduction may contribute to the progression of prostate neoplasia [10].

Within the cardiac treatment model for atherosclerosis, the centralized role of inflammation can be found. Ineffective cardiac remodeling following a myocardial infarction remains a significant cause for future episodes of congestive heart failure. Similarly, the atherogenic streak, or "fatty streak", seen in coronary vessels has been an established inciting agent for atherosclerosis leading to heart disease.

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In both cases, it is the inflammatory cascade and its concomitant inflammatory mediators produced which is seen as playing a role in disease progression.

Detection markers including MMP-9 (Matrix metalloproteinase) has been found to be a potential marker for remodeling progression as its expression has been closely linked to increased inflammation. The epidemic of hypertension continues to be a major public concern. Medication treatment strategies have evolved to incorporate inflammation concerns as well. Specifically, antihypertensives including Amlodipine have been found to increase Vitamin D levels.

Vitamin D levels, in addition, to its relation to osteoporosis, are important in the inflammatory cascade.

In the management of Pain, control of peripheral and sensitization inflammatory mediators has grown to be the central treatment focus in arresting the progression of several acute pain generators manifesting into a chronic pain syndrome. Na^{+} channels, Ca^{++} channel modulation, GABA-ergic pathways induction, NMDA receptor blockade, histamine and bradykinin reduction and reduction of excess glutamate have been linked with the reduction of the "inflammatory soup" central to the development of mixed nociceptive/neuropathic pain states. By addressing the overproduction of several of these inflammatory mediators, functional restoration of basic and advanced activities of daily living through improved and targeted multimodal analgesia is increasingly becoming a reality. Thus, the established neuropathic pain treatment model has been to reduce the inflammatory mediators both centrally and peripherally. Through appropriate and targeted multimodal analgesia, focused targets for treatment have emerged.

IGF-1/inflammation

With the aforementioned representing a minuscule example of the importance of new and long- acting addressment of the inflammatory cascade, the study and usage of IGF-1 has emerged. Auto phosphorylation of the B-subunit allows for activation of tyrosine kinase. IRS (1-4) docking proteins allow for a launching pad for two important pathways (PI3-K and extracellular signal regulated protein kinase ((ERK))) which govern cell survival and cell growth. It is precisely through these pathways that a myriad of health diseases/maladies are being studied with IGF-1. Total IGF-1 levels decrease with age. In malnutrition and low protein states, IGF-1 levels have been shown to decline. Thus caloric status and protein levels play a vital role not only with generalized nutrition, but also with overall health and survival. This has lead to IGF-1 and IGF-1 B supplanting the roles of albumin and thrombin as nutritional markers in chronic illnesses.

Along with senescence and in malnourished states, accompanying inflammatory cytokines has been shown to be increased (IL-1B/3/6/TNF alpha).

In congestive heart failure, IGF-1 and IGFBP-3 have been found to be low (Delafontaine). In heart disease, in general, IGF-1 was found to reduce the pro-remodeling effects of the renin angiotensin system and promoted physiologic cardiac growth in its stead. As prior mentioned, the link between the inflammatory cascades and reduced IGF-1 levels is established. There is a suggestion of three signaling pathways at the center of cardiac muscle cell health (mTOR, ERK, PI3K).

In Chronic neuropathic Pain states, elevated levels of cortisol and insulin resistance (mirroring Diabetes) has been seen. Serving to duplicate as the Neuropathic variant of the metabolic syndrome, central and chronic inflammation with its subsequent insulin/IGF-1 resistance and elevated serum cortisol levels are seen. These elevated levels of cortisol and others (serum pregnenolone) are heralds of the inflammatory cascade. IGF-1 level has been shown to be diminished in acute/chronic Pain conditions as well as chronic neurodegenerative disorders as mentioned above. IGF-1 reduces cell loss and enhances long-term neurologic function in animal models. However, with an acute brain insult, the therapeutic window for IGF-1 administration remains small, requiring administration within a few hours. Existing IGF-1 forms, too, have a limited half-life (hours). These, coupled with a poor central uptake in the central nervous system has contributed to the challenges for more extensive use of IGF-1 in neurologic disease. The sequelae of many neurologic disease/rheumatologic disease states have been profound fatigue, moreover. Resistin levels (negatively associated with fatigue levels) and IGF-1 levels have provided unique insight in the management of exercise and obesity. In Diabetic peripheral neuropathy, the oftentimes labile blood sugar swings has contributed to increased neuropathic pain. At the heart of the disease process is insulin resistance. One can utilize the analogy of a "see-saw". As one end descends (insulin efficacy secondary to resistance) the other side ascends (cortisol levels), and vice versa. The excess level of cortisol heralds worsened neuropathic pain. One can substitute IGF-1 resistance with insulin resistance in this model as well, however. Through IGF-1 consideration, a complementary treatment approach for the management of neuropathic pain is seen.

Persistent, low-grade chronic inflammatory mediators can lay dormant in aging humans for decades. Much of the organic and physical manifestations of some of the most common debilitating diseases such as rheumatoid arthritis, cancer, and heart disease can be traced to these mediators. This bears long-term consequence to the body's immune system.

Longstanding inflammation has been shown to be associated with persistent neutrophil production of Interferon Gamma which is proinflammatory (Immunology May 2013). This immune resistance, if you will, can be seen in complex infectious diseases such as HIV. Chronic inflammation has been seen to afford not only insulin resistance with its concomitant increase in cortisol levels, but also GH/IGF-1 resistance. IGF-1 has been shown to reduce pro-inflammatory cytokines (IL1B/3/6/TNF alpha). Serum IGF-levels are associated with additional inflammatory established biomarkers such as CRP/IL-6/fibrinogen. With malnutrition and low protein states accompanying so many chronic health diseases, restoration of IGF-1 is paramount. Serum IGF-1/IGF1B levels are being monitored as a more sensitive means of measuring the malnourished state. By ensuring adequate caloric intake, 10-11 KCAL/KG/DAY and 0.8-1 G Protein/KG/day, steps to ensure adequate IGF-1 levels so as to promote immune function, cell survivability, and cell growth during chronic illness are taken.

High IGFBP-1 and low IGF-1 levels have been associated with overall mortality, regardless of cause in the older population. With age, it is also known that overall adipose tissue mass increases. A collection of hormones called adipokines are produced and have been found to invade skeletal muscle contributing to decreases in overall muscle strength, with strength training and weight management, IGF-1 treatment strategies have emerged. Moreover, there has been suggestion of a possible association between obesity and cognitive function in healthy young women. With the known link of insulin resistance with increased levels of cortisol and obesity, exploration of IGF-1 as part of a treatment model, with its propensity for lean body mass, continues to be studied. Indeed, a parallel IGF-1 resistance has been proposed mirroring the above insulin resistance model seen in obesity. Extrapolation of these studies has revealed a negative

association between increased adipose levels with learning and memory (cognition).

Summarizing, then, IGF-1 utilization is at the heart of a healthy Mind and Body concept. Additional sequelae of the aging body are a reduction of bone mineral density. As the infrastructure of our bones deteriorates over time, the progression from osteopenia (up to 1.5 standard deviations) to overt osteoporosis (greater than 2 standard deviations). Weight-bearing exercise has been part of the long-established solutions to this progression. This, coupled with Vitamin D levels/calcium levels/parathyroid hormone levels, remain the essential players with normal bone turnover. The inverse correlation with the active form of Vitamin D and age is known. Interestingly, however, there seems to also be a strong relationship with bone mineral density and IGF-1 levels.

With bone mineral density representing a significant risk factor for vertebral compression fractures. IGF-1 consideration has become paramount in Pain Management conditions, especially in the elderly population.

The role of vitamins in reducing oxidative stress and overall inflammation has grown increasing concentration. This can be seen most poignantly in the skin. The skin is the only tissue in the human body that represents a target for Dihydroxyvitamin D as well as has the capacity to make the active form of vitamin D (Dihydroxyvitamin D). Vitamin D, amongst a variety of other important functions, has been seen as an important regulator in the aging process of many tissues, including skin. Ongoing trials combining its benefits along with IGF-1 have shown the promise of synergistic benefit. Vitamin C plays a central role in the formation of connective tissues (collagen formation) as well as potentially serving as an antioxidant within intervertebral disc disorders. IGF-1 levels show upregulation of this antioxidant benefit. Indeed combinations of IGF-1 in combination with Vitamin C have shown to increase tensile strength within ligaments as well as overall collagen growth. Stem cell propagation has been postulated to be linked to Vitamin A. Through, once more, the signaling pathways of IGF-1 (mTor, PI3k), Vitamin A shows a complementary role in cell survival (Figure 1).

PRP-adipocyte mesenchymal stem cell considerations

PRP is autologous blood which contains more than seven identifiable growth factors/cytokines. These growth factors facilitate tissue regeneration and aid in cell viability. Correlating with and focusing upon the prior discussion of inflammation, so does too, platelet rich plasma assist in decreasing chronic inflammation. One purported process is suggested in its decreasing of nuclear factor KB which serves as a protein signaling agent in the pathogenesis of osteoarthritis. Traditional treatment methods have implemented corticosteriod use intraarticularly. Connective tissue degeneration and additional side effect profile limit repetitive use of corticosteriods. Similarly, repetitive administration of dextrose used in prolotherapy, too, can hasten degeneration and tendinosis. Additionally, IGF-1 levels are seen to decrease with corticosteriod use. Thus, once more, addressment of additional treatment options in the addressment of chronic inflammation has implications in a myriad of disease states. Indeed, chronic inflammation exhausts localized stem cells. Replenishment is a concern. PDGF/IGF-1/Cytokines necessary in wound healing and in connective tissue differentiation has been seen. Major sites of obtaining adult stem cells are in bone marrow and adipose tissue. In contradistinction to embryonic stem cells, which can give rise to any cell type, adult mesenchymal stem cells are already partially differentiated (multipotent) and can be found in many connective tissue elements (ligament/tendon/bone/cartilage).

Seemingly, just as important as chronic inflammation is implied in a myriad of disease states, is the depletion and effectiveness of stem cells. Adult Mesenchymal stem cells represent local/central repair elements allowing for the "reconstruction" of the havoc rendered by chronic inflammation. Thus, by addressment of chronic inflammatory mediators and replenishment of the corrective mechanisms, potential rejuvenatory strategies have emerged.

Patient J.C. is an 81 year old female with past medical history significant for extensive lumbar spondylosis characterized by ligamentum flavum hypertrophy, facet joint arthritis, and degenerative disc disease. Despite conservative measures including physical therapy, adjuvant rehabilitative modalities, and various interventional pain procedures, she had a steady decline in functionality with basic/advanced activities of daily living. Adult mesenchymal stem cells have reportedly been significantly more abundant in adipose tissue as opposed to bone marrow (times) (Mizuno, 2009). This coupled with ease of obtainment and decrease in pain complaints during harvesting, lead to adipose tissue targeting. In combination, high-density platelet rich plasma was obtained via autologous blood was mixed with its subsequent administration intradiscally and intraarticularly (zygoapophyseal joints). Improvement of pain of greater than 50% corresponding to improved independence with basic/advanced activities of daily living was seen at one month follow-up and has extended for greater than one year.

Patient M.B. is a 49 year old female with past medical history significant for cervical spondylosis. Patient failed conservative measures once more as physical/chiropractic treatment modalities and interventional pain management afforded no long lasting benefit. Eventually, patient underwent cervical laminectomy/fusion (2 levels) with worsening of her pain complaints. Similarly, patient received adult mesenchymal stem cell (abdomen) in combination with high-density platelet rich plasma placed intradiscally and intraarticularly (superior/inferior margins of spinal fusion levels). Patient reported 30% improvement of her pain with improved cervical range of motion and functional improvement overall.

Patient J.Y. is a 60 year old male with history of osteoarthritis and degenerative joint disease of the right shoulder with rotator cuff impingement. Utilization of high-density platelet rich plasma) has allowed for improved external rotation and abduction of his shoulder enabling overhead reaching and functional tasks to become less cumbersome. Patient had prior failed conservative measures including physical therapy/chiropractic care/corticosteroid injections. Radiography was indicative of a partial rotator cuff tear. Follow-up radiography six months post-procedure revealed no evidence of rotator cuff tear. Adjunctive rehabilitation focusing on isometric/isotonic strengthening and scapular

Stabilization exercises were implemented after the injection, of note. Targeted multimodal analgesia has allowed for >40-50% reduction of pain.

Patient J.Y.J is a 45 year old male with past medical history of grade III osteoarthritis of bilateral knees. Demonstrating radiographic evidence of 50-75% joint space loss with concomitant chondromalacia patellae, patient received prior physical therapy focusing on vastus medialis oblique strengthening/closed kinetic chain exercises/interferential electrical stimulation/corticosteroid injection/hyalgan injections without sustained benefit. With treatment as outlined

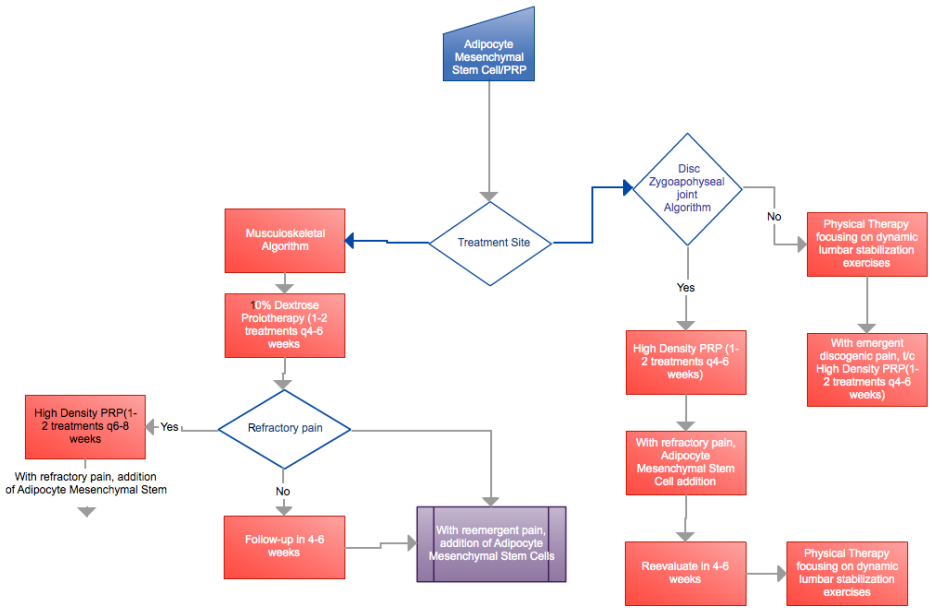

Figure 1: Proposed Adipocyte mesenchymal Stem Cell/PRP Protocol.

above, radiographic evidence of improvement (Grade II) coupled with improved pain and improved functionality has been achieved once more. This has translated into ease with functional transfers and overall mobility without need of an assistive device.

Clearly, from an empirical sense, treatment implication considerations are far-reaching. Furtherance of longitudinal studies is necessary, moreover. However, alternative treatment options via addressment of chronic inflammatory mediators have become a central consideration in the rejuvenatory approach to treatment of spine and neuromusculoskeletal disorders.

With musculoskeletal disorders, peripheral trauma or degenerative changes allows for a buildup of inflammatory mediators leading to peripheral sensitization. Na channel/Ca channel up regulation, histamine/bradykinin/substance P release, Prostaglandins (PGE2)/ Interleukin 1/3/6/TNF-alpha accumulation amongst others are purported as facilitating agents in this process.

Intermediary inflammatory mediators (PGE2) are reportedly key in the inflammatory cascade propagating centrally to the dorsal horn of the spinal cord leading to "central- sensitization" or "wind-up". Similarly, the afferent barrage of peripheral pain signals (joint/ ligament/tendon/muscle) that ascend to the dorsal horn of the cord allow for its own "inflammatory soup" to be formed centrally.

Mesenchymal stem cells are thought to be integral in the repair process in musculoskeletal disorders (Guila). With inflammation onset, mesenchymal stem cells assist in tissue repair, cartilage repair, ligament repair, intervertebral disc repair, tendon repair. With chronic inflammation, as seen in osteoarthritis, mesenchymal stem cell efficacy and production appears blunted both in response and in number.

Thus, at the root of many neuomusculoskeletal disorders is the consideration of inflammation. Its advancement traces a peripheral buildup of mediators which lead to central accumulation of additional inflammatory facilitators. Together, central/peripheral sensitization is suggested as a key target in multimodal analgesic regimens to improve patients' pain and improve their function. Via addressment of these peripheral and central mediators, improved efficacy in disease treatment is sought. The utilization of adult adipocyte mesenchymal stem cells potentially represents the assist, thereafter. Adipocytes provide a stimulus for the repair process via wound healing/ angiogenesis/immunomodulation.

After trauma/injury, platelets provide the impetus for growth factor production. Foremost and inclusive is Insulin-Growth Factor 1, platelet derived growth factor, transforming growth factor beta, fibroblast growth factor. Also included in its rejuvenatory capacity, platelets facilitate additional repair mediators. Thus, in addressment of the inflammatory barrage peripherally (joint/muscle/ligament/tendon) that seemingly accumulates, repair resolution measures are essential. Indeed, within the first two weeks of the repair phase (Gulotta; rotator cuff repair), these growth factors are seemingly focal in promoting healing and likely preventing hyperalgesia and allodynia characteristic of central sensitization. Moreover, muscle regenerative capacity, extracellular matrix and vessel repair are seen with the aforementioned growth factor production (Menetrey). Thus, containing the inflammatory process and promoting rejuvenatory measures in a myriad of neurodegenerative and musculoskeletal disorders including spine are suggested.

Current FDA regulatory concerns are ongoing. The FDA regulates the use of Stem cells of which it defines as being "Human Cells, Tissues and Cellular-based products". However, the exception is made if the Practitioner "removes human cells/tissues/and products from an individual and implants within the same individual during the same surgical procedure. (US Food and Drug Administration, Industry guidelines).

Proposed Intradiscal Protocol

Inclusion Criteria: Persistent radicular pain of at least 6 months. Patient is status post conservative measures including Physical Therapy/adjuvant modalities Physical presentation of radicular>axial Low back pain worsened with flexion/truncal rotation>Extension. No evidence of Annular tears by radiography.

Exclusion criteria: No evidence of systemic infection; No evidence of bleeding disorder Radiographic evidence of severe neuro foraminal stenosis.

Radiographic evidence of Grade 2 or greater spondylolisthesis >4 mm Disc protrusion.

High Density Platelet Rich Plasma (One to Two treatments separated by 6-8 weeks) Adipocyte mesenchymal stem cell (obtained from abdominal liposuction reevaluation).

If doing well, may repeat in 3-6 months.

Musculoskeletal algorithm

Inclusion Criteria: Clinical evidence of tendinosis/tendinopathy >6 month duration of pain symptomology.

At least 3 months of conservative measures with non-sustained benefit.

Patient is status post conservative measures including physical.

Patient is status post corticosteroid injection with non-sustained benefit. Therapy/adjuvant modalities.

Exclusion Criteria: No evidence of systemic infection No evidence of bleeding disorder Radiographic evidence of complete tear.

10% Dextrose Prolotherapy (One to Two treatments separated by 4-6 weeks) with refractory pain.

High Density Platelet Rich Plasma (One to Two treatments separated by 6-8 weeks) with refractory pain,

Addition of Adipocyte mesenchymal stem cells (obtained from abdominal liposuction; gauge liposuction cannula; One-Two treatments) reevaluation. If doing well, may repeat in 3-6 months.

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