

Research Article

Refractory Shoulder Pain with Osteoarthritis, and Rotator Cuff Tear, Treated With Micro-Fragmented Adipose Tissue

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Abstract

Background: Chronic shoulder pain and rotator cuff abnormalities affect a large portion of the population and result in substantial impairments and loss of useful functions, thus affecting patient quality of life. One of the most common causes of shoulder pain in the adult population is osteoarthritis. It is the third most prevalent musculoskeletal disorder after low back and neck pain. If current standard non-operative methods fail, there are few viable options available other than shoulder replacement surgery. Recently biological treatments using adult stem cell treatments, mesenchymal stem cells (MSC's) have been shown to have potential benefits in orthopedic applications. One such source of regenerative cellular tissue is adipose, which is known to be a robust source of stem cells. Adipose tissue is readily accessible, easily harvested and few complications have been reported. This study embarks on reporting the safety, efficacy and long term benefits from ultrasound guided injection of an autologous, minimally manipulated, micro-fragmented adipose tissue.

Materials and Methods: Material and Methods: An explanation of the treatment was provided and informed consent obtained. The micro-fragmented adipose tissue was obtained with minimal manipulation using Lipogems® (Lipogems USA, Atlanta Ga.) a closed system using normal saline cleansing, mild mechanical separation of waste products and reduction filters. The system provides a lipoaspirate without the addition of enzymes or any other additives. The final product consists of adipose tissue clusters with preserved vascular stromal niche of approximately 500 microns. The injections were delivered into the joint and each soft tissue abnormality under direct ultrasound guidance as was found to be clinically relevant. Numeric pain scores and The American Shoulder and Elbow Surgeons Score (ASES) were collected immediately following treatment, and at weeks 1 and 5, months 3, 6 and 12.

Results: Significant improvement was noted through all time points to one year. Outcomes assessed immediately following treatment, at weeks 1 and 5, months 3, 6 and 12 by Numerical Pain Scale (NPS) and The American Shoulder and Elbow Surgeons Score (ASES). NPS ($p < 0.00008$), ASES ($p < 0.00017$). The average improvement of NPS was from 7.5 to 3.6 at one year. The average ASES from 33.7 to 69.2 at one year (0-100 scale 100 perfect function). No post procedural complications or serious adverse events were reported.

Conclusions: While the limitations of this study are a low number of subjects and not a randomized controlled trial, it is noteworthy that most published studies are shorter term follow up 3-6 months. The results from this study demonstrate significant improvements in pain, function and quality of life as represented by positive outcomes in all measured scores through twelve months.

Keywords: : Lipogems®, Adipose Tissue, Osteoarthritis, Rotator Cuff, Tendinopathy, Shoulder Pain, Mesenchymal Stem Cell

Introduction

Treatment of shoulder pain from osteoarthritis, and rotator cuff abnormalities presents a clinical challenge for effective non-surgical methods when current standards of care fail. Ultrasound imaging as a diagnostic tool has been shown to correlate with MRI and ultrasound has shown enhanced accuracy when guiding injections [1, 2]. In a recent study, ultrasound guided injections of the glenohumeral joint

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demonstrated greater improvement in function over blind injections [3]. When injecting tendons, accurate placement may play an even more important role. The dual role of ultrasound may be particularly important when delivering cellular products into specific structures and soft tissue defects.

Regenerative cells in orthopedic applications are typically harvested from bone marrow aspirate or adipose tissue. Adipose tissue has gained interest in this regard. With the ease of accessibility by minimally invasive methods, and simple preparation methods for injection have added to the interest. A point debated is whether bone marrow MSC's may be suboptimal for some clinical applications due to the decline in both their proliferation and differentiation with increasing senescence [4, 5]. While the debate for best sourcing will continue, current thinking of all sources attributes the likely therapeutic effectiveness of cellular treatments not to "cell stemness" but to paracrine activity. More specifically, in addition to many trophic activities, the MSC derived extracellular vesicles, exosomes play important roles as mediators [6]. It has been reported in animal studies that the MSC secretomes mediates regenerative processes in tissue undergoing degeneration, concluding the proteomic analysis revealed the presence of important proteins with muscle regeneration, namely pigment epithelium-derived factor and filastatin [7]. Rotator cuff tears in the adult are usually chronic lesions with pronounced degenerative changes, where advancing fatty degeneration and atrophy can lead to irreparable damage. This study sheds light on the potential for the prevention of muscle changes associated with chronic rotator cuff tear.

In another recent study, aimed at deciphering the secretomes from adipose derived stromal cells more than 600 proteins were detected in conditioned media of adipose derived stem cells. Of those, 100 secreted proteins included key molecules involved in tissue regeneration [8]. A recent study has elucidated the role of TGF- β showing adipocytes can dedifferentiate into precursor cells and that a proliferative cell population could be useful in cellular therapy [9]. Along with anti-inflammatory effects, ASC secrete various factors that may modulate metabolism of extracellular matrix in osteoarthritic (OA) cartilage, suggesting that the presence of ASC could be advantageous for OA cartilage due to the recovery of homeostasis between matrix metalloproteinase's (MMPs) and their tissue inhibitors of metalloproteinase's (TIMPs). [10]. Another recent study of human adipose derived stem cells highlighted that the adipose cells exhibit enhanced proliferative capacity and retain multi-potency longer than donor-matched marrow MSC during expansion [11] As more emphasis is placed on the immunomodulatory component amongst others associated with activities of adipose derived cellular therapy, it has been shown that ASCs exert their immunoregulatory effects mainly through the secretion of paracrine factors. Indeed, oxidative stress induces ASCs to secrete TGF- β , which promotes premature T helper (Th) differentiation toward regulatory T cells. Consequently, the Th1 inflammatory response is down regulated, promoting immune tolerance. ASCs also secrete

galectin-1 and -3, which are essential in T-cell suppression, and metabolize L-arginine, limiting its bioavailability, thereby reducing T-cell proliferation and function [12].

In an animal study of the supraspinatus tendinopathy treated with adipose derived stem cells and platelet rich plasma in 55 canine patients, all showed significant improvement in function along with improved imaging characteristics and tendon size on diagnostic ultrasound imaging follow up [13]. Availability of an autologous, minimally manipulated, micro-fragmented adipose tissue is of potentially great clinical significance. A new non-enzymatic method to obtain an adipose tissue highly enriched in pericyte like elements has been developed. It has also been reported that the digestion of adipose tissue to obtain a stromal vascular fraction loses many important bioactive elements in the processing to a purely cellular product [14].

Case description

Here we present a study of 18 subjects in a 20 subject study where 2 subjects were lost to one year follow up, IRB approved by IRCM (LGSH-104) one year following treatment. The aim of the study is highlighting the safety, efficacy and long term benefits of a non-enzymatic adipose tissue treatment for shoulder pain that is refractory to a variety of conservative treatments. Each subject had chronic progressive shoulder pain and loss of useful function that included restricted range of motion, pain elevating the arm, inability to reach behind the neck or back, difficulty dressing, inability to raise the arm above 90 degrees, pain when sleeping on the affected side, weakness and loss of quality of life. Each subject has pain exceeding one year. Inclusion criteria consisted of pain exceeding one year, no cortisone or other injections within 60 days, evidence of pathology on MRI and one subject diagnostic ultrasound alone, failing prior treatment to include at least three of the following: physical therapy, cortisone injections, home exercise, platelet rich plasma, and viscosupplementation. Abnormalities were demonstrated by MRI and in one subject by musculoskeletal ultrasound alone. **Table 1** lists the individual abnormalities. Exclusion criteria included cortisone injection within 60 days, oral prednisone, rheumatoid arthritis, infectious disease, cancer or other systemic comorbidity researches felt was exclusionary.

Subject Demographics

Table 1 summarizes subject demographics. 20 subjects met criteria. Mean age was 65.9 years old with body mass index (BMI) of 32.2 kg/m². Abnormalities on MRI of the shoulder and rotator cuff are listed below. One subject was confirmed by ultrasound imaging alone.

Materials and Methods

Pre-treatment point of care targets of interest were developed by musculoskeletal ultrasound imaging and collated with historical MRI imaging, to map out the treatment plan and determine the approximate final volume of adipose tissue required to treat the intended clinically