Role of Adipose-Derived Stem Cells in Osteoarthritis

Hamid Rahmatullah Bin Abd Razak[1,2], Nima Heidari[1,3], Adrian J Wilson[1,4]

Abstract

Osteoarthritis of the knee is a leading disability with a significant health and economic burden across the globe. It is a progressive and degenerative condition that causes pain and affects function. Current treatment modalities are targeted towards symptom control until the severity of symptoms and loss of function necessitates surgical intervention with arthroplasty. While advancements in technology and refinement of surgical techniques have led to the evolution of primary arthroplasty, outcomes of arthroplasty for younger patients remain unpredictable and poor. With these inferior outcomes, there is a need for alternative options in younger patients with osteoarthritis. In searching for a more sustainable treatment option for this patient group, there has been a surge in exploring orthobiologic treatment options. One such treatment modality is adipose-derived stem cell therapy. This narrative review summarizes the literature on the role of adipose-derived stem cells in osteoarthritis and offers an outlook based on the experience of the senior authors.

Keywords: knee; osteoarthritis; microfragmented fat; orthobiologics; stem cells

Osteoarthritis: Pathogenesis and disease burden

Osteoarthritis (OA) is a global health issue with a myriad of pathogenetic factors [2]. These factors can be classified broadly into mechanical or biological. Features of osteoarthritis include loss of joint space and cartilage, osteophytosis, subchondral sclerosis and subchondral cyst formation [15]. OA can be primary, with no identifiable cause or secondary, where the onset of OA is a direct result of a known injury. Primary OA is by far more common and is diagnosed in the absence of predisposing trauma or disease but is associated with risk factors such as age, gender, obesity, biomechanical and anatomical factors as well as muscle weakness [5]. Ultimately, it develops from a destructive inflammatory cycle, driven by the pro-inflammatory cytokines interleukin-1β (IL-1β) and tumour necrosis factor alpha (TNFα) [17, 18]. These cytokines play a critical role in the degradation of cartilage matrix by increasing chondrocyte production of matrix metalloproteinases (MMPs) [17, 18]. This breakdown of cartilage matrix initiates the inflammatory response, promoting a positive feedback loop in which inflammatory cytokines induce tissue damage which then stimulates production of more inflammatory cytokines. This results in progressive cartilage degeneration, causing advanced OA [17, 18]. In the literature, the prevalence of OA ranges from 12.3% (self reported in the "Disability-Health" 2009 population-based survey in France) [34] to 21.6% (physician-diagosed OA in the United States estimated by the 2003–2005 US National Health Interview Survey) [20]. The morbidity burden of OA is well documented. In the 2010 World Health Organization (WHO) Global Burden of Disease Study, OA was the 11th cause of years lived with disability in the world [43]. OA also contributes to a significant economic burden. Among treatments for OA, arthroplasty procedures are by far the most expensive. In 2004, the annual cost of arthroplasty stands at US$22.6 billion [33].

Current Treatment Modalities for Osteoarthritis

OA is a progressive and degenerative condition. Therefore, current treatment modalities are targeted towards symptom control unless the degree of morbidity indicates necessity of surgery with arthroplasty. These treatment modalities have been summarized below:

Non-pharmacological management

- Exercise (land and water-based)
- Transcutaneous electrical nerve stimulation (TENS)
- Weight control
- Chondroitin or Glucosamine

Pharmacological management

- Acetaminophen
- Duloxetine
- Oral non-steroidal anti-inflammatory drugs (NSAIDs)
- Topical NSAIDs
- Opioids
- Intra-articular corticosteroids
- Intra-articular viscosupplementation

Joint preserving surgical management

- Cartilage restoration procedures
- Meniscus and ligament reconstruction

[1]The Wellington and Portland Children's Hospitals, Queen Anne Street Medical Centre, 18–22 Queen Anne Street, London W1G 8HU, United Kingdom
[2]Department of Orthopaedic Surgery, Sengkang General Hospital 110 Sengkang East Way, Singapore 544886
[3]Department of Orthopaedics, The Royal London Hospital Barts Health NHS Trust, London, United Kingdom
[4]Department of Sports and Exercise, University of Winchester, Sparkford Road, Winchester SO22 4NR, United Kingdom

Address of Correspondence:
Dr Hamid Rahmatullah Bin Abd Razak
Queen Anne Street Medical Centre, 18-22 Queen Anne Street, London W1G 8HU, United Kingdom
E-mail: hamidrazak@gmail.com

procedures
- Realignment osteotomies
- Joint distraction surgery

Joint sacrificing surgical management
- Partial joint arthroplasty
- Total joint arthroplasty

Outcomes In Total Knee Arthroplasty

Advancements in technology and refinement of surgical techniques had led to the evolution of primary arthroplasty surgery. Utilization rates of knee arthroplasty have increased exponentially over the years. Half of patients with knee OA are expected to undergo a total knee arthroplasty (TKA) and as of 2010, there were an estimated 4.7 million individuals in the United States who had undergone a TKA [26, 28]. The annual number of TKAs has been estimated to increase from approximately 620000 in 2010 to 1.38 million by 2020 [1, 24]. In a study by Losina et al, OA diagnosis peaked at an earlier age group (55–64), consistent with current trends where use of TKA occurs earlier in life with 40% of TKA recipients being younger than 65 years of age [27]. While TKA may be the "easiest" surgical option in patients presenting with advanced knee OA, the outcomes of TKA in younger patients have not been predictable. In a retrospective registry study by Lange et al, 529 younger patients aged 18 to 55 and 2001 older patients aged 65 to 75 were propensity score matched and compared with regards to satisfaction after TKA. There was significant dissatisfaction (14%) in the young patients compared to their older counterparts (9%). In another study by McCalden et al, 6275 consecutive TKA patients were divided into three groups based on their age: <55, 55–70, and >70 years. While the difference in the change in Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) score and Knee Society Score (KSS) favoured the younger populations, the revision rate was higher in the group < 55 years with a Kaplan-Meier survivorship of 95.5% at 5 years and 92.2% at 10 years [29]. This higher revision rate in younger patients undergoing TKA was also reported by Bayliss et al [4]. In their study, 54276 patients who had undergone TKA with a maximum follow-up of 20 years were evaluated. Those who had surgery younger than 70 years had a significantly higher lifetime risk of revision as compared to those who were older than 70 years (35% vs 5%). With these findings of inferior outcomes in younger patients, there is a need for alternative options in this patient population.

Orthobiologics

In searching for a more sustainable treatment model to effectively deal with this growing public health problem of OA, there has been recent focus orthobiologic treatment options. There are many treatments that now fit this overarching label that is also known as regenerative injection therapies or biocellular grafts, depending on use. These options include (in order of appearance over the past decades) whole blood therapy, traditional prolotherapy, platelet-rich plasma (PRP), autologous conditioned plasma or serum, bone marrow aspirate concentrate, adipose biocellular autograft, mesenchymalstell cell (MSC) allograft cellular concentrates, amniotic cellular concentrates, cord-derived cellular concentrates, interleukin receptor antagonist receptor peptides, and alpha-2 macroglobulins. The regenerative potential of injured and damaged tissue with stem cells is a promising new treatment strategy in the field of Orthopaedic surgery. Stem cells can be categorized into two major forms: embryonic stem cells and adult stem cells. These cells are able to self-renew with a high growth rate and possess multipotent differentiation properties. Regardless of course, MSCs of different origin share the common feature of harbouring a "secretome" encompassing multiple trophic mediators that act in a paracrine fashion within the recipient tissue to elicit angiogenic antiapoptotic and antifibrotic responses [7]. Although bone marrow has been used as the main source of MSCs, the harvest of bone marrow is a relatively invasive and painful procedure. Moreover, the harvest of MSCs from bone marrow has been potentially associated with a high degree of viral infection and significant decline in cell viability and differentiation with donor age [39]. Therefore, an ideal MSC source should (i) found in abundant quantities, (ii) be harvested by a minimally invasive procedure, and (iii) provide a MSC population retaining a good cellular viability and potential to difference irrespective of age of the donor. In the last few years, adipose tissue has been identified as possessing a population of multipotent adipose-derived stem cells. This adipose source offers two options for selection of regenerative cells: the stromal vascular fraction (SVF) and the adipose-derived stem/stromal cells (ADSCs) contained therein. SVF is a heterogenous mixture of cells isolated by enzymatic or non-enzymatic dissociation of adipose tissue followed by centrifugation in order to remove the differentiated adipocytes, which float over the aqueous layer. ADSCs can be isolated from the SVF by in-vitro cultivation on plastic surfaces, which results in the accumulation of spindle-shaped cells characterized by their self-renewal potency and ability to give rise to at least adipogenic, osteogenic and chondrogenic lineages.SVF is autologous in nature whereas culture expanded stem cells involve cell growth and cell expansion using various nutrients in a laboratory setting, thus requiring government regulatory clearance and approval. In this narrative review, we will explore the role of both SVF and ADSCs in the treatment of OA.

Stromal Vascular Fraction and Adipose-derived Stem/stromal Cells – Background

Over 300000 liposuction surgeries are performed in the US each year and yield anywhere from < 30ml to >6L of lipoaspirate, which is routinely discarded [42]. ADSCs are isolated as part of the aqueous fraction derived from enzymatic digestion of this lipoaspirate. This aqueous fraction, a combination of ADSCs, endothelial precursor cells (EPCs), endothelial cells (ECs), macrophages, smooth muscle cells, lymphocytes, pericytes and pre-adipocytes among others is what is known as the SVF. Although there is significant inter-individual variation, most efficient methods can isolate 500,000 to 2000000 cells per gram of adipose tissue. ADSCs constitute 1–20% of the SVF cells, which is up to 500 times more than the number of MSCs obtained from bone marrow [44]. ADSCs, like MSCs, have shown promise in regenerative medicine [11, 40]. ADSCs secrete growth factors, chemokines and exosomes known to promote tissue repair. These cells produce a paracrine effect that is angiogenic, mitogenic, immunomodulatory, anti-apoptotic and anti-microbial [13]. Growth factors known to be secreted by ADSCs include vascular endothelial growth factor, insulin growth factor 1, transforming growth factor-ß and epidermal growth factor which have a trophic effect that produces a milieu suitable for local tissue repair. This regenerative environment promotes endogenous cell recruitment, activation and differentiation. Further to this, ADSCs also exert significant immunomodulatory effects through the secretion of interleukin (IL)-4, 8 and 10, prostaglandin-2 and granulocyte-colony stimulating factor (G-CSF) to stimulate the proliferation of regulatory and

helper T-cells important for immunosuppression [6].Secretion of exosomes and extracellular vesicles by ADCSs creates a tissue environment that is anti-inflammatory and chondroprotective. Chondrocytes of patients with osteoarthritis demonstrate increased tumour necrosis factor-α, IL-6, prostaglandin-2 and nitric oxide production when stimulated with IL-1ß. Co-culture with exosomes and micro-vesicles derived from human adipose tissue results in decreased production of these inflammatory mediators as well as collagenases.

Pre-clinical Studies

There have been several pre-clinical studies evaluating the disease-modifying effects of ADSCs on osteoarthritis in dogs [9, 14, 19, 45]. The first of these was published in 2007 when Black et al evaluated the effect of adipose-derived mesenchymal and regenerative cells on lameness in dogs with chronic OA of the hip joints [9]. In their randomized, double-blinded, multicentre controlled trial, they reported that dogs treated with ADSCs had significantly improved scores for lameness compared with control dogs. In this study, autologous ADSCs were isolated from a minimum of 23g of fat collected from each dog. This provided 4.2–5 million viable cells for injection. In 2014, Cuervo et al conducted a study with a aim to compare the efficacy and safety of a single intra-articular injection of ADSCs versus plasma rich in growth factors (PRGF) in dogs with hip OA [14]. This was also a randomized, multicentre, blinded study. The primary outcome measures were pain and function subscales, including radiologic assessment, functional limitation and joint mobility. The found that ADSCs and PRGF were both safe and effective in the functional analysis at 1, 3 and 6 months, reducing dog's pain and improving physical function. However the improvements from basal levels were significantly better for ADSCs at 6 months. In this study, 20g of subcutaneous fat was collected from each dog and after cell expansion, 30 million cells were injected into each joint. In a larger prospective randomized and placebo-controlled efficacy study of intraarticular injection of ADSCs in dogs with osteoarthritis, Harman et al concluded that ADSC treatment was better compared to placebo in alleviating symptoms as well as improving function in osteoarthritis [19]. In this study, each dog received a standardized dose of 12 million ADSCs. However, in none of these studies was there histological or imaging evidence of cartilage regeneration. Mei L et al evaluated the efficacy on intra-articular injections of culture-expanded ADSCs for the treatment of anterior cruciate ligament transection induced osteoarthritis in rats[30]. In their histological analysis, there was evidence of the protective role of ADSCs on the structure of cartilage tissue. Severe cartilage defects and decreased Safranin-O-staining intensity were observed in the control group, whereas fewer cartilage defects and decreased proteoglycan loss were observed in the ADSC group. In a recent study by Li J et al on ADSC treatment in a rat osteoarthritis model, they found that rats treated with ADSCs had reduced expression of matrix metalloproteinase 13 (MMP-13) and discoid domain receptor 2 (DDR2) [25].

Clinical Studies

The first published use of ADSCs for treatment of osteoarthritis was reported by Pak[32]. In his study, ADSCs were obtained from adipose tissue of abdominal origin by digesting lipoaspirate with collagenase. These stem cells, along with hyaluronic acid, platelet rich plasma, calcium chloride and dexamethasone, were injected into the knees of two elderly patients with osteoarthritis. Pre-treatment and post-treatment magnetic imaging resonance (MRI) scans, physical therapy and pain score data were then analyzed. In both patients, MRI showed increased height of medical meniscus as well as articular cartilage. Significant improvements in pain and function was also seen. However, outcomes were also reported only up to 3 months. The lack of long-term follow-up as well as the arbitrary combination of ADSCs with other therapeutic products make it difficult to attribute the positive change with the use of ADSCs alone. Following this initial study, there have been several authors reporting on clinical outcomes following utilization of ADSCs on degenerative OA. However, all of them have been with relatively small number of patients [10, 16, 22, 23]. Of these authors, Koh et al have contributed a few studies over consecutive years. In 2012, they showed encouraging short-term results after a single injection of infrapatellar fat pad-derived ADSCs combined with arthroscopic debridement. In all 25 patients, the mean Lysholm, Tegner activity scale and visual analogue scale (VAS) scores improved. However, due to the lack of a control group, we cannot appreciate the true therapeutic effect of the ADSCs in this study [22]. Subsequently in 2015, the same authors reported outcomes from relook arthroscopy following treatment with SVF and/or PRP. They showed that SVF and PRP therapy mildly improved pain and symptoms compared with PRP-only therapy. Patients who received combined SVF and PRP also demonstrated thicker fibrocartilage [23]. The largest clinical study to date evaluating the effect of SVT in patients in OA was conducted by Michalek et al in 2017 [31]. They conducted a case control prospective multi-centric non-randomized study. A total of 1128 patients underwent standard liposuction under local anaesthesia and ADSCs were isolated and prepared for application into 1–4 large joints. A total of 1856 joints, mainly knee and hip joints, were treated with a single intra-articular dose of SVF containing 20–30 million cells. There was a median follow-up of 17.2 months in 1114 patients. Patients were assessed with Knee Injury and Osteoarthritis Outcome Score (KOOS) at 3, 6 and 12 months following treatment. They reported no serious adverse events with the therapy. 63% of patients reported an improvement of 75% in their outcomes scores and 91% of patients reported an improvement of 50% in their outcome scores. Patients who had follow-up MRI showed slight chondral thickening 6–12 months following treatment. While there was no control group, the large number of patients and sound methodology in this study make a compelling case for the use of ADSCs in the treatment of OA. In the most recent study by Yokota et al, the authors compared 6-month outcomes in 42 patients (59 knees) receiving intra-articular injection with 12.75 million ADSCs and 38 patients (69 knees) receiving a 5ml preparation of SVF. The method of harvesting the SVF was similar to that for the ADSCs, except that a greater quantity of liposuction was required (more than 100ml for a single knee or more than 200ml for both knees), and the cells were not cultured, but isolated and injected on the same day. The number of cells injected was unknown for the SVF group as the entire 5ml of SVF produced was injected. All patients had Kellgren-Lawrence grade 2, 3 or 4 knee OA and had failed medical therapy. They reported that no major complications occurred in either group. The SVF group had a higher frequency of knee effusion and minor complications related to the fat harvest site. Both groups reported improvement in pain VAS and KOOS domains. From these all these clinical studies, it can be reasonably concluded that the use of ADSCs is safe and clinically effective in most

patients with degenerative OA.

Regulatory Issues

In the United Kingdom and Europe, isolation of SVF has to be in accordance to the Good Manufacturing Practice regulations. Extensive use and manipulation of stem cells are not allowed under the European Parliament and Council (EC regulation no. 1394/2007). These regulations vary with countries and affect the method with which SVF can be isolated. On November 16, 2018, the United States Food and Drug Administration (FDA) updated its regulatory guidelines for the appropriate use of all stem cell therapies, including those derived from adipose tissue [3]. In these guidelines, it is stated that the use of adipose tissue must meet "minimal manipulation", which is defined as "processing of the human cells, tissues and cellular tissue-based product (HCT/P) that does not alter the original relevant characteristics of the tissue relating to the tissue's utility for reconstruction, repair or replacement." The FDA expresses reservations that the manufacturer processes adipose tissue by removing the cells (such as after enzymatic digestion), leaving the decellularized extracellular matrix portion. This would generally be considered more than minimally manipulated because this processing alters the original relevant characteristics of the adipose tissue relating to its utility to provide cushioning and support. Likewise, the FDA states that the HCT/P must be meant for "homologous use," meaning that "the repair, reconstruction, replacement, or supplementation of a recipient's cells or tissues with an HCT/P must perform the same basic function or functions in the recipient as in the donor." Currently, there are FDA cleared devices for the harvesting, concentrating, and transferring of autologous adipose tissue for musculoskeletal applications. These devices incorporate "sizing and washing" technology that have been defined by the FDA to preserve the cell and tissue microarchitecture of the adipose tissue, eliminate residues of oil emulsion and blood, and provide a tissue that is minimally manipulated in accordance with the FDA guidelines.

Microfragment Adipose Tissue – An Uncovered Gem?

A new device has been developed and used in a variety of settings to harvest autologous ADSCs with minimal manipulation. The Lipogems®system has been developed to harvest, process and reinject human (or animal) lipoaspirates. The Lipogems device harvests and processes a patient's adipose tissue to form a minimally manipulated (without enzymatic digestion or addition of other biological or pharmacological agents) product. Using a small incision, fat tissue is aspirated from the donor site and gently microfragmented and washed to remove oil and blood residues. The final product is a uniform composite containing many pericytes and MSCs that enhance the natural regenerative properties of the recipient tissue. Throughout the procedure, the processed fat is subjected to only minor mechanical forces, with no deleterious effects on the integrity of the SVF or the tissue itself [41]. The gentle mechanical method produces a ready-to-use product in less than 20 minutes. The procedure is fast, safe and does not require stem cell expansion or manipulation, and therefore, it is not subjected to the regulatory restrictions imposed by current Good Manufacturing Practice Guidelines[8].

Literature in Support of Microfragmented Adipose Tissue

Several studies have demonstrated promising results in the use of microfragmented adipose tissue in the treatment of osteoarthritis. In a safety and efficacy study by Panchal et al conducted on 17 patients (26 knees) with a median age of 72 and history of Kellgren-Lawrence grade 3 or 4 knee OA, it was demonstrated that there was significant improvement in pain, quality of life and function for at least 12 months with no serious adverse events. Common minor adverse events included pain and swelling, which generally resolved in 48 hours to 72 hours after the procedure. Similarly, Russo et al evaluated the 1-year safety and efficacy of a single intra-articular injection of autologous microfragmented adipose tissue in 30 patients with OA [36]. They found no major complications. In a later report, the authors presented 3-year outcomes of the same 30 patients [37]. Of the 30 patients previously treated, one was lost to follow-up and seven received additional treatments in the period of observation. On average, the 22 patients that had no other treatments in the 3-year period showed that the results observed at 1 year were maintained. In other study of 38 patients affected by symptomatic knee OA treated with arthroscopic debridement and intra-articular injection of autologous microfragmented adipose tissue, it was shown there was a steady and statistically significant improvement of all the clinical scores from preoperative to 1, 3, 6 and 12 months [12]. On average, 92% of the patients clinically improved and 100% of them were satisfied with the treatment with no complications reported. More recent studies has also attested to the significant improvement of clinical and functional scores in patients with OA treated with an intra-articular injection of autologous microfragmented adipose tissue without any adverse events [21, 38].

Our Experience with Microfragmented Adipose Tissue

With compelling early evidence on the safety and efficacy of autologous microfragmented adipose tissue, the senior authors of this narrative review (NH & AW) have offered this modality of treatment since 2017 to patients with all stages of knee OA who had exhausted other nonoperative treatment modalities with no improvement in symptoms and not keen for invasive surgical options of treatment. All patients are treated as a day case procedure in an operating theatre by a team comprising of an anaesthetist to administer sedation, a consultant plastic surgeon to perform the lipoaspiration and a consultant orthopaedic surgeon to perform the intra-articular injection. We utilize the Lipogems® system to process the lipoaspirate. A single 6–8ml of the refined product of the system is then injected into the knee joint under ultrasound guidance. Our experience thus far corroborates the improvements in pain and function in patients with knee OA that have been reported in the literature by our colleagues[21, 35-38].Similarly, we have not had any adverse events in our patients. We believe that autologous microfragmented adipose tissue is a safe and efficacious treatment for all grades of knee OA. The results of our prospective case series of patients with knee OA following intra-articular autologous microfragmented adipose tissue will be published soon in a peer-reviewed journal.

What Does the Future Hold?

Patients are now presenting with more severe OA at a younger age. TKA while being a reproducible surgical procedure with predictable outcomes in older patients with advanced knee OA, does not confer similar good outcomes in younger patients. The field of regenerative medicine promises a new milieu of nonsurgical treatment to address various musculoskeletal conditions including

knee OA. The potential for improving patient's quality of life by alleviating pain and dysfunction with as minimal adverse effects as possible, has reinvigorated the interest among researchers and physicians to develop novel technologies that can deliver biologic treatment. Through various preclinical and clinical studies, adipose tissue has demonstrated to be a good source of MSCs for treatment of knee OA through safe and efficacious procedures. While SVF and ADSCs have a higher number of studies evaluating their effects on knee OA, autologous microfragmented adipose tissue represents a FDA-compliant, minimally invasive procedure with good promise that needs to be explored to greater effect with larger scale and controlled clinical trials.

PEARLS OF WISDOM
• Adipose-derived stem cells delivered through SVFor autologous microfragmented adipose tissue have been proven to be a safe and effective option in the treatment of knee OA.
• The mesenchymal stem cells in adipose tissue derived preparations have disease modifying properties in knee OA by direct and paracrine mechanisms.
• Autologous microfragmented adipose tissue is prepared with minimal cell expansion or manipulation. Thus, its use in not subjected to restrictions by most regulatory authorities.
• The Lipogems® system used to isolate autologous microfragmented adipose cells has shown encouraging results for all stages of knee OA in early clinical usage. It can be safely performed as a day-care procedure.
• With randomized controlled trials in humans, the promise of this treatment modality can be harnessed into standard of care for knee OA.

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