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Article

Safety and Efficacy of Autologous Stem Cell Treatment for Facetogenic Chronic Back Pain

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Abstract:

Background: Chronic Back Pain due to Facet Joint Syndrome is a common and debilitating condition. Advances in regenerative medicine have shown that Autologous Unmodified Adipose Tissue-Derived Regenerative Cells (ADRC) provide several beneficial effects [1,2]. These regenerative cells can differentiate into various tissues [3] and exhibit a strong anti-inflammatory potential. ADRCs can be obtained from a small amount of fatty tissue derived from the patient's abdominal fat. **Methods:** We report long-term results of 37 patients (age 31-78 years, mean 62.5) suffering from "Facet Joint Syndrome" The pathology was confirmed by clinical, radiological examinations and fluoroscopically guided test injections. Then liposuction was performed. 50-100 cc of fat were harvested. To recover stem cells from adipose tissue, we use the CE-certified Transpose RT™ system from InGeneron GmbH. The cells were then injected under fluoroscopic control in the periarticular fat. Follow-up examinations were performed at one week 1 and 5 years. **Results:** Every patient reported improved VAS pain at any follow-up (1 week, 1, and 5 years) with ADRCs compared to the baseline. **Conclusion:** Our observational data indicate that facet joint syndrome patients treated with unmodified adipose tissue-derived regenerative cells experience improved quality of life in the long term.

Keywords: facet joint syndrome ; adipose tissue-derived regenerative cells

1. Introduction

Lumbar spinal facet joints were first suggested in the medical literature as a source of lower back and lower extremity pain in 1941 [5]. Since then, the so-called "facetogenic back pain" has become a widely accepted diagnosis, though still controversial in the literature [5-11]. The most substantial support comes from investigations reporting successful back pain relief following peri-articular joint injections [12,13]. Estimates of lumbar facet joint pain prevalence based on single diagnostic blocks have ranged from 7.7% to 75% among patients reporting back pain [14]. The facet joint syndrome is a degenerative process of the facet joint's cartilage following degeneration of an intervertebral disc that leads to height loss of the segment resulting in a mechanically induced overload and arthrosis of the respective facet joints (Figure 1). These small joints are made for flexibility but not for weight bearing. Mechanically-induced chronic weight overload finally results in a chronic inflammatory process involving the immune system, producing local inflammatory reactions with the synthesis of several pro-inflammatory cytokines and metalloproteinases [15]. Due to the inflammatory nature of the disease, local injection of glucocorticoids into the affected joint has become a standard treatment option. However, several studies suggest that such injections represent no long-term treatment for patients with chronic back pain [16]. Recently it could be shown that interactions of human bone



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marrow-derived stem cells (MSCs) can limit and mitigate the inflammatory responses in the peri-articular fat by promoting anti- inflammatory pathways [17].

Bone Marrow derived MSCs are harvested by puncture of the iliac crest. This procedure is likely accompanied by some risks to the patient, such as long-term damage to the regenerative hematopoietic potential of the bone marrow- after the removal of hundreds of millions of valuable bone marrow cells. About 99% of the cells removed are hematopoietic progenitors, less suitable for tissue renewal outside the hematopoietic system. It seems inefficient to recover a small number of actual pluripotent stem cells to damage the pool of valuable bone marrow cells primarily as it is known that the number of vital bone marrow cells declines with increasing age.

With the InGeneronTM process, many stem cells can be recovered from adipose tissue [3]. These stem cells from adipose tissue provide three scientifically proven functions: anti-inflammatory effects, antiapoptosis, tissue repair, renewal, and re-placement [18]. These ADRCs can transform into any somatic cell by appropriately exchanging genetic information within the so-called "micro-environment" of the tissue or organ they are placed in [1]. Consequently, local tissue damage can be treated by injecting stem cells at the site needing repair. Clinical applications have shown that tissue of all three germ lines can be treated with stem cells [2, 25,26]. In degenerative diseases of joints, damage to functional tissue induces an inflammatory process, resulting in pain. It has been shown that painful chronic inflammatory disorders of the musculoskeletal system can successfully be treated by stem cell injection [19]. Stem cells, in general, often called MSCs in an inflammatory environment, can influence the immune response by altering cytokine secretion from macrophages, dendritic and T-cell subsets, resulting in a shift from a pro-inflammatory to an anti-inflammatory environment. Successful treatment of degenerative inflammatory processes of the musculoskeletal system, such as facet joints, knee, or shoulder, with injections of adipose tissue-derived stem cells, are well reported in human medicine [20,21].

Adipose Tissue-Derived Regenerative Cells obtained with the InGeneron process contain many so-called vascular-associated pluripotent stem cells [1, 2]. These cells can be recovered within about 20 minutes from a small amount of fatty tissue, without significant harm to the patient.

2. Materials and Methods

2.1. Inclusion and Exclusion Criteria

Patients aged 18-80 years with suspected facet joint syndrome and ongoing symptoms of more than one-year duration – despite standard therapeutic measures - were screened for inclusion in the study. A Fluoroscopically controlled infiltration of the tissue next to the facet joints by 1ml (5 mg/ml) ropivacaine was performed in all patients. This was done to differentiate the source of pain from other causes. Temporary relief of the patient's pain, an analysis of the patient's MRI findings, and a thorough clinical examination were used to establish the diagnosis of "Facet joint Syndrome" before the patient could be included in the study.

Exclusion criteria were: other causes of chronic back pain such as acute disc-related pain, spinal stenosis, osteonecrosis, evidence of a malignant neoplasm in the last 24 months, a history of basal cell carcinoma, chronic skin diseases, connective, metabolic, or skin diseases, evidence of an active infection, immunosuppressive medication, renal insufficiency (creatinine > 1, 8 mg/dl) or liver failure (GOT, GPT > 2x typical values, bilirubin > 2 mg/dl). Thirty-seven patients met the inclusion criteria (age 31-78 years, mean age 62.5 years) and were enrolled in the study.

2.2 Tissue preparation and treatment

A Mini-Liposuction was performed under local anesthesia with additional conscious sedation affected by propofol iv injection under the supervision of an experienced anesthesiologist. 50-100 ml of abdominal fat tissue was removed by this mini-liposuction and processed using a commercially available system. To recover stem cells from adipose tissue, we use the CE-certified Transpose RT™ system from InGeneron GmbH. The removed adipose tissue sample was transferred into InGeneron's processing tube, and Matrase™ enzymatic reagent was added to the sample before it was processed in the Transpose® Tissue Processing Unit. During the first run, the extracellular enzymatic degradation by the specific Matrase TM enzyme liberates the regenerative cells from their surrounding matrix. Three subsequent filtering and washing steps are performed to separate and purify the regenerative cells from fat and adipocytes, remaining enzymes, and cell debris. Within 60 minutes, purified regenerative stem cells recovered from the patient's abdominal fat tissue were ready for immediate use in the same patient as an autologous transplant Figure 1.

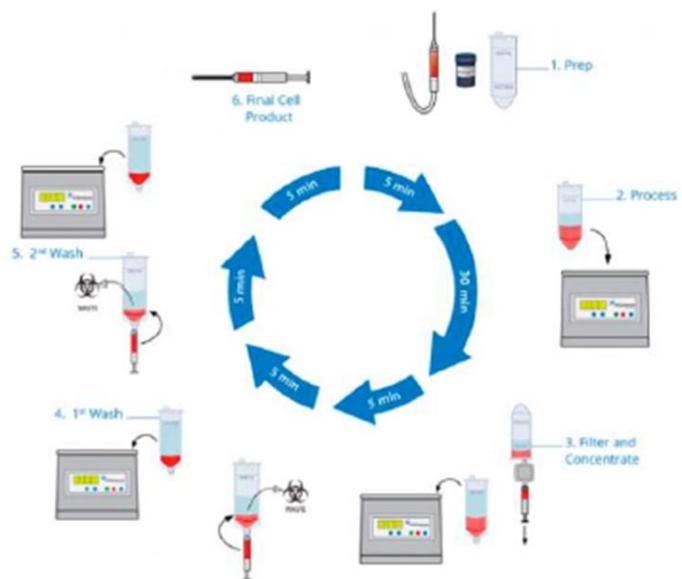


Figure 1 Schematic overview of the lipoaspirate processing procedure. The tissue sample is transferred into the processing tube of the Transpose® Ultra Lipoaspirate Processing System, and the proprietary Matrase™ enzymatic reagent is added to the sample before it is inserted into the Transpose® Ultra Tissue Processing Unit. During the first run, efficient enzymatic extracellular degradation liberates the regenerative cells from their surrounding matrix. Subsequent washing and filtering steps isolate these cells before their immediate therapeutic application. The process shown below takes approximately 60 minutes after lipoaspiration.

The cellular preparation of these fresh, autologous ADRCs was injected under fluoroscopic control para-articular on both sites of the individually affected facet joints (L2/ to L5 and L5/S1) within the same session of fat tissue recovery, preparation of the cells, and injection into the patient. The fat removal to injection procedure was typically finished in two to three hours (Figure 2).

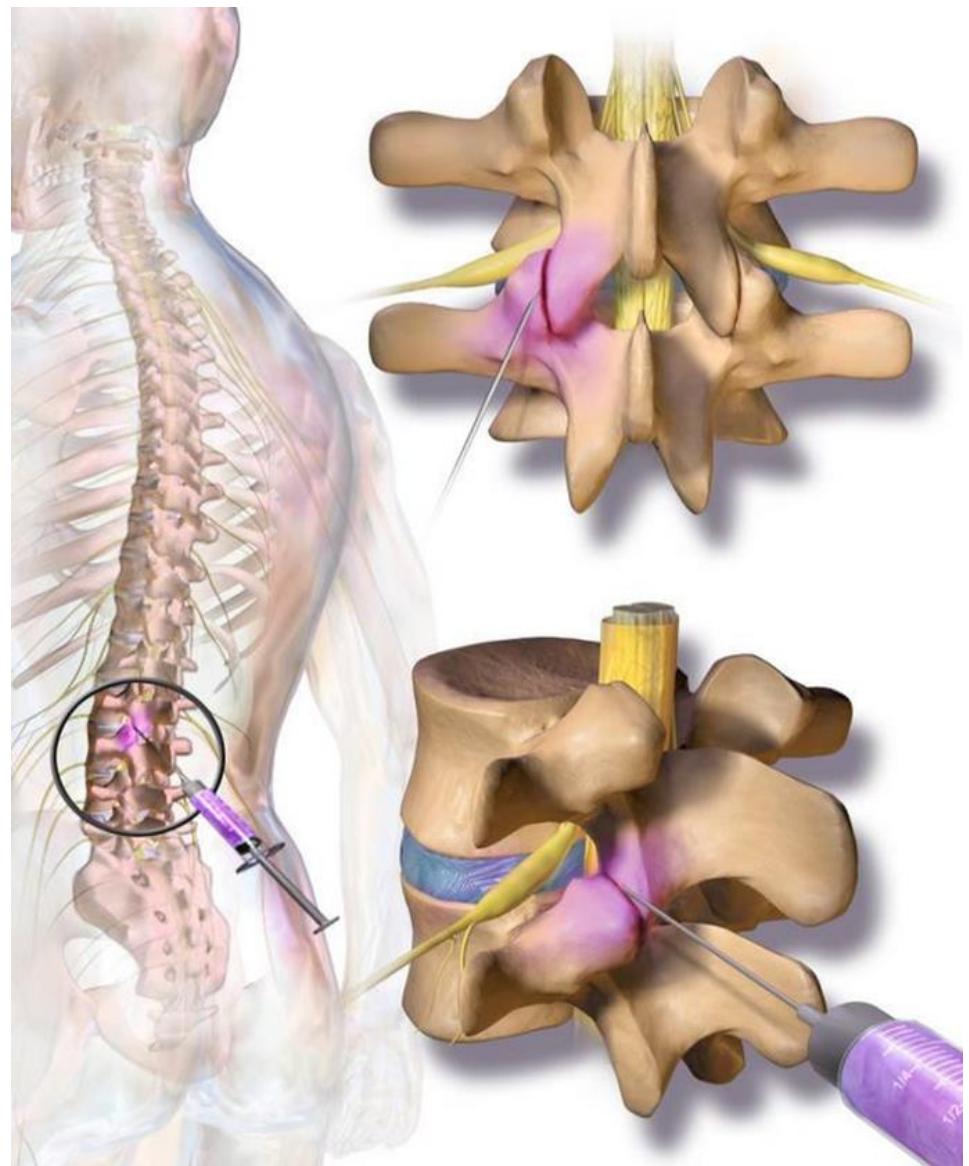


Figure 2 On each level at the back of the spine, two small facet (zygapophyseal) joints - one from an upper and one from a lower vertebra - act as connectors to the spine and provide support as they allow the spine to bend and move. Facet joint syndrome significantly contributes to the high prevalence of back pain observed in western societies. Current therapies include local cortisone injections; however, there are mixed and negative reports regarding long-term efficacy for facet joint syndrome pain relief.

2.3. Follow-up

As part of the follow-up, the Visual Analogue Scale (VAS) for back and leg pain and the Oswestry Disability Index (ODI) were recorded before treatment and postoperatively at one week, one year, and five years after the treatment. Kind and type, severity and duration of any adverse events were recorded at each postoperative visit.

3. Results

3.1. Preoperative symptoms

The most common preoperative symptom was local back pain (in 100% of cases). Before treatment, none of the patients had a motor deficit. One patient had suffered from a sensory deficit at L5 on the right side (2.7%) after six previous operations on the lumbar

spine. Only lumbar pain syndromes were included in the evaluation. In the preoperative MRI, nerve root compression was ruled out in all patients, and all patients showed degenerative changes in facet joints. In 7 patients (18,9%), there were radiological signs of osteochondrosis Modic I and II (Figure 3).

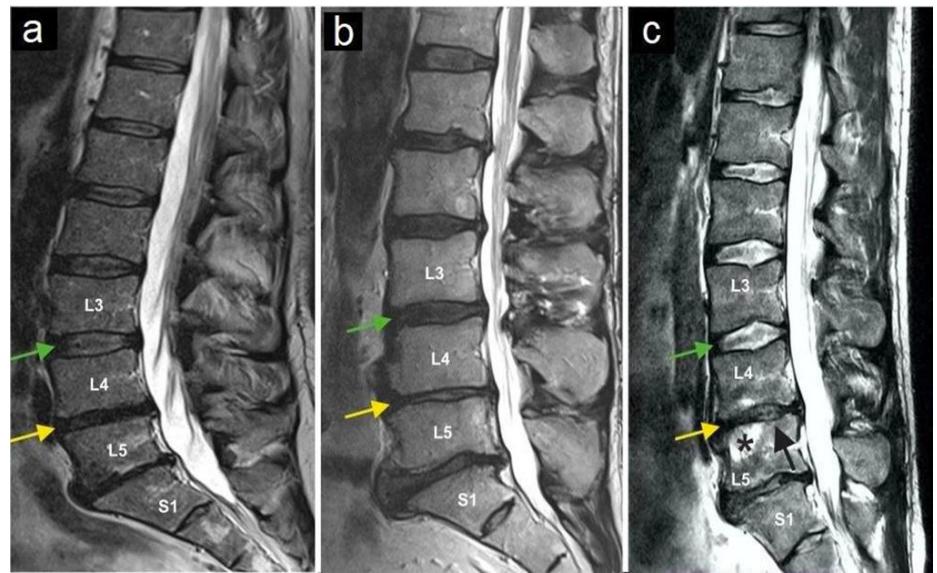


Figure 3 Magnetic resonance imaging of three lumbar spine patients (a-c). The green arrows mark the L3/L4 disc, and the yellow arrows the L4/L5 disc. Note the normal structure of the L3/L4 disc, while the yellow arrows indicate a reduced intervertebral disc height (and thus the disc space) at L4/L5, as observed in all three patients. The star (1c) marks bone marrow edema in vertebral body L5, and the black arrow (1c) indicates the collapse of the superior endplate of the L5 vertebral body.

3.2. Pain Levels and Oswestry Disability Index

The preoperative pain level measured by the Visual Analog Scale means level was VAS 6.8 with an individual range of 5-10 (on a scale of 0= no pain, 10=maximum pain), and the Oswestry Disability Index (ODI) was assessed at 71.05% (range 43-91). After one week, patients already reported an improvement reflected by a decreased Visual Analog Scale pain level. At the one-year follow-up (mean 13.2 months, range 12-16 months), the mean VAS level was 1.5, and the mean ODI was 17.5%. At the five-year follow-up (mean 61.7 months), the mean VAS level was 1.4, and the mean ODI was 18.7%. Every patient reported improved VAS pain after treatment with ADRCs compared to the baseline (Figures 4 and 5). This result was observed in the short term (one week and one month) and in the longer term after five years of follow-up.

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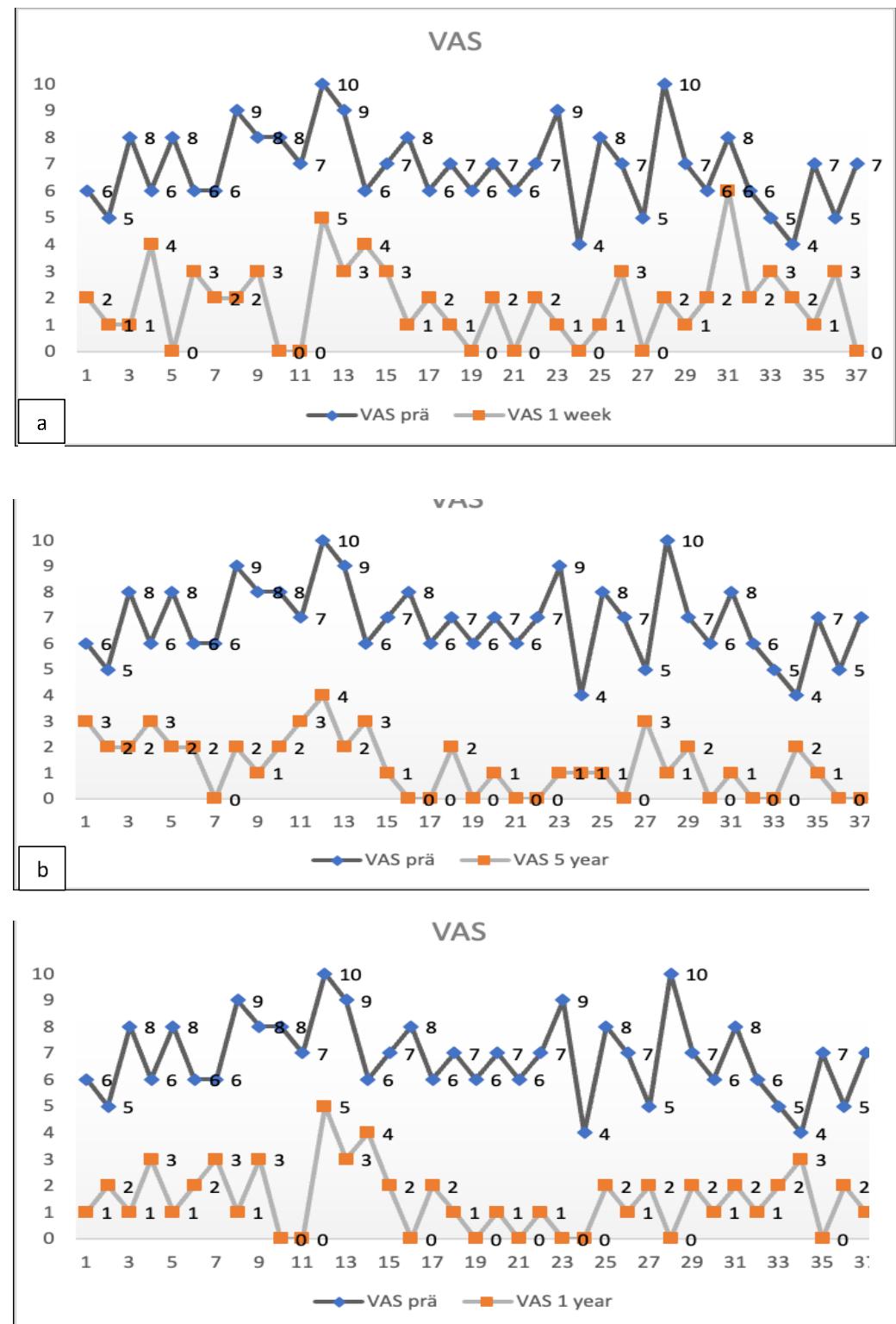


Figure 4 Visual analog pain score (VAS) of 37 facet joint pain patients, shown as pre-treatment and post-treatment VAS score with adipose-derived regenerative cells at one week (a), one year (b), and five years (c). The comparison is shown before treatment (upper points in blue), a) after one week, b) after one year, and c) after five years (lower points in orange). Each patient serves as their internal control.

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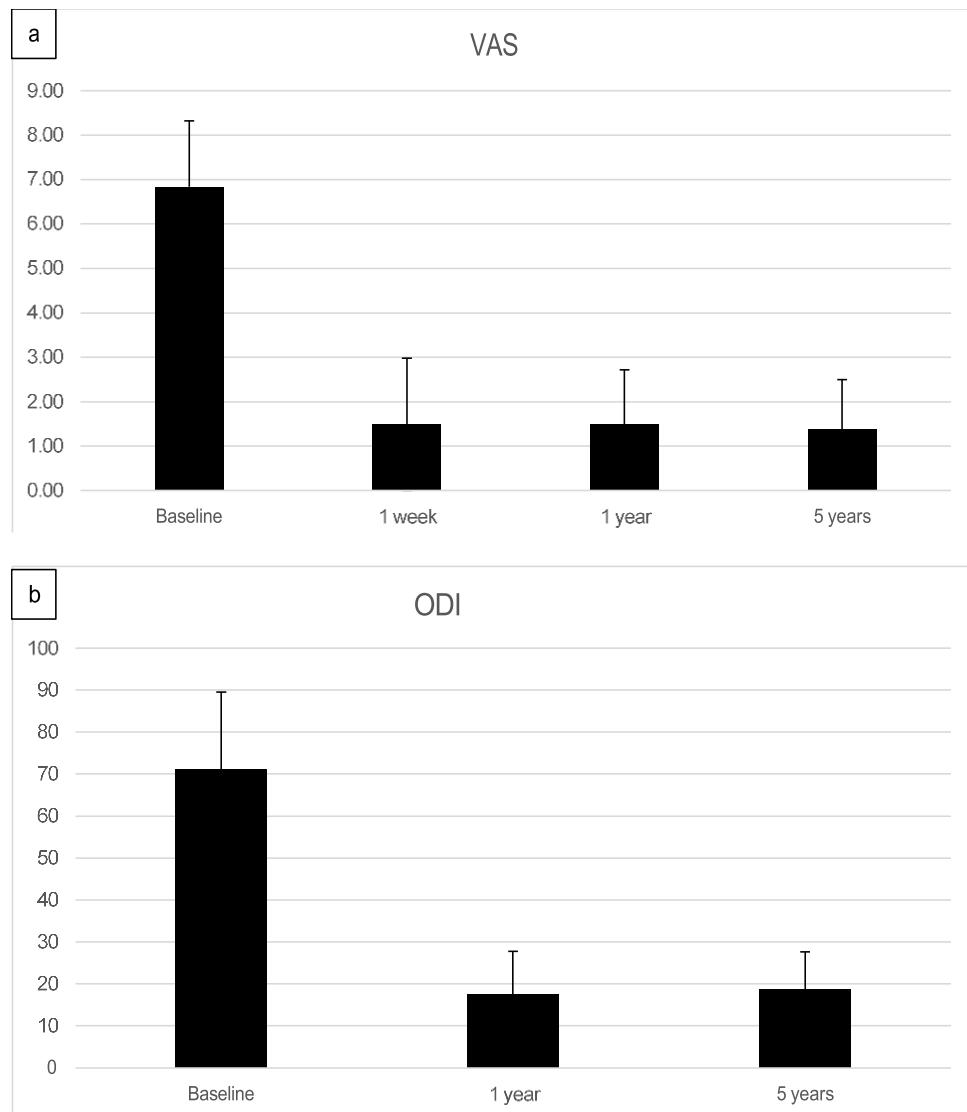


Figure 5 a) Summary of Visual analog pain score (VAS) depicted as a bar graph of facet joint patients treated with adipose-derived regenerative cells at baseline, after one week, after one year, and five years post-treatment. b) Mean Oswestry Disability Index (ODI) score pre-treatment, at one year, and five years post-treatment.

3.3. Complications

After liposuction, one patient developed a relatively sizeable subcutaneous hematoma of about 10 x 15 cm at the liposuction site. This condition was treated conservatively. It caused local pain for 17 days and resorbed spontaneously without further consequences. There were no other minor or severe complications, particularly no infections; no local or systemic minor or significant adverse events related to the procedure.

4. Discussion

Around 70% of all people will suffer at least once from severe lower back pain, as about 25% of all people suffer from chronic lumbago. Causal therapy is unknown, and regular use of NSAIDs often leads to unfavorable comorbidities and is associated with considerable socio-economic costs. In the current study, we report initial clinical results of ADRC treatment and five-year follow-up in patients with facet joint syndrome.

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In the context of degenerative lumbar spine diseases, pain is primarily due to inflammatory reactions resulting from degenerative changes. Inflammatory cytokines have been demonstrated in the facet joint [7] to produce arthropathic changes in degenerative lumbar spine disease. As a result, pain is linked to chemical factors associated with inflammatory responses and cytokines. This theory corroborates the better clinical effects of non-steroidal anti-inflammatory drugs and corticosteroids over opioids or other analgesics [12]. The immune-modulatory impact of stem cells is, therefore, of great interest for the prevention of inflammatory reactions in degenerative diseases of the musculoskeletal system. Successful treatment has also been reported with experimental autoimmune disorders such as collagen-induced arthritis and multiple sclerosis. However, conflicting results on how immune modulation is achieved by stem cells are still discussed [10]. Our study used adipose tissue stem cells (ADSCs) because several prior studies have found a significant qualitative difference between bone marrow stem cells and adipose tissue stem cells. The main difference is the significantly higher number of vascular-associated pluripotent stem cells found in adipose tissue, plus the more facilitated access to adipose tissue compared to bone marrow [2,3]. Harvesting a small amount of fatty tissue less damages the patient than removing millions of valuable bone marrow cells. Bone marrow yields a relatively low number of genuinely regenerative cells. Culturing these cells (MSCs) before use in clinical applications is custom, leading to gene expression changes [22]. Adipose tissue-derived stem and regenerative cells can be isolated and administered in large numbers at the “point of care” without cell expansion/culturing [23]. These non-engineered cells also lead to high clinical safety and efficacy [24, 25, 26].

Our data suggest an initial anti-inflammatory impact of the cells used. We also clinically observed an acute anti-inflammatory effect of the ADSCs, evidenced by the first clinical improvement often seen already 48 hours after treatment. This result suggests an additional therapeutic benefit for other degenerative diseases of the musculoskeletal system. Like regulatory T cells (TREG), ADSCs can migrate to joints where they can act locally within the inflamed synovium to reduce immune cell proliferation and function through the secretion of soluble inhibitory factors. They can also systematically suppress the host immune response through a shift in T1/T2 cell balance, suggesting that ADSC-induced immune modulation is not only mediated by a single mechanism indicating critical therapeutic applications well beyond the field of degenerative joint disease. Further studies should help better understand stem cells' underlying mechanisms of immune modulation and how stem cells derived from adipose tissue exert the same function in a new location as they do in the initial site of adipose tissue harvested from.

5. Conclusions

The current study is the first publication in the scientific literature of a 5-year follow-up long-term assessment evaluating the treatment of chronic facet joint syndrome with autologous adipose tissue-derived stem cells. All patients in this study served as their internal paired control. The authors' results warrant further investigation of ADRCs for facet joint syndrome treatment. Future randomized prospective controlled trials assessing the safety and efficacy of ADRC treatment in comparison to the best-known standard of care interventions should be conducted to corroborate the results of this long-term observational study.

Author Contributions:

Conceptualization, EA. and R.R.; methodology, E.A.; software, RR.; validation EA. and R.R.; formal analysis, EA. and R.R. investigation, J.T., EA. and R.R.; writing—original draft preparation, R.R. writing—review and editing, EA. and R.R.

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Freiburger Ethik Kommision International: Votum Code 013/1372; Autologe Zellanreicherung zur Behandlung der Arthrose

Freiburger Ethik Kommision International: Votum Code 016/1252; Safety and Efficacy of Injection of adipose-derived mesenchymal stem cells (ADRCs) in patients suffering from osteoarthritis of facet joints

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