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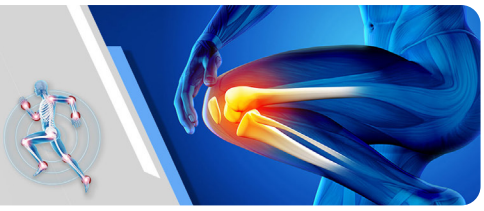

Stromal Vascular Fraction with Platelet-Rich Fibrin for Osteoarthritis Management in Knee and Hip Osteoarthritis: A Retrospective 2-Year Follow-Up Study

Torbjörn Ogéus DC, PgD, MSc*

Abstract

Introduction: In recent years, regenerative medicine has emerged as a promising frontier in the management of various musculoskeletal disorders, including OA. Among the plethora of regenerative therapies, stromal vascular fraction (SVF) therapy combined with platelet-rich fibrin (PRF) has garnered significant attention for its potential to mitigate OA progression and promote joint regeneration.

Methods: This is a retrospective database cohort study. The clinic database was searched for patients that had undergone SVF and PRF for hip- or knee OA between January 2020 and January 2022. 104 patients were included in the study. The analyzed data were 2-year follow-up WOMAC scores and radiographic pictures before and 6 months after the treatment.

Results: Statistically significant positive changes on WOMAC scores (p = 0,0001) were presented for both hip- and knee OA. Radiographic increase of joint space in the treated joints were presented; a mean increase of 2 mm for knees and 1,6 mm for hip joints (p = 0,0001).

Conclusion: SVF combined with PRF is an effective treatment for hip- and knee osteoarthritis. Significantly lowered WOMAC scores 2 years after the treatment, combined with a significant radiographic increase in joint space were presented.

Keywords: Stem cell; SVF; PRF; Regenerative medicine; Knee; Hip; Osteoarthritis; Radiographic; WOMAC

Abbreviations: OA: Osteoarthritis; SVF: Stromal Vascular Fraction; PRF: Platelet Rich Fibrin; WOMAC: Western Ontario and McMaster Universities Arthritis Index; NSAIDs: nonsteroidal anti-inflammatory drugs; MSC: mesenchymal stem cells; TGF-β: transforming growth factor-beta; PDGF: platelet-derived growth factor; PPP: platelet-poor plasma; ALB-PRF: heat coagulated albumin-PRF; C-PRF: Concentrated PRF; SD: Standard deviation; ROM: Range of motion

Introduction

Osteoarthritis (OA) stands as a prevalent chronic joint disorder characterized by progressive degeneration of articular cartilage, subchondral bone alterations, and synovial inflammation [1]. With an aging population and increasing rates of obesity worldwide, the burden of OA continues to escalate, posing substantial challenges to healthcare systems globally. Traditional management strategies such as nonsteroidal anti-inflammatory drugs (NSAIDs), physical therapy, and ultimately joint replacement surgeries

Affiliation:

Stockholms led- & smärtklinik, 11424, Stockholm, Sweden

***Corresponding Author:**
Torbjörn Ogéus, Stockholms led- & smärtklinik, 11424, Stockholm, Sweden.

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offer symptomatic relief but often fall short in halting disease progression or providing long-term benefits [2]. Hence, there exists a pressing need for innovative therapeutic modalities that not only alleviate symptoms but also address the underlying pathophysiological mechanisms driving OA.

In recent years, regenerative medicine has emerged as a promising frontier in the management of various musculoskeletal disorders, including OA. Among the plethora of regenerative therapies, stromal vascular fraction (SVF) therapy combined with platelet-rich fibrin (PRF) has garnered significant attention for its potential to mitigate OA progression and promote joint regeneration [3]. SVF, a heterogeneous cell population derived from adipose tissue, harbors mesenchymal stem cells (MSCs), endothelial progenitor cells, and various growth factors [4]. PRF, on the other hand, is a concentrate of platelets and leukocytes obtained from the patient's own blood, rich in bioactive molecules such as transforming growth factor-beta (TGF-β) and platelet-derived growth factor (PDGF) [5]. When administered in combination, SVF and PRF exhibit synergistic effects, harnessing the regenerative capacity of both cell-based and growth factor-mediated approaches.

In 2014 data on cartilage regrowth was presented after a single dose of Mesenchymal stem cells injected in knees, using arthroscopic before- and after pictures [6].

To our knowledge, no previous long-term data has been published on a combination of SVF and PRF treatment in knee and hip osteoarthritis.

This study presents 2-year follow-up data from 104 patients with hip and knee OA that sheds light on the regenerative potential of SVF combined with PRF as a novel therapeutic paradigm for OA management.

Materials and Method

Various types of autologous platelet concentration protocols have been proposed to be used to treat osteoarthritis and cartilage defects. Some studies have indicated a positive effect on pain, function and stiffness symptoms however, the effect of injected platelets in the injured joint might require multiple injections and no standard protocols exist [7]. One way of extending the effect of the injected platelets is to heat a liquid platelet-poor plasma (PPP) layer, the resorption properties of heated albumin (albumin gel) can thereby be extended from 2 weeks to greater than 4 months (ALB-PRF) [8].

The use of autologous mesenchymal stem cells harvested from the Stromal Vascular Fraction (SVF) has been used increasingly in the treatment of osteoarthritis with promising results in cartilage repair. The combination of autologous blood products such as PRF intra-articular has shown beneficial effects for OA treatment [9].

Preparation of PRF, ALB-PRF, SVF

All patients that underwent SVF and PRF treatment of hip- and knee OA at the clinic during the reported time frame received the same treatment protocol:

40ml blood was collected from the patients before each of the PRF injections. Four 10ml Plastic, round-bottomed vacuum tubes (Liquid PRF tubes) were used to collect the blood, after collection, the tubes were spun on a horizontal swing-out bucket rotors centrifuge system. Two PRF protocols were utilized in the treatment a series including a Concentrated-PRF (C-PRF) protocol of 2000xg for 8 min and a Heat-Coagulated Albumin Gel -PRF (ALB-PRF) protocol of 2000xg for 8 min followed by a heating and cooling down process before injection was performed. The two protocols were utilized following international guidelines for PRF preparation published by Miron et al. in 2019 [10].

The PRF injections consisted of concentrated Platelet Rich Fibrin (C-PRF) [11] injection of 4ml, centrifuged at 2000×g for 8 min. The ALB-PRF injections that were given were 5ml ALB-PRF, 2000xg for 8 min on a horizontal centrifuge, the albumin layer was heated according to the ALB-PRF protocol; 75 degrees for 10 min [12]. In the last step, the heat- coagulated albumin gel was cooled down to room temperature and mixed with the remaining C-PRF to create ALB-PRF. The centrifuge utilized in all PRF treatments was the Bio-PRF horizontal centrifuge (Bio-PRF, USA).

The SVF preparation followed the MyStem™ system protocol (MyStem evo Bi-Medica, Treviolo, Italy). 80 ml of adipose tissue from the abdomen was harvested through a liposuction and then added to the MyStem system, after filtration and wash cycles, the residual fluid and oil was removed. 10 ml of the SVF suspension was extracted and prepared for injection.

Administration of PRF, ALB-PRF and SVF

The patients underwent a series of intra-articular C-PRF, ALB-PRF injections and one intra-articular SVF injection in the osteoarthritic joints. In the first week one intra-articular C-PRF injection two days prior to the SVF treatment followed by two intra-articular C-PRF injections in the following week spaced two days apart, finishing with one intra-articular ALB-PRF injection. The treated joints were instructed to avoid weight bearing for 5 weeks using crutches from the day of the SVF injection. All intra-articular joint injections were performed with ultrasound guidance to ensure needle placement inside the joint capsule.

After the non-weight-bearing phase ended, all patients received a simple rehabilitation program consisting of stationary bicycling for 15 minutes per day and strength training exercises with a slow progression of resistance.

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Study design

This is a retrospective database cohort study. The clinic database was searched for patients that had undergone SVF and PRF for hip- or knee OA between January 2020 and January 2022.

According to the Ethics Commission of Stockholm, Sweden, retrospective database-based studies do not require ethical approval and patient informed consent whenever the data were acquired, saved and treated anonymously. This applies to the present study.

Subjects

123 patients (58 female and 60 male) underwent SVF and PRF treatment for hip or knee OA at the clinic during the above-referred period.

On the first day of treatment, patients were informed about the data collection that routinely takes place in the clinic and were asked to give written consent for data collection. With patient's consent, all patients were given Western Ontario and McMaster Universities Arthritis Index (WOMAC) form to fill in, before the treatment started, after 6 months and after 2 years. Radiographic pictures were taken on all treated joints before the treatment and after 6 months.

The patients were included if they were scheduled for SVF and PRF treatment of knee and hip OA and if WOMAC data was available. The patients were excluded in case all WOMAC data was not available or if they failed to follow the instructions to avoid weight bearing impact of the treated joint after the treatment.

The inclusion criteria were met by 104 patients (50 female and 54 male) that were treated for hip or knee OA with SVF and PRF. The data contains 53 knee OA patients and 51 hip OA patients.

Radiographic database

During the treatment protocol, radiographic pictures of the affected OA joints were taken before the treatment and 6 months after the treatment. The joint space was measured digitally in millimeter (mm) and compared on the before and after pictures and later added to the WOMAC file for each corresponding patient for easy database access.

The instrument

The WOMAC instrument evaluates three dimensions (pain, stiffness, and physical function) it uses 24 items: pain (5), stiffness (2) and physical function (17) items. It produces three subscale scores, one for each dimension, and a total index score [13]. The WOMAC version used in this study uses a scale of 0–4, with lower scores indicate lower levels of symptoms or physical disability. Each subscale is summarized to a maximum score of 20, 8, and 68 score points, for pain, stiffness and physical function respectively. WOMAC total index score or global score is usually calculated by summarizing the scores for the 3 dimensions [14]. The questionnaire is self-administered and takes approximately 5–10 min to complete.

Statistical analysis

Mean and standard deviation (SD) or frequencies (percentage) were used to characterize the sample. The normal distribution of the data was tested with the use of T-test and ANOVA tests. Demographic data comparisons between the groups (Hip vs. Knee OA) were performed based on data gathered before the treatment series with the use of t-tests for independent samples.

To investigate whether there were significant differences in the mean WOMAC scores of patient's multiple comparisons between the pairs of means were performed with t-tests and ANOVA for independent samples.

All statistical tests were performed with Prism 10 for Windows (Microsoft, USA). For all statistical tests, the 0.05 level of probability was set as the criterion for statistical significance.

Results

WOMAC data

The data of the 104 patients that met the inclusion criteria were analyzed. The patients in the sample were on average 62.55 ± 3.93 years old. There were no significant differences between the patients in the Hip- and Knee OA groups concerning their mean age ($p = 0.2$). The distribution of male and female patients was not significantly different between the knee OA and the hip OA groups ($p = 0.5$) (the demographic data can be seen in Figure 1).

The treated knee patients (n=53) were analyzed using an ANOVA test and showed a significant improvement in total WOMAC score ($p = 0,0001$) with a mean change from 50,5 on the baseline measurement, 13.8 on the 6-month follow-up, and 7.8 on the 2-year follow-up (84,5% decrease in total).

Table 1

Demographic data of the patients in the sample.

	Knee OA	Hip OA	p-value
n	53	51	
Age (years)	63,9 ± 5,68	61,2 ± 2,19	p = 0.17
Gender (%) Male	27 (50,9)	26 (50,9)	p = 0.53
Female	26 (49,1)	25 (49,0)	

Figure 1: Demographic data, Values are mean ± SD for age.

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The hip patients (n=51) were also analyzed used using an ANOVA test and showed a similar positive change in WOMAC score (p = 0,0001) but with a slightly higher value where the mean changed from 58.4 to 14.8 after 6 months and 9.1 on the 2-year follow-up (84.4% decrease in total) (changes can be seen in Figure 2).

The pain dimension of the WOMAC scores was also analyzed used using an ANOVA test. The pain levels in the treated knees were significantly lower (p = 0,0001) both on the 6-month follow-up and even lower on the 24-month follow-up with a total decrease of 94% (10.1 to 0.6). The treated hips showed a similar change in pain levels after the treatment, but with a higher mean of pain level still after 24 months, the changes were statistically significant (p = 0,0001) where the mean changed from 12.2 to 5.2 after 6 months and 2.5 on the 2-year follow-up (79.5% decrease) (changes can be seen in Figure 3).

The stiffness dimension of the WOMAC scores was also analyzed using an ANOVA test. The stiffness levels in the treated knees were significantly lower on the 6-month follow-up and showed an 89% decrease on the 24-month follow-up (3.6 to 0.4, p = 0,0001). In the treated hips a similar significant reduction in stiffness was seen between the baseline and the 24-month follow-up (89%, p = 0,0001) (changes can be seen in Figure 4).

The last dimension of the WOMAC scores, physical function (PF) was also analyzed used using an ANOVA test. The physical function scores in the treated knees were also significantly improved on the 6-month follow-up and showed a total 81% improvement on the 24-month follow-up (36.7 to 6.8, p = 0,0001). The positive changes on physical function on the treated hips was also significant (85%, p = 0,0001) (changes can be seen in Figure 5).

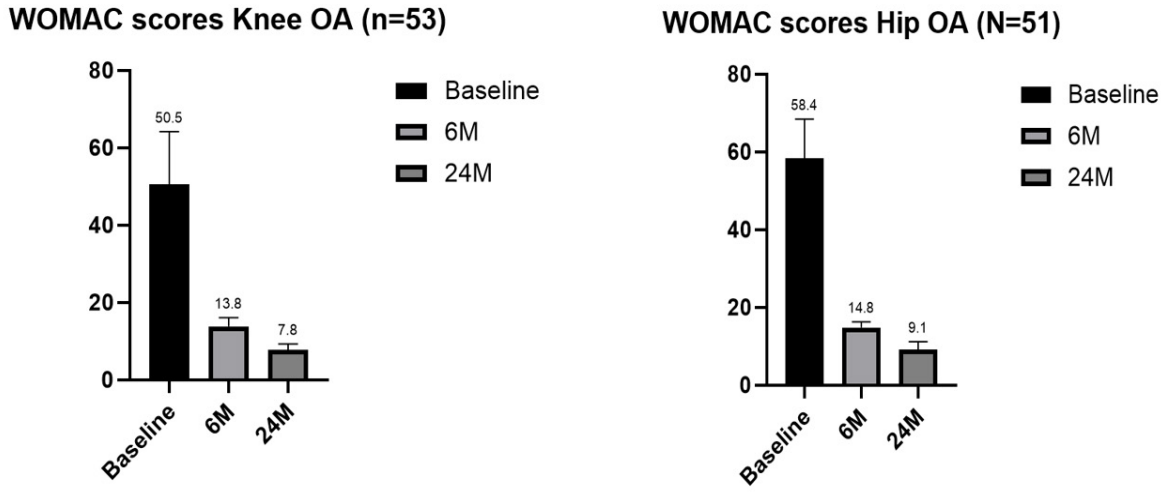

Figure 2: Mean values of WOMAC scores on the treated knees and hips with SD marked.

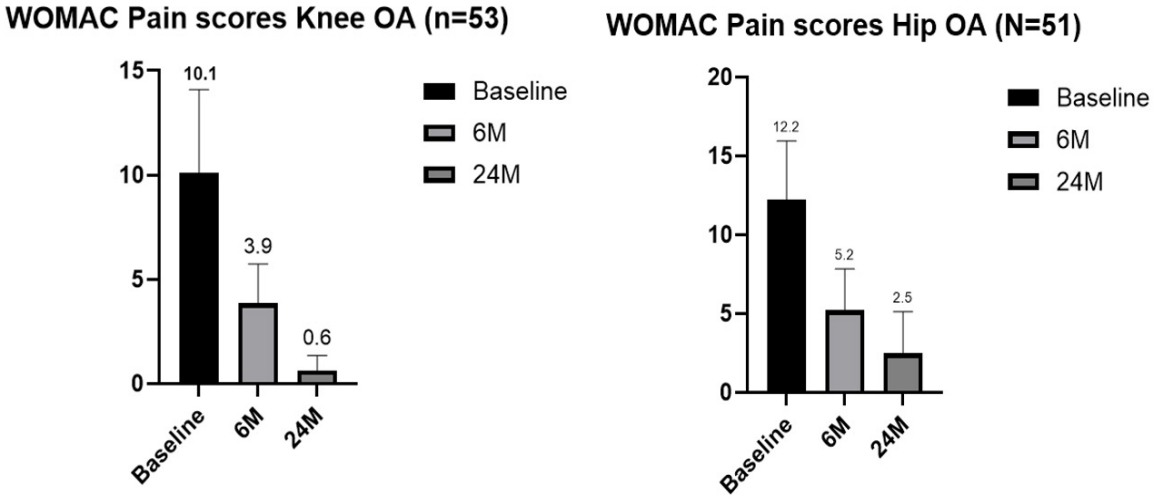

Figure 3: Mean values of WOMAC pain scores on the treated knees and hips with SD marked.

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There were no statistically significant differences between the genders in any of the analyzed dimensions.

A final analysis of the WOMAC data was performed to determine the total combined changes in all the treated patients, both knees and hips. A combined statistically significant (p = 0,0001) WOMAC improvement of 84,5% was seen (with a mean change of 54.3 to 8.4 at the 24-month follow-up) (changes can be seen in Figure 6).

Radiographic data

The radiographic data of the 104 patients that met the inclusion criteria were analyzed with a two-tailed unpaired T-test and compared, before- and 6 months after the treatment.

The two groups hip- and knee OA were analyzed and compared. Both groups showed a statistically significant increase in joint space, the knee patients showed a larger

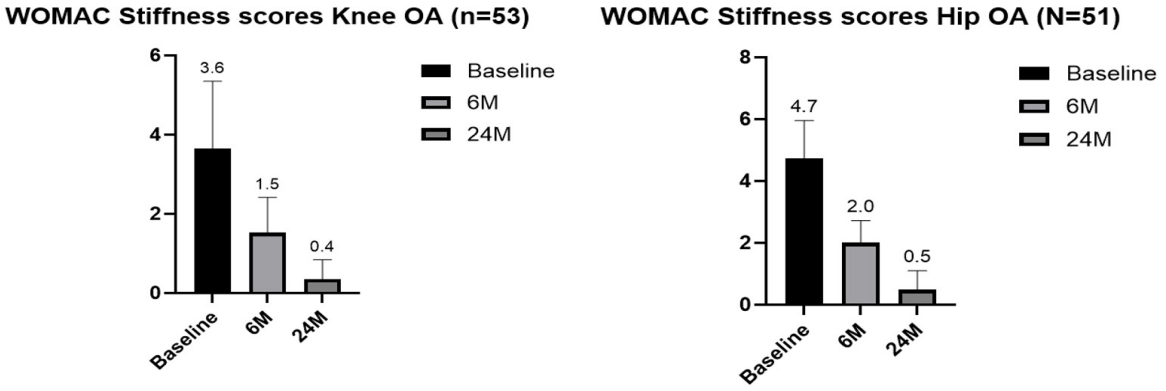

Figure 4: Mean values of WOMAC stiffness scores on the treated knees and hips with SD marked.

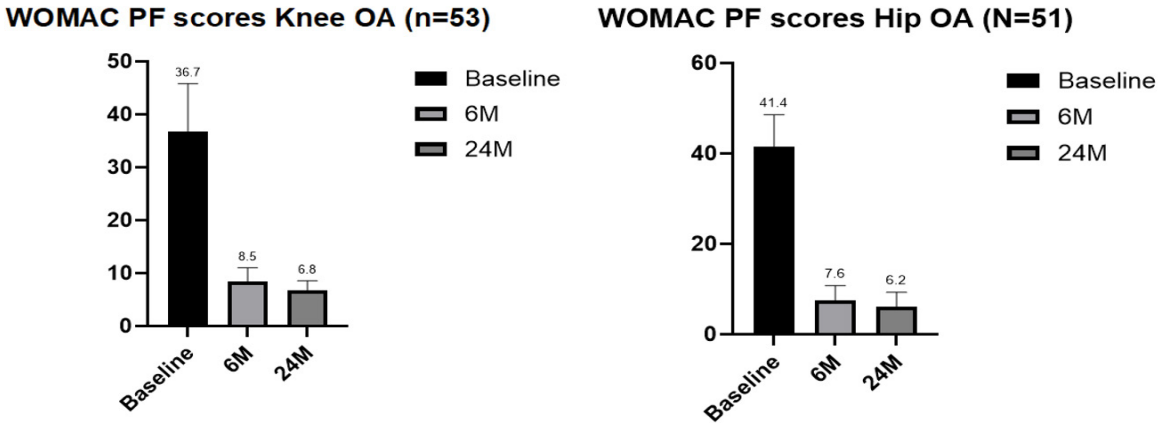

Figure 5: Mean values of WOMAC physical function scores on the treated knees and hips with SD marked.

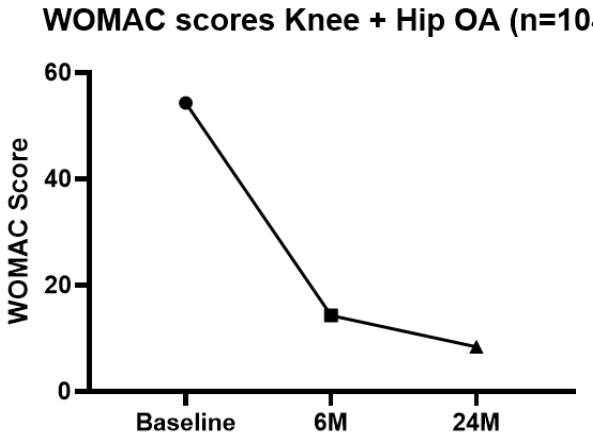

Figure 6: Change of mean values of the combined total WOMAC scores on the treated knees and hips in a line graph.

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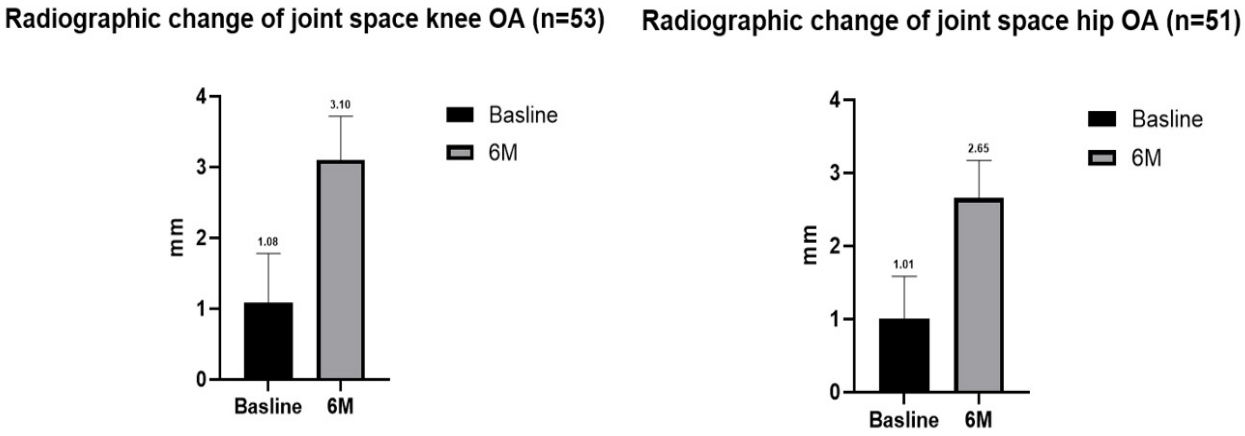

Figure 7: Mean values of joint space increase in mm on the treated knees and hips with SD marked.

mean increase of 2.02mm (p = 0,0001), whereas the hip joints treated showed a mean of 1.64 mm increase according to radiographic picture analysis (p = 0,0001) (changes can be seen in Figure 7).

Discussion

The data presented herein describe a successful novel use of a combination of SVF, PRF, and ALB-PRF thus providing us insight into an alternative intervention for patients where the standard conservative treatment has failed or as an option to surgical intervention.

SVF treatment alone or in combination with platelet injections has been studied and has seen a growing level of evidence for its use, especially for symptom alleviation in the short term for knee osteoarthritis [15].

The WOMAC scores showed a significant improvement in both hips and knees that were treated; however, the knees showed a slightly better improvement than hips with OA in all the dimensions measured with WOMAC. The radiographic changes examined showed the same pattern; where both hips and knees that were treated had significant positive changes, but slightly lower in the treated hips with OA (it may be noted that the joint space and cartilage in hip joints usually is smaller in size than knees in comparison, making the radiographic findings logical as smaller measurements in mm is to be expected). The WOMAC score changes presented in this study show very similar results in comparison to joints that underwent replacement surgery [16], however the pattern in joints that underwent total replacement surgery was completely opposite, it showed a slightly lower positive WOMAC change in operated knees compared to hips. The same pattern was published in a similar study on WOMAC outcomes after total knee- and hip replacement surgery, it was reported that hip patients improve quicker and achieve better WOMAC outcome scores than knee patients [17].

An interesting observation is that the WOMAC scores in this study match the outcome scores on replacement surgery for hips- and knees with OA, however it takes longer time to reach the results, the full results are not achieved after 6 months but may take as long as 2 years. On the other hand, these results present an indication of long-term results, something that has been warranted as most current studies have focused on 1-year outcome data so far [18].

SVF combined with PRF has shown positive effects up to two years after the treatment, in the future an even longer follow up time is needed to indicate the real long-term effects. Even if most patients in this current study experienced a very positive result, of course all treatments are not equally successful and in such cases, where an improvement was seen however not meeting the patients expectations, one positive effect is that a total replacement surgery was delayed for some years, as this can be a difficult situation for a “younger” patient with severe OA, they are usually recommended to wait longer until a replacement surgery can be performed [19]. One of the most positive advantages of the studied treatment is the minimally invasive approach to joint treatment in OA.

With autologous mesenchymal stem cells (as utilized in SVF) the potential risk of a rejection reaction is minimal since only the patient’s own cells are used. Some studies have shown a beneficial effect if repeated injections are utilized [20], while others have reported that a repeated booster injection shows no beneficial effects after the initial treatment [21]. However, indications of potential antibody build-up with risks of severe arthritis and degeneration have been presented if repeated injections of adipose derived stem cells are performed [22].

The WOMAC score for stiffness and physical function gives a good indication on the perceived joint mobility, however one limitation in this study is the lack of data comparing joint mobility in degrees and range of motion (ROM), which could be valuable especially in hip OA.

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The radiographic analysis adds valuable data besides the WOMAC score. One way of getting even more accurate data would be to let future patients undergo magnetic resonance imaging (MRI) before and after the treatments, to evaluate lesions in the cartilage instead of only joint space, however the relative high cost is still an issue that must be considered. The radiographic changes presented in this study is in line with similar studies published before [23,24]. The earlier studies both utilized only SVF and reported slightly inferior clinical outcomes (WOMAC) than the present study. One hypothesis is that the combination of SVF and PRF might be advantageous.

Besides SVF, many other stem cell therapies are emerging for the use against OA, some studies have focused on the comparison between the different types, however no conclusion regarding differences in effectiveness can be made at this point, but the relative ease of extracting SVF compared to extracting bone marrow derived mesenchymal cells is one advantage, compared to other sources where the stem cells are donated, such as umbilical cord blood, the main advantage with SVF would be the minimal risk of rejection after injection since the patient's own cells are used [25,26].

One of the inclusion criteria for this study was the successful non-weight bearing phase of 5 weeks after injection. Since the patients that didn't meet this criterion were excluded, some valuable data is missing, one central question that is still unanswered is if the success of the treatment and the joint space increase is depending on the non-weight bearing phase in the beginning of the rehabilitation after the treatment. An increasing number of studies have focused on radiographic examination to evaluate the potential cartilage regrowth, however no standard protocol regarding the weight-bearing or non-weight bearing regime exist and the results regarding visual signs of cartilage repair are varying [27-29].

This study has some limitations in its design, no control or placebo group can be included and some data points (for instance ROM data or MRI pictures) that would add valuable insights are missing. A larger-scale study with appropriate control is also required for further application.

In summary, the combined SVF and PRF treatment presented offers a minimally invasive, low risk treatment to patients with OA in knee or hip joints as an alternative to total joint replacement surgery. Further studies on even longer follow-up periods are warranted to enhance the long-term evidence for the treatment.

Conclusion

In conclusion, SVF combined with PRF is an effective treatment for hip- and knee osteoarthritis. Significantly lowered WOMAC scores 2 years after the treatment, combined with a significant radiographic increase in joint space were presented.

Declarations

Ethics Approval

According to the Ethics Commission of Stockholm, Sweden, retrospective database-based studies do not require ethical approval and patient informed consent whenever the data were acquired, saved and treated anonymously. This applies to the present study.

The study was conducted in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments.

Consent to participate

Not applicable.

Consent for Publication

This manuscript does not contain any individual person's data. All data exposed in this manuscript was anonymized.

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The author was the main and only contributor to the manuscript.

Competing Interests

The author declares that he has no competing interests.

Authors' Contributions

All texts, design, literature review and drafting of this study was done by TO, responsible for the submitted manuscript.

Availability of Data and Materials

All data generated or analyzed during this study can be provided by the corresponding author upon reasonable request and is available for review by the Editor-in-Chief of this journal.

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