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Research Article

Range of Motion of Metacarpophalangeal and Proximal Interphalangeal Joints in Patients with Systemic Sclerosis Treated with Adipose Derived Stromal Vascular Fraction

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Abstract

Objective: The limitation of digital mobility very commonly affects patients with Systemic Sclerosis (SSc). In this study, we aimed to report the changes in the active Range of Motion (ROM) of the Metacarpophalangeal (MCP) and Proximal Interphalangeal (PIP) joints after local injection of the Adipose-Derived Stromal Vascular Fraction (ADSVF).

Methods: This was a retrospective study in which the results regarding the active ROM of the digital joints in 10 patients treated using the ADSVF were reviewed. The patients were diagnosed with SSc according to the criteria of the American College of Rheumatology and LeRoy and Medsger's criteria. The right hand of a patient was treated through local injection of the ADSVF, and the left hand of the patient was considered the control hand. The active ROM of the MCP and PIP joints in both hands was evaluated before and 168 days post-treatment.

Results: We found that the ROM of the MCP joint in each finger of the control hand had decreased significantly; in contrast, there was a significant increase in the active ROM of the MCP joints in the treated hand. There were no significant changes in the active ROM of the PIP joints in the treated hand. The changes in the active ROM did not lead to a significant modification of the Cochin-Hand-Function-Scale scores.

Conclusion: Statistical analysis showed that local injection of the ADSVF into the hands of patients with SSc led to an improvement in the active ROM of the MCP joints.

Keywords: Articular; Finger joint; Metacarpophalangeal joint; Systemic sclerosis; Range of motion

Introduction

Approximately 90% of patients with Systemic Sclerosis (SSc) complain of the loss of digital mobility, digital strength, and dexterity of the hand and also complain of a decreased quality of life [1,2]. Most studies that reported information regarding these manifestations mainly considered digital ulcers and their impact on hand disability [3]. However, in such cases, ulcers develop after other manifestations, such as digital contractures, the loss of digital mobility, and/or joint deformities [4]. Synovitis occurs more common in cases of Diffuse SSc (dSSc) than in cases of limited SSc, and is a predictive factor for dSSc, pulmonary hypertension,

muscle weakness, new digital ulcers, and left ventricular failure [5,6]. Polyarticular synovitis is more commonly present in the Metacarpophalangeal (MCP) and Proximal Interphalangeal (PIP) joints and is a cause of contractures and the subsequent loss of digital mobility. Thus, digital contractures in SSc are related to synovitis, increased skin fibrosis, edema of the subcutaneous tissue, tendinitis and subsequent tendon retraction, and arthropathy [7-9]. Of the different digital joints, flexion contractures most commonly affect the PIP joints. and are associated with extension contractures of the MCP joints and adduction contractures of the thumb, which cause the typical claw-hand deformity [10]. An individual's dominant hand is most affected by contractures. The presence of more than four joint contractures in a single hand is associated with a poor prognosis [11,12]. Joint deformities that constitute the manifestations of SSc include arthralgia and arthritis. They occur in 47%-97% of SSc cases [6]. However, according to the European Alliance of Associations for Rheumatism, the frequency of occurrence of such deformities is 16% [5]. In one study in which the articular manifestations of progressive SSc were studied in 38 patients with SSc, 66% of the patients had joint pain and 45% had joint-mobility limitation [13] In the same study, the identified radiological abnormalities included periarticular osteoporosis (42%), erosions (40%), and joint space narrowing (34%) [13]. Additionally, Avoauc et al. previously reported the incidence of arthritis (18%), acro-osteolysis (22%), flexion contracture (27%), and calcinosis (23%) [14]. in a number of patients with SSc. Erosive polyarthritis frequently involves the Distal Interphalangeal (DIP) and MCP joints [15].

While joint pain, swelling, and tendinopathy commonly occur in cases of SSc, no therapy has been approved for the treatment of arthritis [4]. The treatment methods that are commonly used include medical control of the disease, protection of the hands, and rehabilitation. However, contractures of the small joints of the hand generally remain unchanged despite the administration of appropriate drugs [16,17]. Continuous rehabilitation for one month temporarily improves the total passive Range Of Motion (ROM) of the digital joints [9]. Local injection of the Stromal Vascular Fraction Derived From Adipose tissue (ADSVF) into the hands of patients with SSc has been proposed as a treatment because of its proangiogenic, antifibrotic and regenerative properties. Local injection of the ADSVF into the hands of patients with SSc is secure [18]. Significant improvements with respect to pain, digital ulcer healing, the severity of Raynaud's phenomenon, the level of disability as assessed using the Cochin Hand Function Scale (CHFS), grip and pinch strength, the Kapandji score associated with thumb opposition, the Modified Rodnan Skin Score (mRSS), and the hand mRSS have been reported at 6 and 30 months [19-21]. However, to the best of our knowledge, the active ROM of the MCP and PIP joints was not evaluated in any of the previous studies. The MCP and PIP joints are more frequently affected by SSc, and under normal conditions, they contribute to 80% and 15% of digital mobility, respectively.

Although musculoskeletal involvement is common, few trials investigating joint-mobility treatment have been performed [4]. Therefore, in the present study, we performed a retrospective analysis of the active ROM of the MCP and PIP joints in the hands of patients with SSc who were treated through local injection of the ADSVF.

Materials and methods

The recorded results regarding the active ROM of the MCP and PIP joints of 10 patients with contractures caused by SSc, and who were treated with ADSVF-fat mixture, were retrospectively reviewed. These patients were treated according to the protocol approved by our Institutional Review Committee with the reference SCI-1505-15/15-1, and fulfilled 1980 American College of Rheumatology and 1988 LeRoy-Medsger criteria. The technique of processing, application of ADSVF-fat mixture, cell characterization as well as the clinical results obtained have been pre-published [22], and the surgical technique is under review for publication in Journal of Surgery. In summary, 100 cc of fat grafts were obtained by abdominal liposuction, of which 60 cc were used for processing ADSVF through enzymatic digestion. The ADSVF was mixed with the remaining 40 ml of fat micrografts, to obtain the ADSVF-fat mixture. Of this cell mixture, 1.5 cc were injected along each digital neurovascular pedicle of the right hand (experimental hand). A total of 3 cc was applied to each finger. In the thumb, 1 ml was injected into each side of the neurovascular digital pedicle. Additionally, 10 cc was applied subcutaneously on the palm of the hand and 10 cc on the back. The active ROM was evaluated through goniometry at baseline (0 days) and 168 days after treatment, then, we compared the evaluated changes in the active ROM with the changes in the CHFS assessment that occurred during the same study period. The left hand of the same patient was untreated and was considered as a control group.

Statistical Analysis

Continuous variables are expressed as median with 95% confidence interval. Dichotomous variables are expressed as frequency and percentage. Categorical or dichotomous variables were analyzed with Fisher's exact test. The differences between before and after the intervention were analyzed with the Wilcoxon range test, and the differences between the control and experimental hands at 0 days and 168 days were analyzed with the Mann-Whitney U test. The analysis was enhanced to determine the interaction between time (0/168 days) and treatment (control/experimental) with analysis of variance for repeated measures, and logarithmic transformation was performed before such analysis. A P value of <0.05 was considered statistically significant of a tail. The data were analyzed using SPSS for Windows, version 24.00 (IBM Corp., Armonk, NY, USA) and GraphPad Prism software version 7 (GraphPad Software, San Diego, CA, USA).

Results

The patients in both groups were similar in age, and in the severity of the disease (Table 1). All the patients presented with moderately intense vascular and joint conditions. Eight of the 10 patients presented with dSSc. One patient did not allow the assessment of the total ROM of the control hand.

Table 1: Demographic and Severity Data.

General Data	0 days
Patient n (%)	10
Female	10 (100 %)
Age, mean (95%IC)	55.0(43.4,58.7)
Diffuse Sclerosis	8 (80 %)
Organ Involvement	
mRSS, mean (95%IC)	15.0(6.84,17.7)
Vascular	10 (100 %)
Severe vascular	6 (60 %)
Articular	10 (100 %)
Severe articular	6 (60 %)
FTP, mean (95%IC)	3.15(2.30,3.71)

confidence interval (95%IC)

No adverse events were registered during or after the ADSVF-fat mixture. With respect to the experimental hand, only the records regarding the active ROM of the MCP and PIP joints, evaluated during the initial evaluation and evaluation performed 168 days after treatment, were complete. For several patients, data regarding the DIP joints were absent; therefore, those joints were not considered in the evaluation. With respect to the control hand, during the study period, for nine patients, records regarding only the MCP joints were complete. In the control hand, at the end of the study, the active ROM of the MCP joint in all fingers was significantly lesser than the initial active ROM. In contrast, with respect to the experimental hand, the active ROM of the MCP joint in all fingers on post-treatment day 168 was significantly more than the initial active ROM (Table 2).

Table 2: Active Range of Motion of the Meracarpal Phalangeal joint of all Digits.

All Digits	0 days	168 days	P
Control (n=9)	88.0 (68.0,105)	85.0(67.5,100)	0.01
Experimental (n=10)	40.0(20.0,55.0)	55.0(23.7,71.2)	0.0001

Median (25th and 75th percentile)
Statistical analysis by Mann-Whitney U

The active ROM of the MCP joint in each finger of both hands, before and after treatment, is described in Table 3.

Table 3: Active Range of Motion of the Meracarpal Phalangeal joint of each Digit.

Digit	0 days	168 days	P^1	P^3
Thumb				
Control	58.0(41.0,72.5)	58.00(50.5,74.0)	0.58	0.56
Experimental	32.5(3.75,51.2)	40.0(20.0,61.2)	0.14	
P^2	0.01	0.10		
Second finger				
Control	79.0 (69.5, 102)	87.0(66.5,99.0)	0.78	**0.008**
Experimental	36.5(23.7,55.0)	50.0(23.7,73.7)	**0.004**	
P^2	0.001	0.009		
Third finger				
Control	99.0 (88.5,107)	88.0(76.0,108)	0.10	**0.03**
Experimental	42.5(20.0,57.5)	57.5(18.7,91.2)	0.13	
P^2	0.0001	0.02		
Fourth finger				
Control	88.0(72.0,113)	90.0(51.0,115)	0.19	**0.003**
Experimental	40.0(17.5,56.2)	57.5(31.2,78.7)	**0.003**	
P^2	0.001	0.07		
Fifth finger				
Control	101(82.5,118)	92.0(74.0,108)	**0.02**	**0.02**
Experimental	52.5(27.5,72.5)	62.5(36.2,78.7)	0.21	
P^2	0.004	0.05		
CHFS				
Control	21.5(8.00,36.5)	23.5(11.5,36.5)	0.56	0.99
Experimental	21.5(8.00,36.5)	23.5(11.5,36.5)	0.56	
P^2	0.99	0.99		

Values expressed in Median (25th and 75th percentile)

P^1 = Before and after the intervention for each hand with the paired t test. (p=0.05)

P^2 = Analysis between hands at the same time, with student's t test of independent samples. . (p=0.05)

P^3 = Analysis of the interaction between time (0 and 168 days) and hands (control and experimental) with repeated measures ANOVA test. . (p=0.05)

The active ROM of the MCP joint in each finger of the experimental hand increased after treatment, as observed 168 days after treatment provision; however, the increase was statistically significant only for the 2nd and 4th fingers. On comparing the interaction of the treatment between the fingers of both hands and their relationship with time, we found that the increase in the active ROM of the finger MCP joint was statistically significant in all the experimental-hand fingers except the thumb. In the PIP joint, the active ROM before and after treatment did not appear to differ significantly (Tables 4 and 5). The changes in the active ROM did not significantly modify disability, which was assessed using the CHFS.

Table 4: Active Range of Motion of the Proximal Interphalangeal joint. All the digits.

Digits	0 days	168 days	P
Experimental N=(10)	35.0 (2.25,65.0)	40(8.75,75.0)	0.203

Values expressed in median ($25^{th}$and 75^{th} percentile)

Statistical analysis by Mann-Whitney U

Table 5: Active Range of Motion of the Proximal Interphalangeal Joint of each Digit.

Digit	0 days	168 days	P[1]
Thumb	27.5 (0.00,80.0)	25.0(0.00,61.2)	0.11
Second finger	35.0(0.00,52.5)	45.0(0.00,76.2)	0.02
Third finger	42.5(2.25,61.2)	42.5(7.50,80.0)	0.35
Fourth finger	37.5(7.50,76.2)	52.5(11.2,82.5)	0.26
Fifth finger	52.5(17.5,67.5)	32.5(12.5,76.2)	0.31

Values expressed in median (25th and 75th percentile)
P[1] = Before and after the intervention for each digit with paired t test.

Discussion

A validated measure for SSc as the primary outcome includes the Health Assessment Questionnaire-Disability Index (HAQ-DI), CHFS, and hand mobility in SSc [4,9]. Additionally, hand mobility has been evaluated using the Hand Mobility in Scleroderma (HAMIS) test [9,23]. Grip and pinch strength, and Kapandji-test scores, have also been used [20]. However, their use has not been validated [4]. Although the range of motion of the MCP and PIP joints is related to hand mobility in patients with SSc [24], few studies have reported information regarding this relationship [7,9]. One study reported that a decrease in total passive ROM at nine years, despite continuous stretching of the fingers during the same period, was significantly related to an increase in HAQ-DI values and a decrease in eating and gripping functions [9]. Although we had previously reported that there are no significant changes in mobility with ADSVF administration [22], because the MCP and PIP joints are the joints most affected by contractures and loss of mobility in patients with SSc, and because these two types of joints account for 95% of total digital mobility, we decided to re-evaluate the active ROM of these joints before and after ADSVF injection.

The normal active ROM of the thumb MCP joint is 65°, and that of the finger MCP joint is 135°. According to the American Society for Surgery of the Hand (ASSH), the normal total digital active ROM is classified as excellent when mobility is 100%, good when greater than 75% but less than 100%, fair when mobility is between 50 and 75%, and poor when less than 50%, and worse when mobility is less than preoperatively [25]. In our study, we found that in the treated hand, there was an increase in the active ROM of the MCP joint in all digits, from 40° at the beginning to 55° at the end of the study; this meant that there was a 37.5% increase in the active ROM of those joints according to the basalvalues. However, according to the classification of active ROM by the ASSH, the active ROM of the MCP joints in the patients included in this study was poor preoperative and moderate at the end of the study. There was an 8° increase in the active ROM of the thumb MCP joint from the baseline value, representing a post-treatment mobility that was 25% greater than the initial mobility and 12.3% greater than the normal mobility. Initially, the ASSH rating for the active ROM of the thumb MCP joint was "moderate", and this rating was raised to "good" after treatment. Unfortunately, the active ROM of the PIP joint in each finger of the experimental hand did not show a significant improvement. This can be partially explained by the fact that PIP joints present digital contractures with greater fibrosis in the skin and tendons and joint changes [10]. It has also been reported that for the improvement of digital mobility and treatment of contracture deformities, there are significant limitations associated with medical treatment, rehabilitation, and surgery [16,17]. Although the patients continued with their medical treatment during the study period, the MCP joints of the left hand (control) presented a significant loss of active ROM. The results of our study showed that the changes in the active ROM secondary to ADSVF administration had an exclusively local effect. This result contrasts with that of the report by Park et al., which mentions that the administration of ADSVF to both hands had a positive impact on fibrosis of the arms and face [19].

In one study, finger flexion and extension were reported to be significantly more impaired in the right hand than in the left hand; however, the authors of that study did not know which hand was the dominant hand [23]. In our study, we found that the right hand was the dominant hand and determined that this hand was significantly more affected by SSc than the left hand because it presented a significantly lesser active ROM at baseline. The changes observed in our study, including the significant increase in active ROM of the MCP joints, did not lead to a modification of the CHFS scores. The ADSVF is a heterogeneous cellular mixture obtained through the mechanical treatment or enzymatic digestion of adipose tissue [18]. It contains pre-adipocytes and pericytes; hematopoietic, stromal, stem, and endothelial cells; and various immune cells; thus, it contributes to the regulation of the stemness of adipose-derived stem cells [26,27]. Its main actions are proangiogenic, antiapoptotic, antifibrotic, immune regulatory, anti-inflammatory, and trophic. The specific mechanism of the action of the ADSVF is still unknown, although it appears to be regulated by the microenvironment of local host tissues [18].

The usefulness of using the ADSVF for the treatment of the manifestations of SSc in the hands of patients with SSc was initially reported in 2014 by Granel et al. [20]. Even though they reported that there was a significant improvement in CHFS scores, grip and pinch strength, and Kapandji scores, information about the changes in the active ROM of the different digital joints was not reported [20,28,29]. Other studies in which the ADSVF was used have reported about the consistent and significant improvement in pain, Raynaud's phenomenon, and the healing of digital ulcers in the hands of patients with SSc, which thereby improved the

quality of life of those patients [19,28-30]. However, they did not report data regarding the ROM of digital joints. The outcomes in our study were similar with respect to significant improvements in pain, quality of life (SF-36), digital ulcer healing, and Raynaud's phenomenon [22].

The cellular characterization of the ADSVF in our study showed that the cellular composition was similar to previously reported ADSVF cellular compositions [19,20,28-30]. Differences in cellular composition can be explained by the fact that the cellular characteristics of the ADSVF differ based on the site of fat procurement, obtainment method of the fat and chemical supplies used to process the ADSVF [18]. With respect to ADSVF injection, the results of our study also show that in the treated hand, there was a significant improvement in pain and in the intensity, frequency, and duration of Raynaud's phenomenon [22]. The significant increase in the active ROM of the MCP joints is an additional improvement that we can now add to this list. Although we know that the MCP joint in a finger is the least affected finger joint, an increase in the active ROM of the MCP joints can improve hand function. Since with the single dose administered, there was an increase in the active ROM of the MCP joints, perhaps this use of the ADSVF should have been repeated one or two more times. The total applied doses of ADSVF and fat micrografts were 3 ml per finger and 4 ml in each thumb. Other authors who have exclusively used ADSVF to treat manifestations of SSc in the hands have used 1 ml of ADSVF per finger [19,20].

The limitations of this report include the small number of patients evaluated, short follow-up time of 168 days, absence of active-ROM records for the PIP joints of the control hands, and lack of evaluation of the HAQ-DI and HAMIS scales. For this reason, a study regarding ROM evaluation that involves a greater number of patients than that considered in the present study and a longer follow-up period than that of the present study will have to be specifically designed.

Conclusion

Local injection of the ADSVF into the hands of patients with SSc significantly improved the active ROM of the MCP joints. A significant decrease in the active ROM of the MCP joints in the untreated hands was observed. Additional studies with greater patient populations and longer follow-up periods than those included in the present study are required to specifically evaluate active ROM and its relationship with functional scales.

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