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Original article

TREATMENT OF KNEE OSTEOARTHRITIS WITH MESENCHYMAL STEM CELLS ARTHROSCOPY AND PHYSIOTHERAPY: EVALUATION WITH SF-36

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Abstract

Introduction: Osteoarthritis (OA), a chronic degenerative joint disease, significantly impacts quality of life (QoL) and poses economic burdens, especially as aging populations grow. While no therapy fully regenerates cartilage, mesenchymal stem cells (MSC) offer a promising treatment for the condition.

Aim: This study aimed to evaluate effects of arthroscopically administered MSC therapy in conjunction with an 8-week standard physiotherapy regimen for patients with knee OA.

Material and methods: This monocentric clinical study involved 35 patients with knee OA (aged 45-65 years, of both genders), who treated with arthroscopy and MSC. Health status was assessed pre- and post-treatment using the 36-Item Short Form Health Survey (SF-36). Additionally, the influence of age and gender on treatment efficacy was analyzed to understand demographic impacts on therapeutic response.

Results: The average SF-36 score after treatment among male patients demonstrated better condition compared to female patients across individual concepts or domains, and overall SF-36 score.

The best condition of 100% according to the SF-36 score after treatment was found among males for the role limitations due to physical health and role limitations due to emotional problems. Among females, these domains also represented best post-treatment condition, with half of them achieving SF-36 scores of 100%. Younger age was significantly associated with better outcomes across all SF-36 concepts.

Conclusion: The results of the study highlight the potential of MSC arthroscopy in combination with physiotherapy, in managing knee OA in this group of subjects. To better understand long-term effects and optimize treatment, larger-scale randomized controlled trials are necessary.

Keywords: OA, MSC, SF-36, quality of life

Introductıon

Osteoarthritis (OA) is one of the most prevalent orthopedic conditions, which can affect any joints, but OA in knee is the most frequently observed condition[1,2]. OA significantly affects patients' quality of life by causing chronic pain and progressive functional loss of the cartilage tissue[1,3]. The prevalence of OA is rising, especially due to the aging of population. A study reported that the number of OA cases increased from 247.51 million in 1990 to 527.81 million in 2019, which corresponds to 113.25% increase[4]. OA prevalence in people older than

60 years is estimated to be around 15% globally[5] whereas prevalance in people between the age 70 to 74 years reaches 40%[6].

There are several well-known risk factors for knee OA, including external factors such as major trauma (macrotrauma), repetitive microtrauma, obesity, prior joint surgeries, and unhealthy lifestyle habits like alcohol and tobacco use[2]. Additionally, various studies have shown that OA is not only associated with the external factors or aging but, other clinical conditions, such as obesity, hormonal dysregulation, genetic disposition, low muscle mass and inflammation, all of which contribute to progressive changes in the composition of articular cartilage, leading to structural and functional joint alterations[7-10]. As obesity prevalence is increasing and population is aging, knee OA becomes more important and is expected to show a higher prevalence in the future[11-13].

The pain caused by OA not only leads to discomfort for the patient, but also results in functional limitations, fatigue, and depression. OA patients face a financial burden due to both healthcare expenses and loss of productivity[14,15]. In most cases, pain is related to physical activity of the patient; only in the later stages of the condition patients begin to experience constant pain[16]. Recent research has revealed that osteoarthritis also comprises a psychological dimension, indicating that patients' experience of OA symptoms is affected by their psychological state. Consequently, the management of OA symptoms must take into account the patient's mental and emotional well-being, and this aspect should be effectively communicated with the patient to ensure a comprehensive and holistic approach to treatment[17,18].

An increasing number of patients suffer from OA and related symptoms globally. This leads to a growing interest to develop regenerative treatment approaches for OA, including the use of mesenchymal stem cells (MSC). An effective therapy should relieve the pain, prevent further progression, improve cartilage structure and repair the damage.

The use of intraarticular injections of MSC offers several advantages in treating OA. Since OA is a degenerative joint disease, self-renewal capacity of MSC combined with their ability to support the maintenance and regeneration of adult mesenchymal tissues, including cartilage, enables them to actively participate in the reparative processes in the joints[19,20]. This is very unique advantage offered by MSC use in the treatment compared to the conservative pharmaceutical approach that is only focused on the management of symptoms rather than on preventing progressive joint degeneration[21]. Furthermore, MSC demonstrate the ability to migrate and engraft at sites of injury, where they can undergo site-specific differentiation. These cells also exhibit intrinsic anti-inflammatory and immunosuppressive properties, improving their therapeutic potential in regenerative medicine[22].

Although there is an increasing number of studies focusing on the use of MSC in OA treatment, significant variability between studies still needs to be addressed. These include differences in dosage, the source of MSC, and methods used to process MSC, making it challenging to compare results across studies[23].

Despite the advances, there is still a gap in the literature regarding the effect of MSC, arthroscopy, and physiotherapy on health-related quality of life in knee OA patients. Additionally, few studies have examined how demographic factors, such as age and gender, influence the outcomes of these treatments. To address this gap, the use of validated outcome measures like the Short Form Health Survey (SF-36) is essential for assessing the broader impact of these interventions on physical and mental health of the patients.

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This study aimed to evaluate the health status and impact of clinical and social interventions using the SF-36 in patients with knee osteoarthritis before and after treatment

with MSC arthroscopy, combined with 8 weeks of standard physiotherapy related to gender and age.

Material and methods

This prospective mono-centric clinical study was implemented on 35 patients with third-degree knee OA treated with MSC combined with 8 weeks of standard physiotherapy during the period March-August 2024 at the Ortomedica Hospital in Prizren, Kosovo.
Surgical procedure covered MSC collection from patients under sterile conditions. While the surgery was underway, MSC were processed using centrifugation at 5000 rpm for 10 minutes. Subsequnetly, they were administered into the operated knee during the surgical procedure (Figure 1).

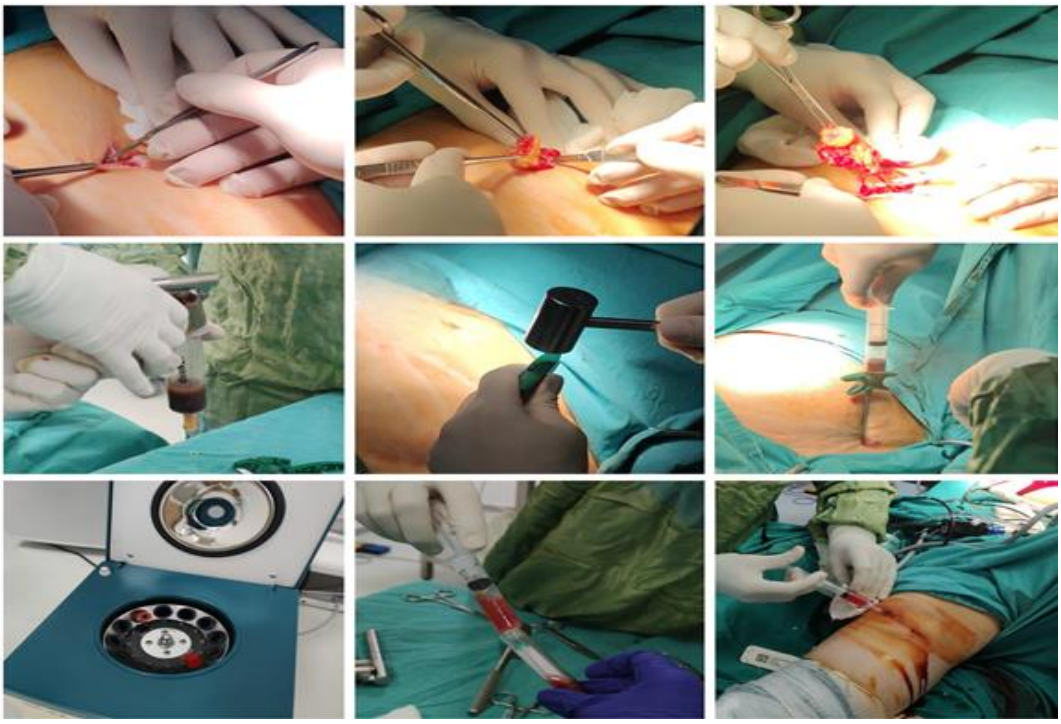

Fig. 1. The collection and administration process of MSC in knee after arthroscopy

During the period of 8 weeks after surgery, a three-phase physiotherapy rehabilitation program was applied to each patient, consisting of: a) first phase with knee exercises focusing on patella mobilizations and combination of isometric and passive exercises to maintain knee extension and avoiding the positions that could trigger pain; b) second phase that aimed to achieve full knee extension through active-assisted exercises to enhance muscle strength; and c) third phase of the physiotherapy that included strengthening and stretching exercises, as well as stationary cycling, balance training, walking, and running.

For evaluation of the health status and impact of clinical and social interventions on the study patients we used SF-36 Questionaire (Version 1.0) that taps 8 health concepts/domains: physical functioning - 10; role limitations due to physical health - 4 questions; role limitations due to emotional problems - 3 questions; energy/fatigue - 4 questions; emotional well being - 5 questions; social functioning - 2 questions; pain - 2 questions; general health - 5 questions. It also includes a single item (health change) that provided an indication of perceived change in health. The questionnaire was administered to all study patients one week before the

intervention and one week after the completion of the physiotherapy program. Scoring the SF-36 questionnaire was made in a two-step process: a) precoded numeric values were recoded per the scoring key scored to ensure that a high score indicated a more favorable health state. In addition, each item was scored so that the lowest and highest possible scores were 0 and 100 with scores representing the percentage of total possible score achieved; and b) items within the same scale were averaged together to create the 8 scale scores. Hence, scale scores represent the average for all items in the scale that the respondent answered. To assess the internal consistency of 8 health concepts, a reliability analysis was performed on the answers received.

This study was conducted in accordance with the principles of the Helsinki Declaration of 1975, as revised in 2000. Informed consent was obtained from all participants prior to study enrolment. The Council of the Kosovo Medical Chamber and the Scientific Board of Ortomedica Hospital, Prizren, Kosovo, approved the implementation of the study.

Statistical analysis

Quantitative parameters were analyzed using mean, median, min/max range and standard deviation. Categorical data were presented as counts and percentages. For chechking the internal consistency of the questions, the reliability analysis of the received answers was applied calculating the Cronbach's alpha coefficient. Association between gender and presence of other chronic diseases was done with the Fisher exact test. The Shapiro-Wilk W test was used to determine the normality of frequency distribution of age. The Mann Whitney U test was used to compare differences between genders related to age. The Wilcoxon signed-rank test was used for the analysis of two dependent quantitative not normally distributed parameters in two time points (before/after the treatment). Spearmen's rang order correation was used as a measure of the strength and direction of association between age and SF-36 concepts and total scores after the treatment. Data obtained in the research were processed in the SPSS software package, version 22.0 for Windows (SPSS, Chicago, IL, USA). A two-sided analysis with a significance level of $p<0.05$ was used to determine the statistical significance.

Results

Study group characteristics

A total of 35 patients that fulfilled the already established inclusion and exclusion criteria were recruited in the study. Among patients with third-degree knee osteoarthritis treated with MSC combined with eight weeks of standard physiotherapy, 14 (40%) were male and 21 (60%) were female. The male-to-female ratio was 0.67:1.

The average age of patients in the study group was 54.97±7.39 years with Median IQR=53 (47-63) and 50% aged ≤53 years. The average age of males was 49.07±4.99 years with median IQR=47.5 (46-51), and of female 58.90±6.01 years with median IQR=61 (55-63). About 50% of male and of female patients were younger than 47.5 *vs*. 61 years, respectively. Female patients were significantly older compared to male (Z=-3.788; p=0.0001). Comorbidity with any kind of chronic disease was reported by 4 (28.57%) of male and 10 (47.62%) of female patients, with no significant association between gender and presence of chronic diseases (p=0.259).

Internal consistency

There was no missing data on SF-36 questions in all 8 health concepts and for single item of health change. The values obtained for Cronbach's Alpha coefficient before and after treatment were as follows: a) 0.91 *vs*. 0.92 for physical functioning (Items - 10); b) 0.81 *vs*. 0.85 for role limitations due to physical health (Items - 4); c) 0.84 *vs*. 0.87 for role limitations due to emotional problems (Items - 3; d) 0.88 *vs*. 0.89 for energy/fatigue (Items - 4); e) 0.92 *vs.*

0.94 for emotional well being (Items - 5); f) 0.82 *vs*. 0.84 for social functioning (Items – 2); g) 0.76 *vs*. 0.77 for pain (Items - 2); h) 0.77 *vs*. 0.79 for general health (Items - 5); and i) health change (Item - 1), respectively. Cronbach's Alpha coefficients indicated high consistency i.e. reliability of received answers in all health concepts of SF-36.

Comparison of the treatment effect

Significant improvement after treatment was found across all SF-36 concepts (physical functioning, role limitations due to physical health, role limitations due to emotional problems, energy/fatigue, emotional well being, social functioning; pain; general health and health change) for both genders as well as for the study sample (Table 1-2).

Table 1. Comparison of SF-36 between male and female patients with third-degree knee osteoarthritis treated with MSC combined with physiotherapy at two time points

SF-16 concepts		Patients with third-degree knee osteoarthritis					p
		N	Mean± SD	Min / Max	Median (IQR)	Difference	
Physical functioning (%)							
male	before	14	33.37±17.38	5/ 70	30 (20-45)	61.43±18.44	Z=(3.300); p=0.001*
	after	21	95.00±10.00	70/ 100	100 (95-100)		
female	before	14	23.09±17.21	0/ 70	20 (15-25)	53.57±15.78	Z=(4.028); p=0.0001*
	after	21	76.67±13.45	45/ 100	75 (65-85)		
total	before	14	27.28±17.95	0 /70	25 (15-30)	56.71±16.76	Z=(5.171); p=0.0001*
	after	21	84.00±15.08	45/ 100	85 (70-100)		
Role limitations due to physical health (%)							
male	before	14	0.00±0.00	0/ 0	0 (0-0)	100.0±0.0	Z=(3.742); p=0.0001*
	after	21	100±0.00	100/ 100	100 (100-100)		
female	before	14	0.00±0.00	0/ 0	0 (0-0)	83.33±24.15	Z=(4.134); p=0.0001*
	after	21	83.33±2.15	25/100	100 (75-100)		
total	before	14	0.00±0.00	0/ 0	0 (0-0)	90±20.29	Z=(5.470); p=0.0001*
	after	21	90±20.29	25/ 100	100 (100-100)		
Role limitations due to emotional problems (%)							
male	before	14	0.00±0.00	0/ 0	0 (0-0)	100.0±0.0	Z=(3.742); p=0.0001*
	after	21	100±0.00	100/ 100	100 (100-100)		
female	before	14	0.00±0.00	0/ 0	0 (0-0)	90.48±15.43	Z=(4.208); p=0.0001*
	after	21	90.47±15.43	66.67/ 100	100 (66.67-100)		
total	before	14	0.00±0.00	0/ 0	0 (0-0)	94.28±12.75	Z=(5.555); p=0.0001*
	after	21	94.28±12.45	66.67/ 100	100 (100-100)		
Energy/fatigue (%)							
male	before	14	30.01±9.62	15/ 50	30 (25-35)	44.92±17.42	Z=(3.301); p=0.001*
	after	21	74.93±13.32	45/ 100	70 (70-85)		
female	before	14	36.67±15.52	10/ 70	35 (30-35)	22.27±21.23	Z=(3.311); p=0.001*
	after	21	59.43±14.92	30/ 95	60 (50-65)		
total	before	14	34.00±13.71	10/ 70	35 (25-35)	31.28±22.60	Z=(4.766); p=0.0001*
	after	21	65.28±16.71	30/ 100	65 (55-70)		
Emotional well-being (%)							
male	before	14	30.02±16.48	0/ 56	30 (20-40)	58.91±19.46	Z=(3.299); p=0.001*
	after	21	88.93±8.64	68/ 100	90 (84-96)		
female	before	14	27.24±18.87	0/ 76	20 (20-40)	41.42±18.16	Z=(4.020); p=0.0001*
	after	21	68.66±18.62	24/ 100	72 (64-80)		
total	before	14	28.34±17.82	0/ 76	24 (20-40)	47.43±20.49	

	after	21	75.77±10.01	24/ 100	80 (68-88)	Z=(5.163); p=0.0001*

Difference = After - Before treatment SD - standard deviation; IQR – Interquartile range, *significant for p<0,05

The average SF-36 score after treatment showed that male patients demonstrated better codition compared to female patients in each concept and in the overall SF-36 score. Male patients showed greater improvements (after/before difference) in each of the SF–36 domains as well as in the overall SF-36 score (Table 1-2).

Table 2. Comparison of SF-36 between male and female patients with knee osteoarthritis treated with MSC combined with physiotherapy at two time points

SF-16 concepts		Patients with knee osteoarthritis					p
		N	Mean± SD	Min / Max	Median (IQR)	Difference	
Social functioning (%)							
male	before	14	31.39±21.75	0/ 75	25 (25-37.5)	63.25±25.66	Z=(3.316); p=0.001*
	after	21	94.64±10.64	62.5/ 100	100 (87.5-100)		
female	before	14	28.07±17.58	0/ 75	25 (25-37.5)	46.33±26.57	Z=(3.653); p=0.0001*
	after	21	74.40±14.51	25/ 87.5	75 (75-87.5)		
total	before	14	29.40±19.12	0/ 75	25 (25-37.5)	53.10±27.16	Z=(4.930); p=0.0001*
	after	21	82.5±16.38	25/ 100	87.5 (75-100)		
Pain (%)							
male	before	14	33.21±16.79	10/ 100	32.5 (22.5-45)	58.75±20.21	Z=(3.303); p=0.001*
	after	21	91.96±10.29	77.5/ 100	100 (77.5-100)		
female	before	14	22.38±10.88	0/ 55	22.5 (22.5-22.5)	54.52±16.76	Z=(4.088); p=0.0001*
	after	21	76.90±15.35	37.5/ 100	77.5 (77.5-77.5)		
total	before	14	26.38±14.37	0/67.5	22.5 (22.5-32.5)	56.21±18.05	Z=(5.197); p=0.0001*
	after	21	82.93±15.33	37.5/ 100	77.5 (77.5-100)		
General health (%)							
male	before	14	28.57±9.29	15/45	27.5 (20-35)	57.86±14.77	Z=(3.306); p=0.001*
	after	21	86.43±11.34	60/100	90 (80-95)		
female	before	14	22.88±17.60	0/65	20 (10-30)	45.22±12.91	Z=(4.021); p=0.0001*
	after	21	68.09±9.81	55/ 90	70 (60-75)		
total	before	14	25.15±14.94	0/65	25 (15-35)	50.27±14.86	Z=(5.166); p=0.0001*
	after	21	75.43±13.74	55/100	75 (65-90)		
Health change (%)							
male	before	14	30.36±17.48	0/50	25 (25-50)	66.07±21.05	Z=(3.342); p=0.001*
	after	21	96.43±9.08	75/ 100	100 (100-100)		
female	before	14	19.04±15.62	0/50	25 (0-25)	63.09±16.99	Z=(4.104); p=0.0001*
	after	21	82.14±11.57	75/ 100	75 (75-100)		
total	before	14	23.57±17.09	0/50	25 (0-25)	64.28±18.48	Z=(5.261); p=0.0001*
	after	21	87.86±12.68	75/ 100	100 (75-100)		
SF-36 Total (%)							
male	before	14	24.12±9.29	7.8/ 38.8	21.6 (19.7-30.2)	67.98±11.53	Z=(3.296); p=0.001*
	after	21	92.09±6.34	73.7/ 98.4	94.2 (90.3-95.7)		
female	before	14	19.93±10.27	3.3/ 45.8	19.0 (14.6-25.0)	55.35±9.78	Z=(4.015); p=0.0001*
	after	21	75.28±10.84	53.7/ 95.5	79.7 (68.5-81.4)		
total	before	14	21.61±9.96	3.3/ 45.8	10.7 (15.2-30.0)	60.39±12.10	Z=(5.159); p=0.0001*
	after	21	82.01±12.43	53.7/ 98.4	82,7 (70,6-94,2)		

Difference = After - Before treatment, SD - standard deviation, IQR - Interquartile range
*significant for p<0,05

The greatest average improvement of the condition (after/before difference) of the SF–36 concepts was observed in the role limitations due to physical health (90±20.29%), and in the role limitations due to emotional problems (94.28±12.75%). The smallest average improvement of the condition was related to energy/fatigue (31.28±22.60%), followed by the emotional well being (47.43±20.49%), and general health (50.27±14.86%) (Table 1-2).

The best condition of 100% according to the SF–36 score was found among males after treatment for the role limitations due to physical health as well as for the role limitations due to emotional problems. Among females, these two concepts also represented the best condition after treatment, with average of 83.33±2.15% *vs*. 90.47±15.43% respectively, and with half of them achieving SF–36 scores of 100% (Table 1).

We also found a significantly better condition after treatment in both genders related to energy/fatigue, which was 74.93±13.32% among males, where 50% of them had scored ≥ 70%. This was higher compared to females (59.43±14.92%), where 50% declared ≥ 60% better condition. After/before improvement in energy/fatigue was 44.92±17.42 among males, which was nearly twice as high as the improvement among females, 22.27±21.23 (Table 1).

Both genders had similar after/before treatment differences in pain that was 58.75±20.21 among males and 54.52±16.76 among females. Regarding the emotional well being and general health, the condition was significantly better after treatment in both, males and females, for 88.93±8.64% *vs*. 68.66±18.62%, and 86.43±11.34 *vs*. 68.09±9.81%, respectively. In half of the male patients, the general health score was ≥ 90% after treatment, and it was higher than in females where half of them scored ≥ 70% (Table 1-2).

The average health change after treatment was 87.86±12.68%, with 50% of patients evaluating their improvement as 100%. Among males, the average health change after treatment was 96.43±9.08%, with half of them scored 100% compared to females where it was 82.14±11.57%, with quarter of them scored 100% (Table 2).

The average overall SF-36 of the study patients after treatment was 82.01±12.43%. In males, it was higher than in females - 92.09±6.34% *vs.* 75.28±10.84%, respectively (Table 2).

Table 3. Frequencies of SF-36 therapeutic effect change at two time points in patients with knee osteoarthritis treated with MSC combined with physiotherapy

Parameters	**SF-36 health concepts**		
	Physical functioning (%)	**Role limitations due to physical health (%)**	**Role limitations due to emotional problems (%)**
p - value	0,0001*	0,0001*	0,0001*
Determined change	A< B - 0 A> B - 35 A = B - 0 N=35	A< B - 0 A> B - 35 A = B - 0 N=35	A< B - 0 A> B - 35 A = B - 0 N=35
Parameters	**Energy/ fatigue (%)**	**Emotional well-being (%)**	**Social functioning (%)**
p - value	0,0001*	0,0001*	0,0001*
Determined change	A< B - 0 A> B - 35 A = B - 0 N=35	A< B - 0 A> B - 35 A = B - 0 N=35	A< B - 0 A> B - 34 A = B - 1 N=35
Parameters	**Pain (%)**	**General health (%)**	**Health change (%)**
p - value	0,0001*	0,0001*	0,0001*
Determined change	A< B - 0 A> B - 35 A = B - 0 N=35	A< B - 0 A> B - 35 A = B - 0 N=35	A< B - 0 A> B - 35 A = B - 0 N=35

A - After; B - Before, *significant for p<0,05

All patients in each of the SF–36 concepts/domains experienced improvement of the related condition after treatment, except in the domain of social functioning, where in 1 patient the condition after treatment was the same as before (Table 3).

There was a significant negative correlation between the age of patients with knee osteoarthritis after treatment with MSC combined with eight weeks of standard physiotherapy and the SF-36 score for each of the conceps. We found: a) a significant negative strong correlation between age and physical functioning for $R_{(35)}$=-0.708; p=0.00002; b) a significant negative moderate correlation between age and role limitation due to physical health for $R_{(35)}$=-0.558; p=0.0005; c) a significant negative week correlation between age and role limitations due to emotional problems for $R_{(35)}$=-0.377; p=0.0257; d) a significant negative moderate correlation between age and energy/fatigue for $R_{(35)}$=-0.617; p=0.0008; e) significant negative strong correlation between age and emotional well being for $R_{(35)}$=-0.760; p=0.00001; f) a significant negative strong correlation between age and social functioning for $R_{(35)}$=-0.734; p=0.00001; g) a significant negative moderate correlation between age and pain for $R_{(35)}$=-0.515; p=0.0015; h) a significant negative strong correlation between age and general health for $R_{(35)}$=-0.718; p=0.00001; and i) a significant negative moderate correlation between age and health change for $R_{(35)}$=-0.602; p=0.0001. After treatment, younger age significantly correlated with better condition across all SF-36 concepts (Figure 1).

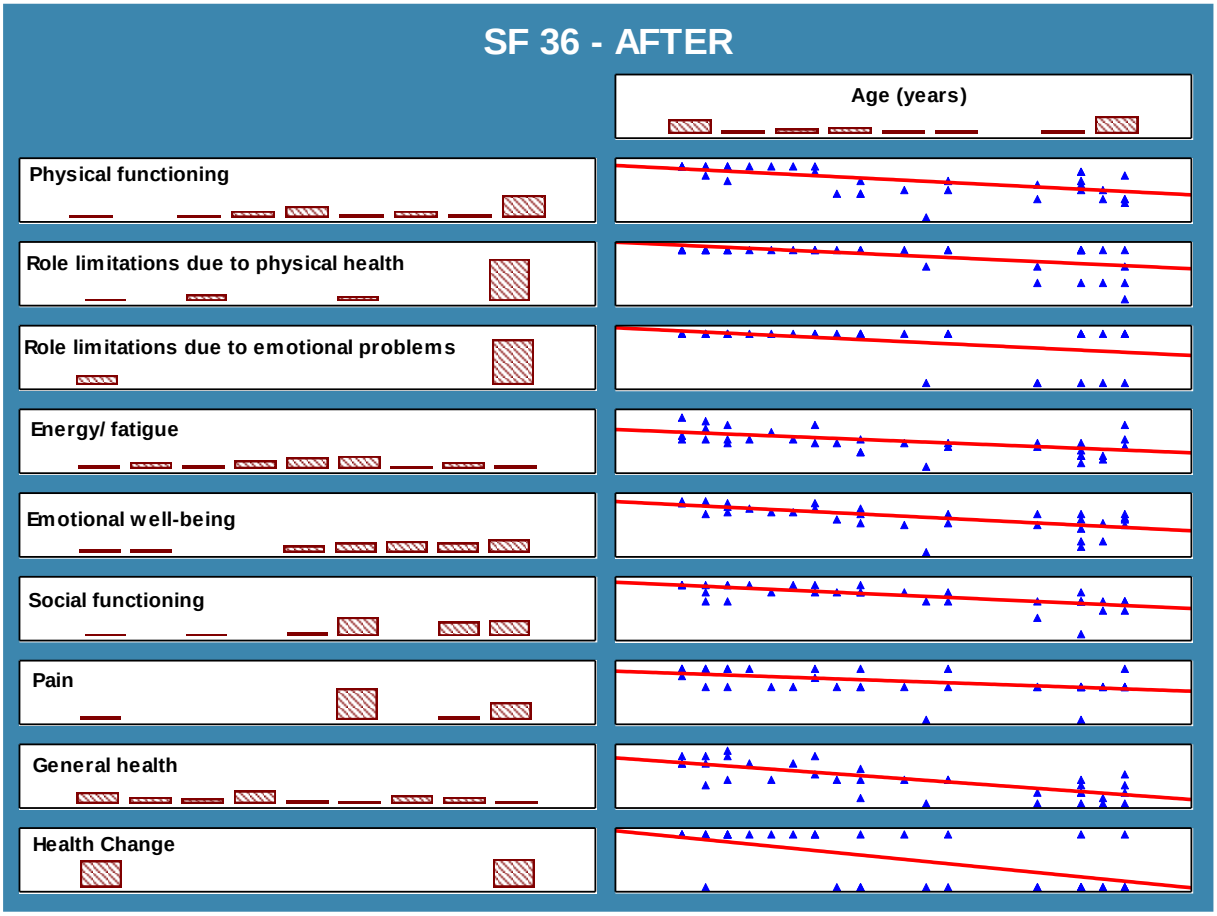

Fig. 1. Correlation between SF-36 concepts scores and age of patients with knee osteoarthritis after tretament with MSC combined with physiotherapy

Dısscussıon

OA is a common chronic joint disease that significantly reduces quality of life and imposes a substantial economic burden. Its prevalence increases with aging, raising concerns as the global population ages. While no therapy fully regenerates cartilage, MSC offer a promising treatment due to their self-renewal, differentiation potential, and immunomodulatory properties[24-26].

Our study evaluated the impact of MSC therapy via arthroscopy combined with an 8-week physiotherapy regimen on knee OA patients, using the SF-36 health survey to assess pre- and post-treatment health status. It also explored how gender and age influence treatment efficacy.

The key findings of this study demonstrated that treatment with intra-articular MSC application combined with physiotherapy led to significant improvements across all SF-36 domains. These improvements were observed in both male and female participants, indicating that the treatment positively impacted both clinical outcomes and overall quality of life in the short term. When comparing post-treatment SF-36 scores between genders, males showed greater improvement across all SF-36 domains and the overall score. We also found that after the treatment, younger age significantly correlated with better condition in all SF-36 concepts. Some authors have noted that OA prevalence and pain severity are higher in females, but there is limited information on sex-specific differences in treatment effectiveness for OA[27]. Espinosa-Salas *et al.* reviewed systemic pharmacological treatments for OA pain management and found insufficient sex-specific data and small sample sizes, making it difficult to assess treatment efficacy by sex. Other studies similarly highlight the lack of information on sex differences in OA, and suggest that females often delay surgical treatment, potentially explaining their reduced post-treatment improvement[28-29].

Although many studies in the literature suggest that intra-articular MSC injections represent a promising treatment approach for knee OA, there is still no consensus on the optimal source or dosage of MSC[5, 30-32].

To optimize the treatment and understand long-term effects, larger-scale randomized controlled trials are required. As the global population ages, developing regenerative treatments like MSC therapy becomes important to manage the increasing burden of OA, helping individuals maintain mobility, independence, and a better quality of life in older age.

This study demonstrates that MSC therapy, delivered via arthroscopy and combined with a standard physiotherapy regimen, offers promising improvements in the health status of knee OA patients. Our findings suggest that while the treatment is generally effective, demographic factors such as gender and age play a role in the overall response, with males and younger age showing greater improvement across various health domains. The results highlight the need for further research in OA treatment efficacy, to optimize therapeutic approaches for diverse patient populations.

Conflict of interest statement. None declared.

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